Systematic Review

Comparison of Clinical Efficacy of Epidural Injection With or Without Steroid in Lumbosacral Disc Herniation: A Systematic Review and Meta-analysis

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Background: Epidural injection is performed for treatment of back and radicular pain in patients with lumbosacral disc herniation (LDH). Steroids are usually administered to effectively remove inflammatory mediators, and local anesthetics or saline also contribute to pain reduction by washing out chemical mediators or blocking the nociceptor activity. Controversy exists regarding whether steroids produce superior clinical effects compared with local anesthetics or saline.

Objectives: This study investigated whether epidural injection of steroids produces better clinical effects than local anesthetics or saline in the treatment of LDH.

Study design: A literature search was performed in MEDLINE, EMBASE, Cochrane review, and KoreaMed for studies published from January 1996 until July 2017. From among the studies fulfilling the search criteria, those that compared the clinical efficacy of steroids and control agents, such as local anesthetics or saline, in terms of pain control and functional improvement were included in this study. Exclusion criteria included a previous history of lumbosacral surgery, non-specific low back pain, severe spinal stenosis, and severe disc degeneration.

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

Methods: After reviewing titles, abstracts, and full texts of 6,711 studies that were chosen following removal of duplicates after the initial database search, 15 randomized controlled studies were included in our qualitative synthesis. Data including pain score, functional score, and follow-up period were extracted from 14 studies and analyzed using a random effects model to calculate the effect size and its corresponding statistical significance. Quality and level of evidence were established in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Results: Steroids and local anesthetics were shown to be effective. Steroid showed significantly better pain control than control agents at 1 month, 3 months, and 6 months. The superiority of steroid in pain control was more prominent at one month, but diminished from 3 months to 1 year, showing no significant superiority in terms of mean difference, With respect to functional score, no significant difference was observed between steroids and control agents. The subgroup analysis showed that steroid revealed significant superiority in pain and functional score at 1 month to saline rather than local anesthetics. Generally, the quality of included studies was evaluated as high-grade, but the evidence level was determined to be moderate, due to inconsistencies.

Limitation: Analyses of safety or adverse effects could not be performed due to a lack of available data from the included studies.

Conclusions: Steroid is recommended over local anesthetics or saline for pain control in

patients with LDH, with a weak strength of recommendation. The superiority of steroids was remarkable, especially at relatively short-term follow-ups, and maintained until the 1 year follow-up. The clinical benefits of steroids at 1 month were more prominent when compared with saline, than when compared with local anesthetics.

Key words: Steroid, local anesthetics, saline, epidural injection, pain, function, meta-analysis, systemic review

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L ow back and/or radicular pain due to lumbosacral disc herniation (LDH) is a major cause of physical morbidity and economic burden. The pathophysiology of low back and radicular pain is believed to include not only a mechanical component, but also other factors, including chemical inflammation (1). The leakage of nucleus pulposus tissue in LDH might induce immunological reactions in the epidural space, where cytokines and other pro-inflammatory substances react with epidurally released nucleus pulposus materials to foster the development of epidural inflammation. This stimulates the spinal nerve roots, induces endoneural edema formation, and increases the permeability of the nerve root microvasculature, which aggravates inflammatory reactions and consequently produces back and radicular pain (1,2).

Epidural injections are performed for the treatment of back and radicular pain resulting from chemical irritation of nervous tissues; the underlying mechanism is the elimination of inflammatory mediators that irritate nervous tissues in epidural spaces (3). Steroids are commonly used in epidural injections because they play the role of eliminating these inflammatory mediators, alleviating damage to nerve fibers, and inhibiting neurotransmission of pain signals in C-fibers in LDH (4-7). A previous experimental report has stated that the increased vascular permeability and inflammatory reactions induced by nucleus pulposus materials were reduced by pretreatment with methylprednisolone (8).

The role of local anesthetics or saline in epidural injections is emerging. These agents play a role in diluting corticosteroids to increase injection volumes, based on the hypothesis that increased volume might facilitate rupture of possible adherence between the spinal root and nearby structures or wash out inflammatory mediators around nervous tissues (5). Furthermore, clinical advantage of local anesthetics had

been explained by the various mechanisms including the suppression of ectopic discharges from inflamed nerves, change of nociceptive circuit, the lysing of iatrogenic and inflammatory adhesions, or anti-inflammatory effects (9,10). There have been contradicting opinions regarding whether steroids produces superior clinical effects compared with local anesthetics or saline. A meta-analysis (11) stated that epidural injections with only local anesthetics obtained comparable clinical benefits to those with mixture of local anesthetics and steroids. Some studies have reported that local anesthetics and steroids are equally effective in pain control and functional improvements in patients with low back pain or stenosis, and that it is not necessary to use epidural injections of steroids in such cases (10,12-16).

Thus, this systematic review and meta-analysis investigates whether epidural injection of steroid produces better clinical results than local anesthetics or saline for the treatment of LDH.

Methods

Study Selection Criteria

We included articles of human subjects that were written in Korean or English and met the following criteria: patients aged ≥ 18 years, clinical presentation of low back and radicular leg pain, and diagnosis of LDH on a radiological evaluation such as computed tomography or magnetic resonance imaging. Exclusion criteria included a previous history of lumbosacral surgery, non-specific low back pain without a definite diagnosis of LDH on radiological evaluation, severe spinal stenosis, severe disc degeneration (Pfirmann grade IV and V), intradiscal derangement or a bulging disc, or prominent spinal instability. Of the studies fulfilling these criteria, those that compared the clinical efficacy of steroid and a control injectate, such as local anesthetics or saline,

in terms of pain control and functional improvements were included in the analysis.

Information Sources and Search Strategy

The MEDLINE (PubMed), EMBASE, Cochrane review, and KoreaMed databases were searched for articles published from January 1996 until July 2017. We established individual search terms in each database's search engine (Appendix). The decision to include an article was primarily made based on title and abstract review, followed by full-text screening. The articles included in our analysis were restricted to randomized controlled trials (RCT) involving human subjects, written in English or Korean. The study screening and data extraction were independently performed by 2 reviewers, and any discrepancies were resolved by discussion between the 2 reviewers or with the entire research group.

Data Collection

Reference data such as the number of subjects, type and dose of injected medication, type of approach techniques (transforaminal, interlaminar, or caudal), follow-up period, clinical evaluation tools, and comparative results of the clinical outcomes were extracted from the selected articles. Dichotomous variables such as the number of patients with successful clinical outcomes with respect to pain and functional score were extracted for the estimation of relative risk ratios, and continuous variables such as mean and standard deviations of pain and functional scores were extracted for the estimation of mean differences. If standard deviations were not reported, they were calculated from the confidence intervals, means, and number of patients.

Quality Assessment of Selected Studies, Establishment of Level of Evidence, and Strength of Recommendation

Quality assessment of each study and level of evidence was established in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (17). The bias assessment for each RCT was performed using the risk of bias (ROB) method, which consisted of 7 domains: random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases. The bias for each non-RCT was assessed using the Risk of Bias Assessment tool for Non-randomized Study (RoBANs), which consists of the following domains: selection of participants,

confounding variables, intervention (exposure) measurements, blinding outcome assessment, incomplete outcome data, selective outcome reporting, and other biases. All the domains were evaluated as either "low risk," "high risk," or "unclear." These evaluations were performed by 2 independent reviewers, and disagreements were resolved by discussion between the 2 reviewers or with the whole research group.

We comprehensively considered inconsistency, indirectness, imprecision, and publication bias components, in addition to the risk of bias of all studies, to classify evidence levels into either high, moderate, low, or very low grades. The strength of recommendation was determined as strong or weak by comprehensively assessing not only the evidence level, but also other factors such as balancing benefits and harms, resources required, values and preferences, and acceptability/feasibility (17). The level of evidence and strength of recommendation were determined by discussion of entire research group.

In addition, quality assessment was performed utilizing Cochrane review criteria and Interventional Pain Management techniques Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB) (18-21). The studies meeting the inclusion criteria with a score of at least 8 of 12 or 32 to 48, respectively, were considered high quality, 4 to 7 or 16 to 31 were considered moderate quality, and these were included in the review. Those with a score of less than 4 or 16 were considered as low quality (20).

Meta-analysis

Review Manager software (RevMan version 5.3; The Cochrane Collaboration 2014) was used for data analysis. The analysis was performed in terms of pain control and functional improvement at various follow-up time points. Tests of heterogeneity were performed using I2 statistics. Categories with I2 values of 75% or higher were regarded as having a high degree of heterogeneity and were considered for the subgroup analysis (22). A random effects model was applied to obtain the effect size and statistical significance, because we assumed that the subjects and methods of included studies performed by independent researchers were not entirely equivalent, and therefore, could not have common effect sizes. $P < 0.05$ was considered statistically significant. The results were expressed as mean differences and 95% confidence intervals (95% CIs) for continuous outcome data and as relative risk ratios and 95% CIs for dichotomous outcome data.

Results

Study Selection

Our database search initially yielded 9,088 articles, and after the removal of 2,377 duplicates, 6,711 potentially eligible articles remained. After title and abstract screening, 6,407 articles were excluded because they did not meet the inclusion criteria. Thus, 304 articles were retrieved for full-text analysis, of which 289 were subsequently excluded because they were irrelevant to this study, and ultimately, Fourteen RCTs were included in this study. Except for one study that did not provide data applicable to the meta-analysis (23), 13 studies were included in meta-analysis (Fig. 1). The pain intensities in the selected studies were measured using either the visual analog scale (VAS) or the numerical rating scale (NRS). Both scores were considered the equivalent in the meta-analysis because they were highly correlated, and when transformed, could be used interchangeably (24). The most frequently used functional measurement tool in the selected studies, the Oswestry Disability Index (ODI), was chosen as the functional evaluation tool. The follow-up period was

Fig. 1. *Flow diagram of study selection.*
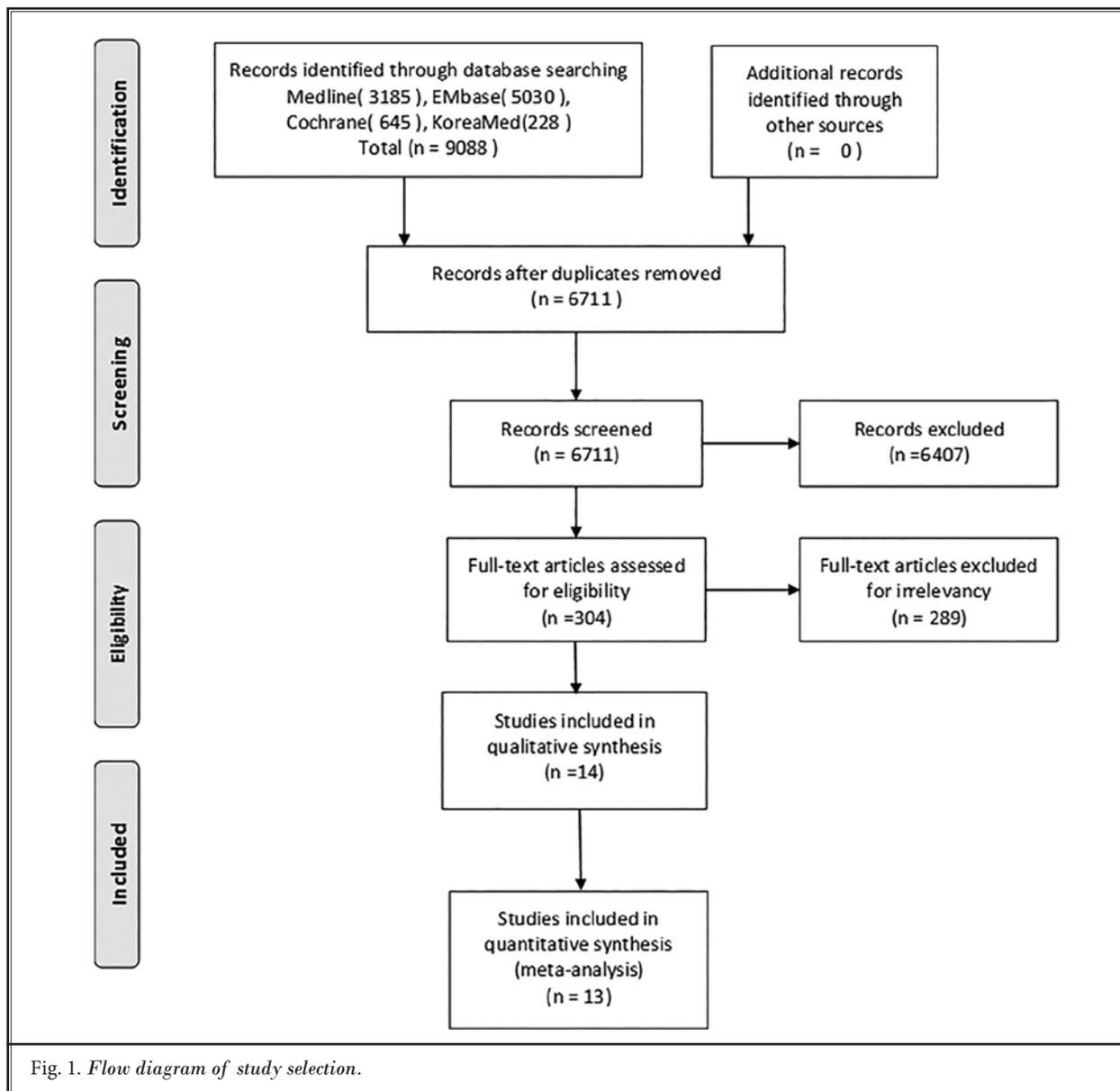
variable across the studies, ranging from 2 weeks to 1 year. One month, 3 months, 6 months, and 1 year were established as follow-up periods for the meta-analysis because of the availability of clinically meaningful pain and functional data at these time points.

Risk of Bias

The risk of bias of all selected studies was illustrated in Fig. 2. Except for 1 (25) RCT that was assessed as having unclear risk, all RCTs were assessed as low risk, in random sequence domain. The domain associated with bias most frequently was blinding of outcome assessment, in which 4 RCTs (26-28) were rated as unclear risk of bias because they did not provide an adequate description of this procedure. Of 98 domains across all studies, 86 domains (87.8%) were determined as low risk. Thus, overall risk of bias was assessed as low and

the studies selected for this analysis were evaluated as high-quality.

Individual Study Results and Synthesis of Results

Among the 14 randomized studies that were ultimately selected, no significant differences in clinical efficacy were found between steroid and control such as saline or local anesthetics in 8 studies (26,28-34). While the other 6 studies reported the additive or better clinical outcomes were obtained by steroid. One study showed that steroids with mixture of isotonic saline were moderately more effective in leg pain reduction at 3 months follow up, but not significantly different in functional improvement than isotonic saline (35). Two articles demonstrated superiority of steroid with mixture of bupivacaine or normal saline than normal sa-
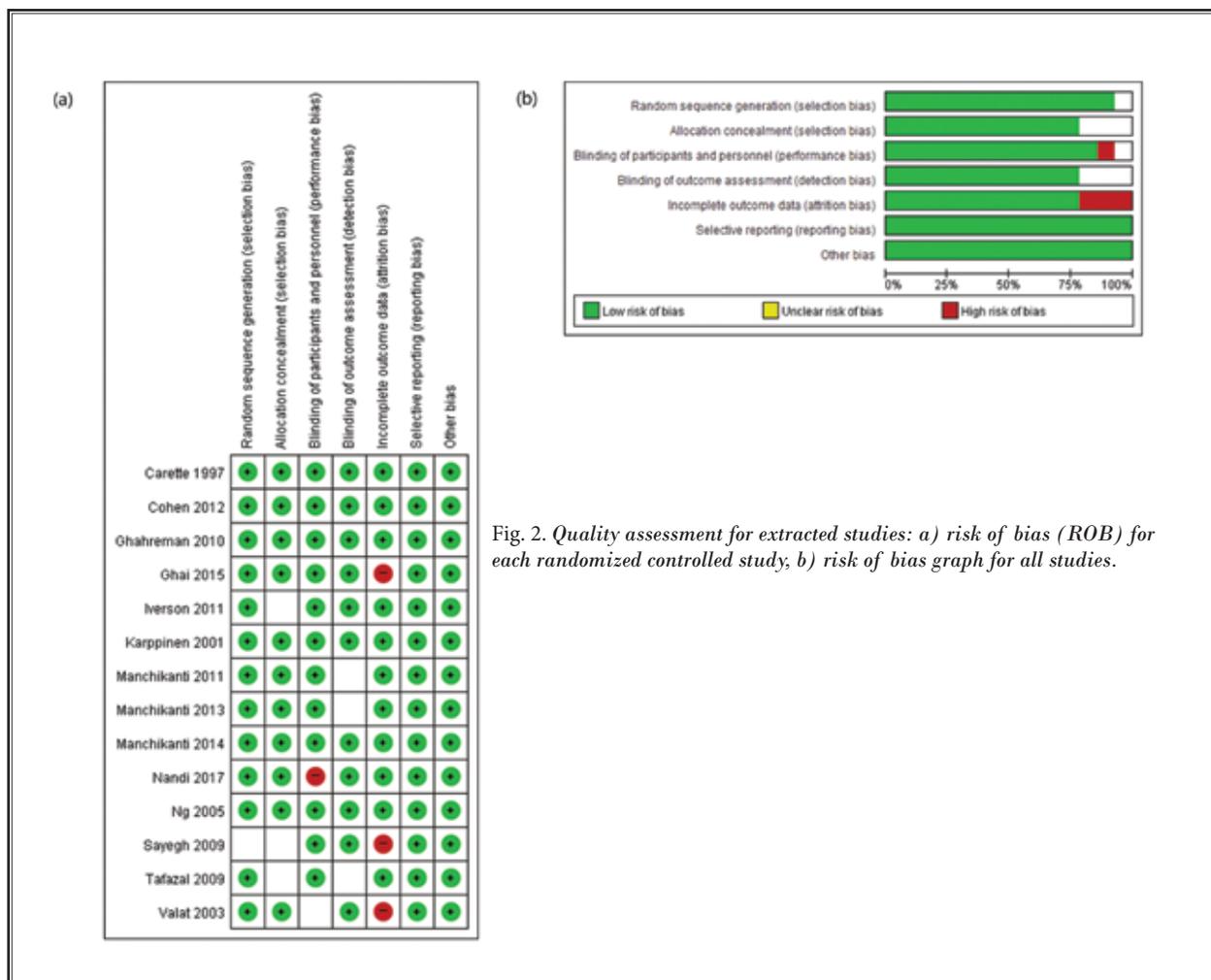

Fig. 2. *Quality assessment for extracted studies: a) risk of bias (ROB) for each randomized controlled study, b) risk of bias graph for all studies.*

line, which was limited in short term follow up (23,36). The other three reports revealed that the group using steroid with mixture of local anesthetics attained better clinical results than the other group using local anes-thetics alone, which maintained until 12 months follow up (25,27,37). Comprehensively, steroids in epidural injections obtained superior or at least not inferior, clinical results in comparison with controls (Table 1).

Table 1. *Summary of studies included in this study.*

Study	Method	Medication		Evaluation	Follow up	Outcome
		Steroid	Control			
Carette 1997 (35)	interlaminar	N = 78 80 mg of methylprednisolone acetate & 8 mL of isotonic saline	N = 80 1 mL of isotonic saline	VAS ODI McGill score	3 weeks, 3 months	Steroid is moderately more effective in leg pain reduction but no significant improvement in functional improvement
Karppinen 2001 (23)	transforaminal	N = 80 40 mg of methylprednisolone & bupivacaine total 2-3 mL	N = 80 2-3ml of isotonic saline	NRS ODI	2 and 4 weeks, 3 and 6 months, 1 year	Steroid showed better short term effect, but no significant difference at 3 months,
Valat 2003 (30)	interlaminar	N = 43 2 mL (50mg) of prednisolone acetate	N = 42 2ml of isotonic saline	VAS, RMI	1 month	No significant difference
Ng 2005 (29)	transforaminal	N = 41 2 mL of 0.25% bupivacaine & 40 mg of methylprednisolone	N = 40 2 mL of 0.25% bupivacaine	NRS, ODI, RMI	6, 12 weeks	No significant difference
Sayegh 2009 (25)	caudal	N = 93 12 mL of 2% xylocaine & 1 mL of betamethasone dipropionate and betamethasone phosphate	N = 90 12 mL of 2% xylocaine & 8 mL of saline	ODI	1,6, 12 months	Steroid is more effective than control
Tafazal 2009 (28)	transforaminal	N = 65 2 mL of 0.25% bupivacaine & 40 mg of methylprednisolone	N = 59 2 mL of 0.25% bupivacaine	NRS, ODI	6 ,12 weeks	No significant difference
Ghahreman 2010 (31)	transforaminal	N = 28 0.75 mL of 0.5% bupivacaine & 1.75 mL of triamcinolone (40 mg/mL).	N = 27 2 mL of 0.5% bupivacaine N = 37 2 mL of normal saline	NRS, RMI, SF-36	1 month	No significant difference
Manchikanti 2011 (26)	caudal	N = 60 9 mL of 0.5% lidocaine & 1 mL of steroid	N = 60 10ml of 0.5% lidocaine	NRS, ODI	3, 6, 12 months	No significant difference
Iverson 2011 (32)	caudal	N = 37 40 mg of triamcinolone & 29 mL of 0.9% saline.	N = 39 30 mL of 0.9% saline	VAS, ODI	6, 12, 42 weeks	No significant difference
Cohen 2012 (36)	transforaminal	N = 28 60 mg of methylprednisolone acetate & 0.5 mL of saline Total 2 ml	N = 30 2 mL of normal saline	NRS, ODI	1, 6 months	Short-term superiority but limited long-term benefit for epidural steroids
Manchikanti 2013 (27)	interlaminar	N = 60 5ml of 0.5% lidocaine & 1 mL of betamethasone	N = 60 6 mL of 0.5% lidocaine	NRS, ODI	3,6 12 months	Steroid is more effective than control

Table 1 (cont.). *Summary of studies included in this study.*

Study	Method	Medication		Evaluation	Follow up	Outcome
		Steroid	Control			
Manchikanti 2014 (33)	transforaminal	N = 60 1% lidocaine & 3 mg of betamethasone	N = 60 1.5 mL of 1% lidocaine & 0.5 mL of sodium chloride	NRS, ODI	3,6,12,18,24 months	No significant difference
Ghai 2015 (37)	interlaminar	N = 35 6 mL of 0.5% lidocaine & 80 mg (2 mL) of methylprednisolone	N = 34 8ml of 0.5% lidocaine	NRS, MODQ	2 weeks, 1, 2, 3, 6, 9, 12 months	Addition of steroid provides superior effectiveness
Nandi 2017 (34)	caudal	N = 47 Total 20 mL 80mg of methyl prednisolone & 18 mL of isotonic saline	N = 46 20 mL of isotonic saline	NRS, ODI, RMI	4, 12 weeks	No significant difference

VAS : visual analogue scale, ODI : oswestry disability score, NRS : numeric rating scale,
RMI : roland morris index, SF-36 : Short Form-36, MODQ : Modified Oswestry Disability Questionnaire

Quality assessment results of Cochrane review criteria and IPM-QRB were presented in Table 2 and Table 3 respectively. All studies were rated as high quality for Cochrane review criteria, and 10 studies and 4 studies were determined as high and moderate quality, according to IPM-QRB.

Pain Score at 1 Month

Eight studies provided the continuous pain score data at one month and were included in the analysis of effect size by mean difference (28-32,34-36). The overall mean difference was measured as 0.83 (95% CI:0.39-1.28), which supported the superiority of steroids over control agents with statistical significance (P = 0.0003). Additionally, a high degree of heterogeneity was observed (I^2 = 87%).

A subgroup analysis was conducted after division of the studies into 2 subgroups, depending on whether the control was local anesthetics or saline. Six studies were included in the subgroup of saline (30-32,34-36), while the other 2 studies were included in the subgroup of local anesthetics (28,29). The saline subgroup showed more significant favorable results to steroid than before subgroup analysis (P < 0.0001) with effect size of 1.19 (95% CI, 0.66-1.71), and the level of heterogeneity was reduced to I^2 = 31%. Whereas, the local anesthetics subgroup showed no significant favorable results to steroid (P = 0.19) with an effect size of 0.43 (95% CI -0.21-1.07). A high degree of heterogeneity was also observed for this measurement (I^2 = 97).

Four studies provided the number of patients with a successful pain score reduction at one month, which allowed estimation of relative risk ratio (30,31,34,36). Successful pain reduction was observed in 90 of the 146 patients from the steroid group and 45 of the 155 patients from the control group. The steroid group had a higher proportion of patients who experienced successful pain control than the control group, with an overall estimated effect size of 4.04 (95% CI, 1.89-8.61), and this difference was statistically significant (P = 0.0003). The heterogeneity was found to be I^2 = 55% (Fig. 3a).

Pain Score at 3 Months

Continuous data on pain measurement scores at 3 months were available in 8 studies (26-29,32-35). The overall mean difference was calculated as 0.19 (95% CI : 0.00-0.37) which favored steroid use with considerable degree of statistical significance (P = 0.05). The level of heterogeneity was found as I^2 = 39%.

Six studies provided the number of patients with a successful pain score reductions at 3 months, which allowed estimation of relative risk ratio (26,27,33,34,36,37). Successful pain control was observed in 246 of the 290 patients of steroid group and 222 of the 290 patients in the control group. The steroid group had a higher proportion of patients with successful pain control than the control group, with an overall estimated effect size of 1.86 (95% CI: 1.13-3.07), which was statistically significant (P = 0.02). The heterogeneity was found to be I^2 = 26% (Fig.3b).

Table 2. *Methodological quality assessment utilizing Cochrane review criteria.*

	Carette 1997 (35)	Cohen 2012 (36)	Ghahreman 2010 (31)	Ghai 2015 (37)	Iverson 2011 (32)	Karppinen 2001 (23)	Manchikanti 2011 (26)	Manchikanti 2013 (27)	Manchikanti 2014 (33)	Nandi 2017 (34)	Ng 2005 (29)	Sayegh 2009 (25)	Tafazal 2009 (28)	Valat 2003 (30)
Randomization adequate	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y
Concealed treatment allocation	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	U	U	Y
Patient blinded	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Care provider blinded	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	U
Outcome assessor blinded	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	U	Y
Drop-out rate described	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
All randomized participants analyzed in the group	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Groups similar at baseline regarding most important prognostic indicators	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Co-interventions avoided or similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Compliance acceptable in all group	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Score	12	12	12	12	11	12	11	11	12	11	12	10	10	11

Y : yes. N : no U : unclear

Table 3. *Methodological quality assessment utilizing IPM-QRB.*

	Carette 1997 (35)	Cohen 2012 (36)	Ghahreman 2010 (31)	Ghai 2015 (37)	Iverson 2011 (32)	Karppinen 2001 (23)	Manchikanti 2011 (26)	Manchikanti 2013 (27)	Manchikanti 2014 (33)	Nandi 2017 (34)	Ng 2005 (29)	Sayegh 2009 (25)	Tafazal 2009 (28)	Valat 2003 (30)
I. TRIAL DESIGN AND GUIDANCE REPORTING														
1. CONSORT or SPIRIT	1	1	1	3	1	1	3	3	3	1	1	1	1	1
II. DESIGN FACTORS														
2. Type and Design of Trial	3	3	3	3	3	3	3	3	3	3	3	3	3	3
3. Setting/Physician	1	2	2	2	1	2	2	2	2	2	1	1	1	1
4. Imaging	0	3	3	3	1	3	3	3	3	0	3	0	3	0
5. Sample Size	3	2	2	2	2	3	3	3	3	2	2	3	3	2
6. Statistical Methodology	1	1	1	1	1	1	1	1	1	1	1	1	1	1
III. PATIENT FACTORS														
7. Inclusiveness of Population	2	2	2	2	2	2	2	2	2	2	2	2	2	2
8. Duration of Pain	0	0	0	1	1	0	2	2	2	1	2	0	0	0
9. Previous Treatments	0	0	0	2	0	0	0	0	0	0	2	2	2	0
10. Duration of Follow-up with Appropriate Interventions	1	1	2	2	1	2	2	2	2	1	1	2	1	0
IV. OUTCOMES														
11. Outcomes Assessment Criteria for Significant Improvement	0	2	2	2	0	0	3	3	3	1	1	1	1	0
12. Analysis of all Randomized Participants in the Groups	2	2	2	2	2	1	2	2	2	2	2	2	2	2
13. Description of Drop Out Rate	1	1	1	0	1	1	1	1	1	1	1	1	1	1
14. Similarity of Groups at Baseline for Important Prognostic Indicators	2	2	2	2	2	2	2	2	2	2	2	2	2	2
15. Role of Co-Interventions	0	1	1	1	1	1	1	1	1	1	1	1	1	1
V. RANDOMIZATION														
16. Method of Randomization	2	2	2	2	2	2	2	2	2	2	2	0	2	2
VI. ALLOCATION CONCEALMENT														
17. Concealed Treatment Allocation	2	2	2	2	0	2	2	2	2	2	2	0	0	2

Table 3 (cont.). *Methodological quality assessment utilizing IPM-QRB.*

	Carette 1997 (35)	Cohen 2012 (36)	Ghahreman 2010 (31)	Ghai 2015 (37)	Iverson 2011 (32)	Karppinen 2001 (23)	Manchikanti 2011 (26)	Manchikanti 2013 (27)	Manchikanti 2014 (33)	Nandi 2017 (34)	Ng 2005 (29)	Sayegh 2009 (25)	Tafazal 2009 (28)	Valat 2003 (30)
VII. BLINDING														
18. Patient Blinding	1	1	1	1	1	1	1	1	1	1	1	1	1	1
19. Care Provider Blinding	1	1	1	1	1	1	1	1	1	0	1	1	1	0
20. Outcome Assessor Blinding	1	1	1	1	1	1	0	0	1	1	1	1	0	1
VIII. CONFLICTS OF INTEREST														
21. Funding and Sponsorship	3	3	3	3	3	3	3	3	3	3	3	3	3	3
22. Conflicts of interest	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Score	30	36	37	41	30	35	42	42	43	32	38	31	34	28

Pain Score at 6 Months

Continuous data of pain measurement scores at 6 months were available in four studies (26,27,32,33). The overall mean difference was calculated as 0.15 (95% CI: -0.85-1.15), which favored steroid use, although this difference was not statistically significant ($P = 0.77$). Furthermore, no heterogeneity was observed ($I^2 = 0\%$).

Dichotomous data on number of patients with successful pain score reductions at 6 months were provided by 5 studies (26,27,33,36,37), which allowed an estimation of relative risk ratio . Successful pain control was observed in 208 of the 243 patients in the steroid group and in 192 of the 244 patients in the control group. The steroid group had a higher proportion of patients with successful pain control than the control group, with an overall estimated effect size of 1.86 (95% CI, 0.80-4.36), which was not statistically significant ($P = 0.15$). The heterogeneity was found to be $I^2 = 64\%$ (Fig. 3c).

Pain Score at 1 Year

Continuous data on pain measurement scores at one year were available in 3 studies (26,27,33). The overall mean difference was calculated as 0.14 (95% CI: -1.07-1.35) which favored steroid use, but this difference was not statistically significant ($P = 0.82$). No heterogeneity was observed ($I^2 = 0\%$).

Dichotomous data about number of patients with a successful pain score reductions at 1 year were provided by same 3 studies, which allowed an estimation of relative risk ratio (26,27,33). Successful pain control was observed in 162 of the 180 patients in the steroid group and in 162 of the 180 patients in the control group. The steroid group had a higher proportion of patients with successful pain management than the control group, with an overall estimated effect size of 1.94 (95% CI, 1.05-3.59), which was statistically significant ($P = 0.03$). No heterogeneity was observed ($I^2 = 0\%$) (Fig. 3d).

Functional Improvement at 1 Month

Seven studies presented continuous data on functional scores at 1 month and were available for the analysis of effect size by mean difference (25,28,29,32,34-36). The overall mean difference was estimated as 4.07 (95% CI: -0.98-9.12), which favored steroid use over control agents, but the difference lacked statistical significance ($P = 0.11$). A high degree of heterogeneity was revealed ($I^2 = 98\%$).

A subgroup analysis was conducted after division of the studies into 2 subgroups depending on whether local anesthetics or saline was used as control. Four studies (32,34-36) were included in the subgroup of saline, while the other 3 studies (25,28,29) were included in the subgroup of local anesthetics. In the saline subgroup, steroid revealed significantly better clinical results than control ($P = 0.0002$) with effect size of 5.04 (95% CI, 2,35-
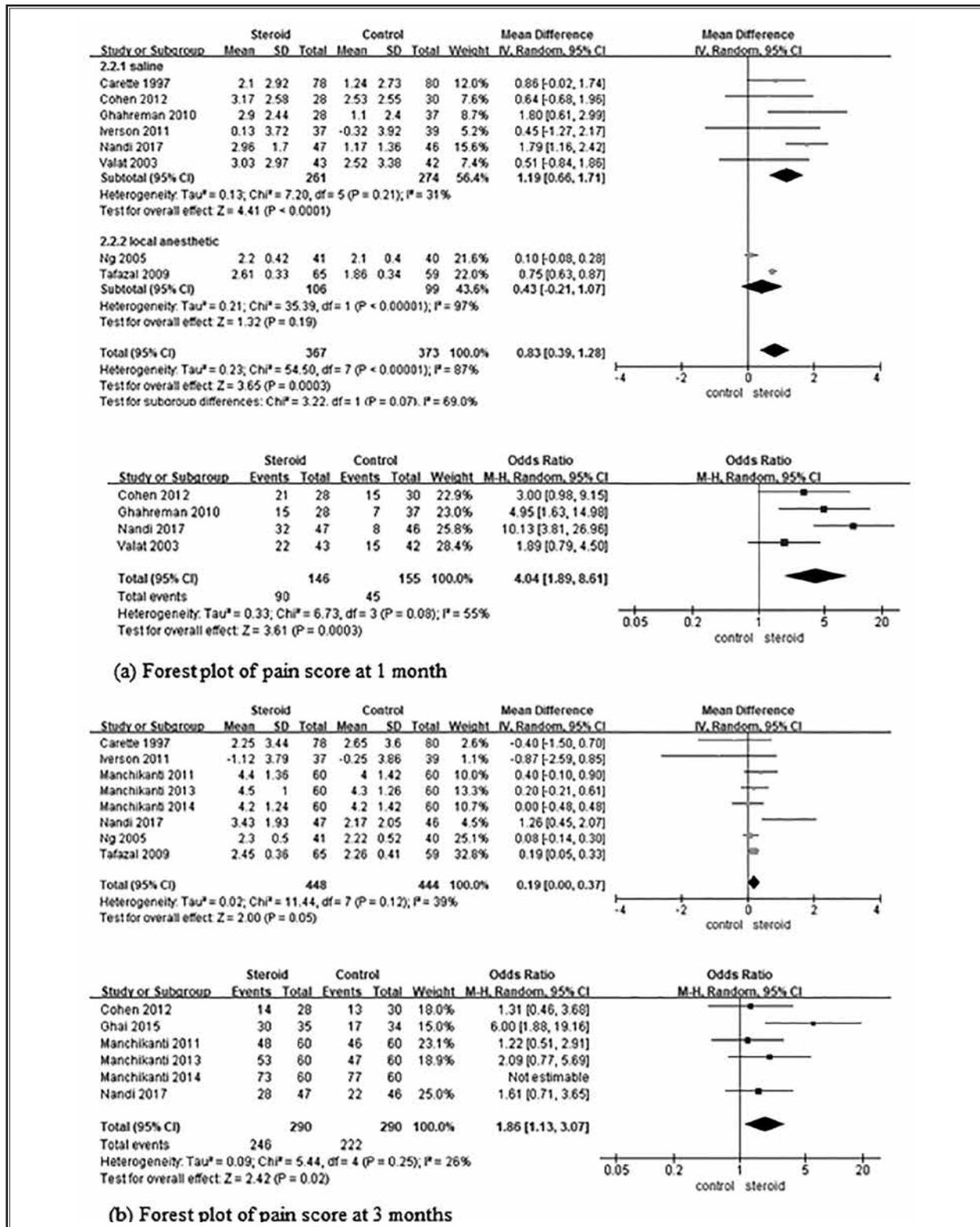
	Steroid			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.2.1 saline									
Carette 1997	2.1	2.92	78	1.24	2.73	80	12.0%	0.86 [-0.02, 1.74]	
Cohen 2012	3.17	2.58	28	2.53	2.55	30	7.6%	0.64 [-0.68, 1.96]	
Ghahreman 2010	2.9	2.44	28	1.1	2.4	37	8.7%	1.80 [0.61, 2.99]	
Iverson 2011	0.13	3.72	37	-0.32	3.92	39	5.2%	0.45 [-1.27, 2.17]	
Nandi 2017	2.96	1.7	47	1.17	1.36	46	15.6%	1.79 [1.16, 2.42]	
Valat 2003	3.03	2.97	43	2.52	3.38	42	7.4%	0.51 [-0.84, 1.86]	
Subtotal (95% CI)			261			274	56.4%	1.19 [0.66, 1.71]	
Heterogeneity: Tau² = 0.13; Chi² = 7.20, df = 5 (P = 0.21); I² = 31%									
Test for overall effect: Z = 4.41 (P < 0.0001)									
2.2.2 local anesthetic									
Ng 2005	2.2	0.42	41	2.1	0.4	40	21.6%	0.10 [-0.08, 0.28]	
Tafazal 2009	2.61	0.33	65	1.86	0.34	59	22.0%	0.75 [0.63, 0.87]	
Subtotal (95% CI)			106			99	43.6%	0.43 [-0.21, 1.07]	
Heterogeneity: Tau² = 0.21; Chi² = 35.39, df = 1 (P < 0.00001); I² = 97%									
Test for overall effect: Z = 1.32 (P = 0.19)									
Total (95% CI)			367			373	100.0%	0.83 [0.39, 1.28]	
Heterogeneity: Tau² = 0.23; Chi² = 54.50, df = 7 (P < 0.00001); I² = 87%									
Test for overall effect: Z = 3.65 (P = 0.0003)									
Test for subgroup differences: Chi² = 3.22, df = 1 (P = 0.07), I² = 69.0%									

control steroid

	Steroid		Control			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Cohen 2012	21	28	15	30	22.9%	3.00 [0.98, 9.15]	
Ghahreman 2010	15	28	7	37	23.0%	4.95 [1.63, 14.98]	
Nandi 2017	32	47	8	46	25.8%	10.13 [3.81, 26.96]	
Valat 2003	22	43	15	42	28.4%	1.89 [0.79, 4.50]	
Total (95% CI)		146		155	100.0%	4.04 [1.89, 8.61]	
Total events	90		45				
Heterogeneity: Tau² = 0.33; Chi² = 6.73, df = 3 (P = 0.08); I² = 55%							
Test for overall effect: Z = 3.61 (P = 0.0003)							

control steroid

(a) Forest plot of pain score at 1 month

	Steroid			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Carette 1997	2.25	3.44	78	2.65	3.6	80	2.6%	-0.40 [-1.50, 0.70]	
Iverson 2011	-1.12	3.79	37	-0.25	3.86	39	1.1%	-0.87 [-2.59, 0.85]	
Manchikanti 2011	4.4	1.36	60	4	1.42	60	10.0%	0.40 [-0.10, 0.90]	
Manchikanti 2013	4.5	1	60	4.3	1.26	60	13.3%	0.20 [-0.21, 0.61]	
Manchikanti 2014	4.2	1.24	60	4.2	1.42	60	10.7%	0.00 [-0.48, 0.48]	
Nandi 2017	3.43	1.93	47	2.17	2.05	46	4.5%	1.26 [0.45, 2.07]	
Ng 2005	2.3	0.5	41	2.22	0.52	40	25.1%	0.08 [-0.14, 0.30]	
Tafazal 2009	2.45	0.36	65	2.26	0.41	59	32.8%	0.19 [0.05, 0.33]	
Total (95% CI)			448			444	100.0%	0.19 [0.00, 0.37]	
Heterogeneity: Tau² = 0.02; Chi² = 11.44, df = 7 (P = 0.12); I² = 39%									
Test for overall effect: Z = 2.00 (P = 0.05)									

control steroid

	Steroid		Control			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Cohen 2012	14	28	13	30	18.0%	1.31 [0.46, 3.68]	
Ghai 2015	30	35	17	34	15.0%	6.00 [1.88, 19.16]	
Manchikanti 2011	48	60	46	60	23.1%	1.22 [0.51, 2.91]	
Manchikanti 2013	53	60	47	60	18.9%	2.09 [0.77, 5.69]	
Manchikanti 2014	73	60	77	60		Not estimable	
Nandi 2017	28	47	22	46	25.0%	1.61 [0.71, 3.65]	
Total (95% CI)		290		290	100.0%	1.86 [1.13, 3.07]	
Total events	246		222				
Heterogeneity: Tau² = 0.09; Chi² = 5.44, df = 4 (P = 0.25); I² = 26%							
Test for overall effect: Z = 2.42 (P = 0.02)							

control steroid

(b) Forest plot of pain score at 3 months

Fig. 3. *Forest plot of pain score: a) at 1 month, b) at 3 months, c) at 6 months, d) at 1 year.*

(c) Forest plot of pain score at 6 months

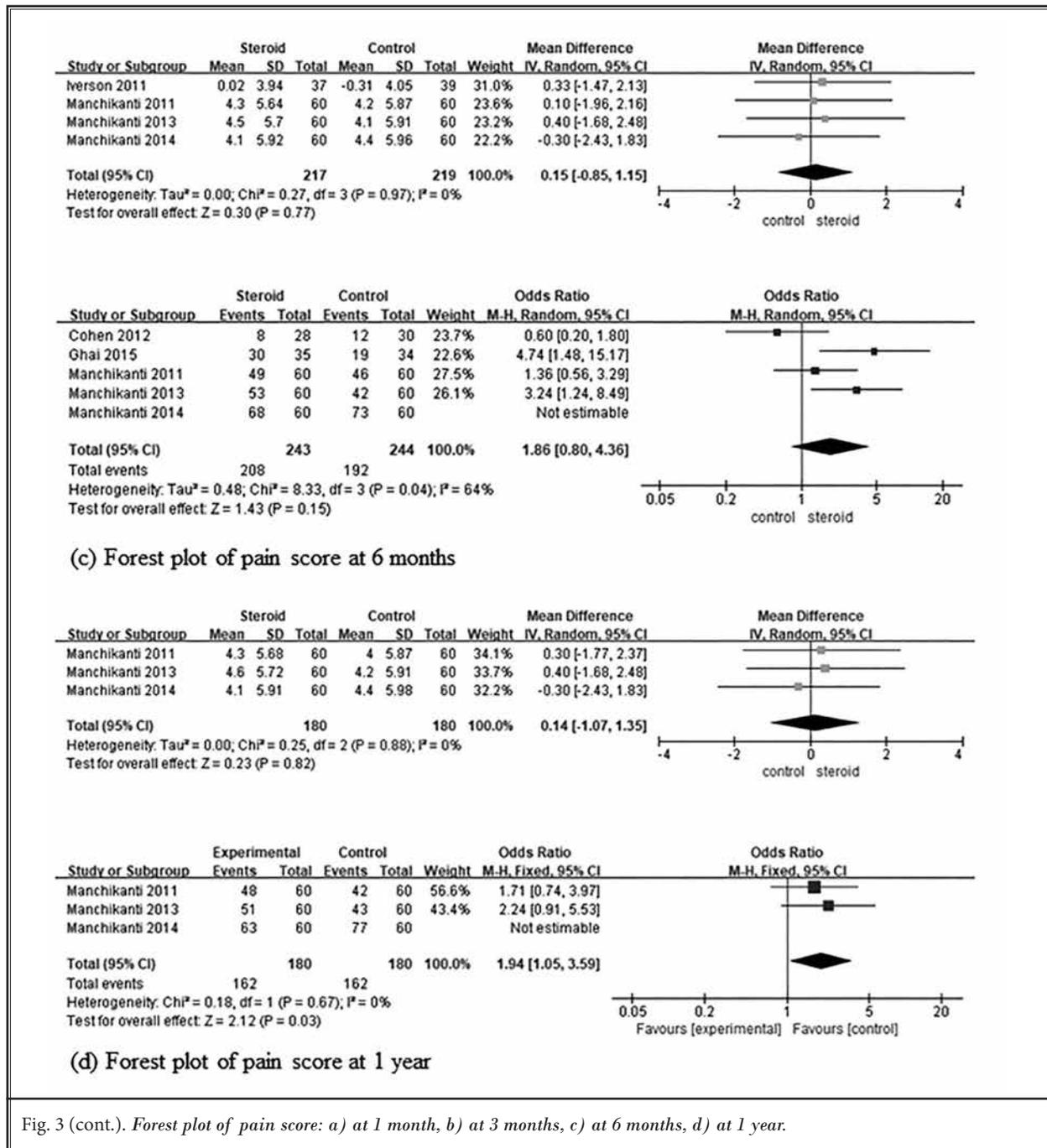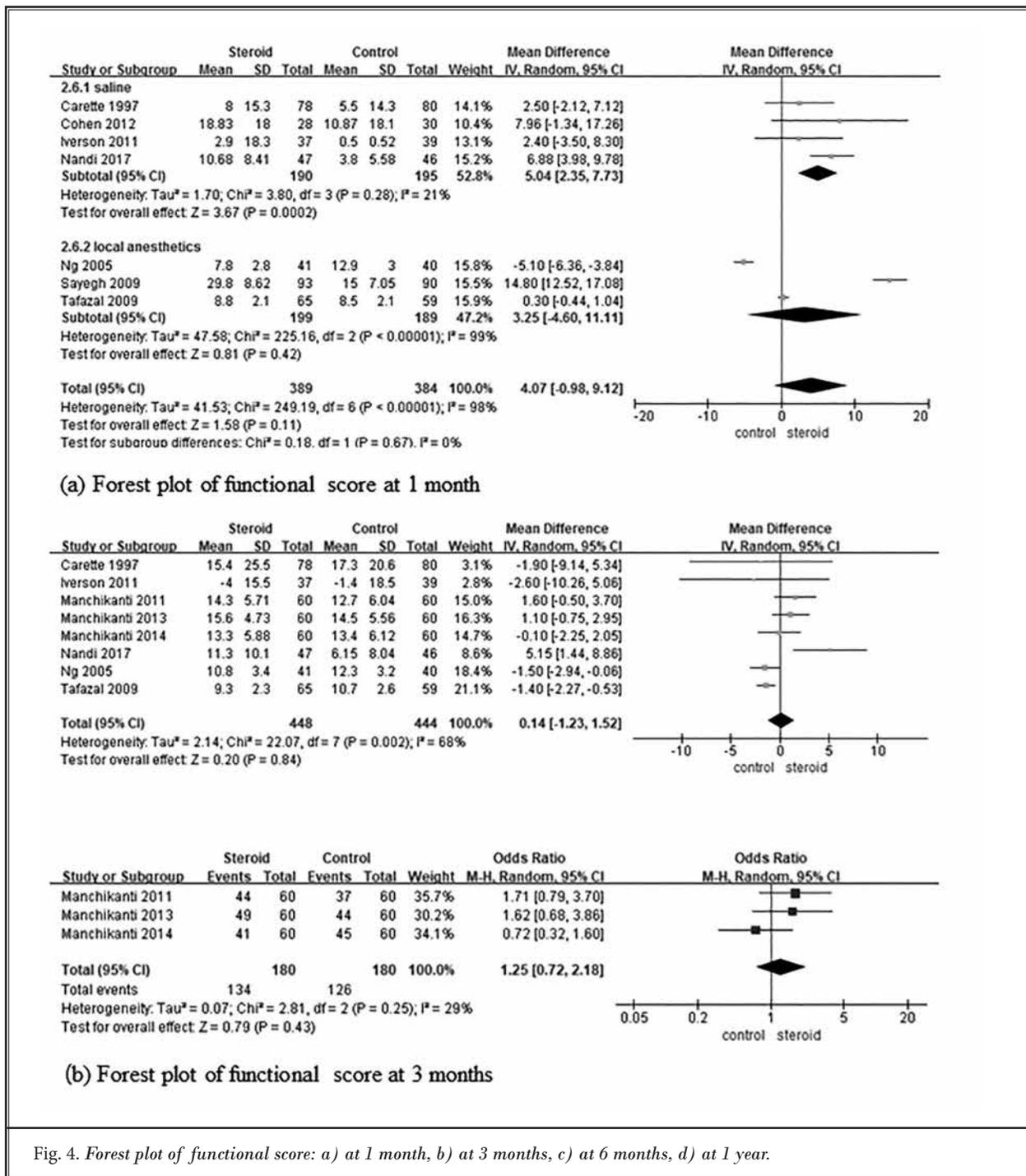(d) Forest plot of pain score at 1 year

Fig. 3 (cont.). *Forest plot of pain score: a) at 1 month, b) at 3 months, c) at 6 months, d) at 1 year.*

7.73), and the level of heterogeneity was reduced to I2 = 21%. However, in the local anesthetics subgroup, no significant difference was observed between steroids and local anesthetic (*P* = 0.42), with an effect size of 3.25 (95% CI: -4.60-11.11). The level of heterogeneity was also measured as high (I² = 99) (Fig.4a).

Functional Improvement at 3 Months

Eight studies (26-29,32-35) were available for the analysis of effect size based on the mean difference for functional improvement at 3 months. The estimated overall mean difference was calculated as 0.14 (95% CI: -1.23-1.52), which favored steroid use, although this

(a) Forest plot of functional score at 1 month

(b) Forest plot of functional score at 3 months

Fig. 4. *Forest plot of functional score: a) at 1 month, b) at 3 months, c) at 6 months, d) at 1 year.*

difference lacked statistical significance (*P* = 0.84). The degree of heterogeneity was I² = 68%.

Three studies presented dichotomous data about the number of patients with successful functional improvements at 3 months, which allowed an estimation

of relative risk ratio (26,27,33). Successful pain reduction was found in 134 of the 180 patients of steroid group and in 126 of the 180 patients of the control group. The steroid group achieved a higher proportion of successful functional improvement than the control
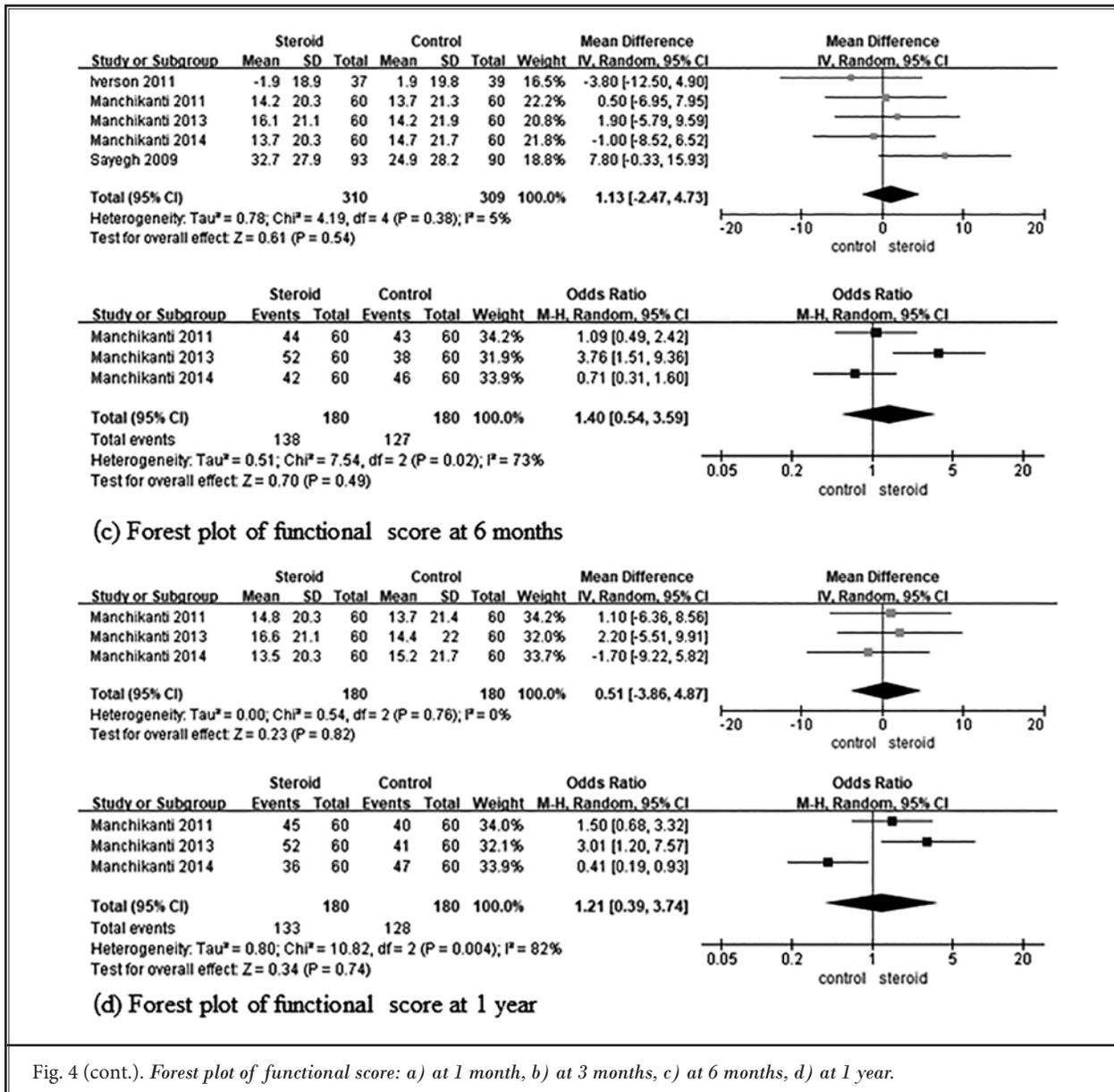
Fig. 4 (cont.). *Forest plot of functional score: a) at 1 month, b) at 3 months, c) at 6 months, d) at 1 year.*

group, with an overall estimated effect size of 1.25 (95% CI: 0.72-2.18), which lacked statistical significance (*P* = 0.25). The heterogeneity was found to be I² = 29% (Fig. 4b).

Functional Improvement at 6 Months

Five studies (25-27,32,33) provided the continuous data on functional improvement at 6 months, which were applied to analyze the effect size based on the mean difference. The estimated overall mean difference was 1.13 (95% CI: -2.47-4.73), which favored

steroid without statistical significance (*P* = 0.54). The degree of heterogeneity was observed to be I² = 0%.

Three studies (26,27,33) presented the dichotomous data about number of patients with a successful functional improvement at 6 months, which allowed an estimation of relative risk ratio. Successful pain reduction was observed in 138 of the 180 patients in the steroid group, and in 127 of the 180 patients in the control group. The steroid group had a higher proportion of patients with successful functional improvement than the control group, with an overall estimated effect size

of 1.40 (95% CI: 0.54-3.59), which lacked statistical significance (P = 0.49). The degree of heterogeneity was I^2 = 73%.

Functional Improvement at 1 Year

Three studies (26,27,33) provided the continuous data on functional improvements at 1 year, which were available for the analysis of effect size by the mean difference. The estimated overall mean difference was calculated as 0.51 (95% CI: -3.86-4.87), which favored steroid use, although this difference was not statistically significant (P = 0.82). No heterogeneity was observed (I^2 = 0%).

The same 3 studies (26,27,33) presented dichotomous data about the number of patients with a successful functional improvement at 1 year, which allowed an estimation of relative risk ratio . Successful pain reduction was observed in 133 of the 180 patients in the steroid group, and in 128 of the 180 patients in the control group. The steroid group had a higher proportion of patients with successful functional improvement than the control group, with an overall estimated effect size of 1.21 (95% CI: 0.39-3.74), which was not statistically significant (P = 0.74). A high degree of heterogeneity was found (I^2 = 82%), however, the subgroup analysis could not be performed due to the small number of studies (Fig. 4d).

Level of Evidence and Strength of Recommendation

The risk of bias was evaluated as low level as previously mentioned. Directness was not considered problematic because all included studies directly compared steroid with controls. Publication bias was not assessed because fewer than 10 studies were included in each meta-analysis. However, the consistency was considered to have serious problems because diversity in the type of steroid used, type of control injectate (local anesthetics or saline) or approach techniques (transforaminal, interlaminar, or caudal) existed across studies, and considerable heterogeneity was found in part of the meta-analysis. The degree of precision was considered to be no serious problematic because most studies included the number of subjects, which satisfied the sample size calculation criteria determined by previous studies.

All reviewers agreed that steroids in the injectate of epidural injections allowed better pain control than local anesthetics or saline, as supported by meta-analysis of selected studies in patients with LDH, while no signif-

icant functional improvement benefits of steroid were found. Notably, the clinical superiority of steroid was more prominent in comparison with saline than with local anesthetics at relatively short-term follow-ups, such as 1 month, than at long-term follow-ups. Steroids did not require high cost and were as easily accessible as local anesthetics or saline. There are concerns regarding the side effects associated with repeated steroid injections (6,38), but they can usually be avoided if the several sessions of steroid injections produce satisfactory pain control and excessively repetitive injections are not required (39-41). Epidural injection of steroids is recommended over local anesthetics or saline for the treatment of patients with LDH, but the strength of recommendation was determined as weak, mainly due to the moderate degree of evidence through discussion of all reviewers.

Discussion

There were concerns for adverse effects related to steroid overdose during epidural injection, especially in case of repetitive steroid injections. Because steroid results in suppression of immunologic reaction, it might increase susceptibility to infectious disease such as epidural abscess, bacterial meningitis, or subarachnoiditis (42). Furthermore, repetitive epidural injections of steroid, even if locally administered, could lead to minor or major systemic side effects including skin change, adrenal insufficiency, glucose intolerance, Cushing syndrome, etc (6,38,43).

Thus, conflicting opinions exist with respect to whether steroid injections have advantages over local anesthetics or saline injections. If steroids help enhance clinical outcomes in comparison with local anesthetic or saline, steroids could fulfill clinical goals without causing systemic side effects by reducing the need for repeated injections. When epidural steroid injections were appropriately planned and conducted, less than 3 injections per year using 2.5 to 5 mg dexamethasone per injection were usually required to achieve clinically successful results (39,40). If satisfactory results are not achieved with epidural steroid administration, other treatment options should be considered. In addition, the use of local anesthetics in the epidural space is not without risks; they may cause side effects such as nausea, allergic reaction, hypotension, headache, or lower limb paralysis. Moreover, when excessive dosages were used, systemic reactions including vasovagal reaction, loss of consciousness, convulsions and respiratory depression have also occurred (44,45). Consequently,

physicians should be cognizant of the potential risks of any substance injected into the epidural space; not just steroids.

To summarize our study, the quality of 14 selected articles was measured as high quality with regard to GRADE and Cochrane review criteria as well as high or moderate quality for IPM-QRB. The reviewed articles revealed that steroid showed superior or non-inferior clinical results to controls. Meta-analysis showed that steroids achieved significantly better pain reduction than controls, but no significantly better functional improvement. The superiority of steroid in pain control was observed in continuous data as well as dichotomous data at 1 month, but was found only in dichotomous data, not in continuous data at 3 months and 1 year. Besides, although not strictly satisfying the degree of statistical significance, steroid showed considerable degree of significance in continuous data at 3 months (P = 0.05). The subgroup analysis performed at 1 month showed that steroids achieved better pain control and functional improvement than saline, but not than local anesthetics. Briefly, the superiority of steroid was more remarkable in terms of pain control than functional improvement; in the short term rather than the long term; and when compared to saline than local anesthetics.

Eight studies (26,28-34) demonstrated no significant difference between steroid and controls. Steroid alone or mixture of steroid and isotonic saline was compared with isotonic saline in 3 studies (30,32,34). Steroid with mixture of bupivacaine or lidocaine was compared with bupivacaine or lidocaine alone in other 5 studies (26,28,29,31,33). Whereas, among the 3 studies reporting the long-term superiority of steroid, 1 study compared mixture of steroid and xylocaine with mixture of saline and xylocaine (25), and 2 studies compared mixture of steroid and lidocaine with lidocaine alone (27,37). Three studies which showed only short-term superiority of steroid compared mixture of steroid and local anesthetics/normal saline with normal saline (23,35,36). The inspections of each study included in this review suggested that the advantage of steroid was could be obtained in comparison not only with saline but also active control, local anesthetics.

Rather, it seemed that approach method seemed to influence the clinical advantage of steroid over controls, irrespective of types of control injectate. Among the 8 studies without significant difference, transforaminal approach was used in 4, interlaminar approach was 1, and caudal approach was 3 studies. Among the 3 studies showing short term benefits of steroid, 2 stud-

ies and 1 study used transforaminal and interlaminar approach respectively. Of the 3 studies obtaining long-term benefits of steroid, 2 studies and 1 study used the interlaminar and caudal approach respectively. The tendency was observed that the transforminal approach eliminated or reduced the advantage of using steroids over local anesthetics or normal saline. Analyzing date using the literature from 3 RCTs using 3 different approaches indicated that the superiority of steroids was more distinct in the caudal and interlaminar approaches than with the transforaminal approach (46). This could suggest that the transforaminal approach, a more target-specific method, could provide clinical advantages over the other 2 approaches with or without steroids.

Steroid superiority deteriorated from 3 months to 1 year, which could be explained by the fact that the steroid efficacy was usually not maintained over the long term, thus the differences in clinical efficacy diminish over time. Several reports have stated that clinical data at long-term follow-up are difficult to be considered as clinical effects from previously performed epidural steroid injection because the effects substantially deteriorate over this duration (47-49). However, physicians should not be discouraged because about 2-3 sessions per year usually achieve satisfactory results, and other strategies such as exercise and lifestyle modification may help to maintain the clinical benefits obtained through epidural injection (37,40,50,51).

Despite no significant differences in mean and standard deviation, relative risk ratio with successful proportion of pain control revealed that steroids maintained superiority over controls at 3 months and 1 year. Most studies established successful pain control as a 50% NRS or VAS score reduction or more pretreatment. These criteria were presumed as generous so to show significant improvements that were not found by mean values. However, a 50% or more improvement in pain scores was frequently used in clinical practice as well as in research, and was felt to represent a clinically meaningful difference (20,27,33,52).

Not surprisingly, the subgroup analysis revealed that the superiority of injections with steroids at 1 month was significant compared with saline-only injections. This was not the case when steroids were compared with local anesthetics at the 1 month interval. The function of steroids is to remove inflammatory mediators, decrease vascular permeability, and block neurotransmission of pain signals; while the function of local anesthetics is to play a role in inhibiting pain

signal transmission or high-frequency neuronal discharges (7,9,10,22,53). However, saline does not functionally inhibit inflammatory action or nerve impulse transmission, and simply acts as an agent which clears and dilutes chemical mediators and enhances volume effects (25). This might explain why steroids showed more predominant differences than saline, but did not differ from local anesthetics as substantially.

Limitations

This study has a few limitations. The supportive strength of this study was weak, which was mainly because the evidence level was moderate despite high quality of studies, and this was primarily due to inconsistencies from diversities across the studies. Second, analyses about safety or adverse effects could not be performed because such data was not provided by the included studies. Third, the subgroup analysis of functional score at 1 year could not be conducted due to the small number of studies, in spite of high degree of heterogeneity.

CONCLUSION

In conclusion, steroids performed better than control agents for pain control in patients with LDH, with weak strength of recommendation. The superiority of steroids for pain control was more remarkable at relatively short-term follow-up, but was maintained until 1 year follow-up. The clinical benefits of steroids at 1 month were more prominent when compared with saline only and the benefits were not as prominent when compared with local anesthetics.

Acknowledgements

Appendix

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