Systematic Review

Comparative Effects of Different Epidural Injection Approaches on Lumbosacral Radicular Pain: A Systematic Review and Network Meta-analysis

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Background: Lumbar disc herniation (LDH) is the main cause of low back pain and/or radiculopathy. Currently, epidural intervention is a widely used and effective conservative treatment method for managing low back and radicular pain caused by LDH.

Objectives: To explore the effectiveness of different epidural injection approaches in adult patients with lumbosacral radicular pain.

Study Design: Systematic review and network meta-analysis (NMA).

Methods: An electronic literature search was performed in the Pubmed, Embase, Cochrane Library, and Web of Science databases. Two authors independently performed data extraction and quality assessment. A Bayesian random effects model was conducted to incorporate the estimates of direct and indirect treatment comparisons and rank the interventions in order. Effect estimates from Bayesian NMA were presented as mean difference (MD) with 95% credible intervals (CrI).

Results: This NMA assessed caudal (C), interlaminar (IL), transforaminal (TF) and parasagittal interlaminar (PIL) epidural injection approaches for lumbosacral radicular pain from 7 trials. A statistically significant treatment difference for pain relief was reported for midline interlaminar (MIL) vs PIL (MD, 1.16; 95%CrI, 0.31-2.06), MIL vs TF (MD, 1.12; 95%CrI, 0.51-1.85), C vs TF (MD, 1.07; 95%CrI, 0.01-2.18) in short-term follow-up and MIL vs TF (MD, 1.8; 95% CrI, 0.3-3.48) in intermediate-term follow-up. For functional improvement, a statistically significant difference was observed with MIL vs PIL (MD, 9.9; 95% CrI, 0.64-19.94) and MIL vs TF (MD, 1.08; 95% CrI, 1.08-17.08) in short-term follow-up. Moreover, the PIL approach and TF appeoach were ranked in the top 2 for pain relief and functional improvement, both in short-term and intermediate-term follow-up.

Limitations: 1) The number of studies included was small; 2) some treatments lacked direct comparisons; 3) only scores from the visual analog scale for pain and the Oswestry Disability Index were included in the result; 4) important outcomes, such as complications, were not included.

Conclusion: In short-term and intermediate-term follow-up, the PIL approach has the highest probability for pain relief and functional improvement.

Key Words: Injections, epidural, lumbosacral region, sciatica, nerve block

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Lumbar disc herniation (LDH) is the main cause of low back pain and/or radiculopathy (1-5). The pathophysiology of LDH involves both mechanical compression and chemical sensitization (6-8). The protruding nucleus pulposus tissue may cause immunological reactions in the epidural space and further promote the development of epidural inflammation. The inflammation stimulates the spinal nerve roots, resulting in nerve root edema and the increasing vascular permeability of nerve roots, which exacerbates inflammatory reactions and then causes low back and radicular pain (5-7). Currently, an epidural intervention is a widely used and effective conservative treatment method for managing low back and radicular pain caused by LDH (4,9-16).

Epidural injection was used to treat low back and lower extremities pain in the early twentieth century, with steroids added to local anesthetics half a century later (17-20). Three injection approaches— caudal (C), interlaminar (IL), and transforaminal (TF)— are the most commonly performed in clinical practice (2,9,15,21-24). Among them, the IL route can be divided into 2 types, namely the midline interlaminar (MIL) between adjacent spinous processes, and the parasagittal interlaminar (PIL) of the lateral-most part of the lamina (25,26). The analgesic effect of an epidural injection depends on drug delivery near the pathological site (21,25,27,28). It is probably for this reason that TF and PIL injections provided better outcomes in some previous studies (21-23,25). However, which epidural injection approach is the best is still controversial.

In this study, we aimed to do a systematic review and network meta-analysis (NMA) to explore the effectiveness of different routes of epidural injections in adult patients with lumbosacral radicular pain.

Method

Study Design

The present study was conducted using a Bayesian model for NMA. It complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines extension statement for NMA (29,30). The protocol for this study is registered in PROSPERO (Registration No.CRD42021243844). Ethical approval and informed consent were not required as this study is an NMA based on published studies.

Search Strategy

An electronic literature search was performed in the Pubmed, Embase, Cochrane Library, and Web of Science databases to identify relevant studies that were published through March 15, 2021. The search strategies are presented in Supplementary Table 1. Additional studies from the reference list of the identified studies were also viewed. The language of included studies was restricted to English. Two researchers (Z. Yun and C. Wang) examined the studies independently and conflicts of opinions were discussed and resolved with the help of the third investigator (Q. Liu).

Inclusion and Exclusion Criteria

Studies were included in this NMA if they met the following criteria: 1) were a randomized controlled trial (RCT); 2) patients ≥ 18 years old; 3) there was a clinical presentation of low back and radicular leg pain; 4) there was a diagnosis of LDH on a radiological evaluation such as computed tomography or magnetic resonance imaging; 5) there was reported available detailed data about the effects of the intervention on lumbosacral radicular pain; 6) patients received epidural steriod injections through different approaches.

Studies were excluded from this NMA due to the following criteria: 1) patients had a previous history of lumbosacral surgery; 2) patients had nonspecific low back pain without a definite diagnosis of LDH on radiological evaluation; 3) patients had spinal stenosis, severe disc degeneration, intradiscal derangement, or prominent spinal instability; 4) case reports, abstracts, or a meeting paper; 5) articles were published by the same authors or from the same project.

Data Extraction

Data from the original articles were extracted by 2 researchers (Z. Yun and C. Wang). Data included study characteristics (authors, year, design, method, medication, sample size, age and follow-up). Continuous variables such as mean and standard deviation of pain and functional scores were extracted for the estimation of mean differences. If standard deviations were not reported, they were calculated from confidence intervals, mean, and the number of patients. If there was any disagreement, the discrepancy was resolved by discussion with the third author (Q. Liu).

Quality Assessment

The quality of each study used in this anlysis was assessed by Cochrane review criteria (Supplementary Table 2) and Interventional Pain Management Techniques - Quality Appraisal of Reliability and Risk of Bias

Assessment (IPM-QRB) (Supplementary Table 3) (31,32). Utilizing Cochrane review criteria, studies meeting the inclusion criteria with at least 8 of 12 criteria were considered high quality and 5 to 7 were considered moderate quality. Those meeting criteria of less than 5 were considered as low quality and were excluded. Based on IPM-QRB criteria, studies meeting the inclusion criteria scoring of 32 to 48 were considered highquality trials; studies with scores between 25 and 31 were considered moderate quality; studies scoring less than 25 were considered low quality and were excluded.

Statistical Analysis

First, we performed regular pairwise meta-analysis under random effects model using RevMan 5.3 (The Nordic Cochrane Centre for The Cochrane Collaboration). Mean difference (MD) with 95% credible intervals (CrI) was estimated. Second, a Bayesian random effects model was conducted to incorporate the estimates of direct and indirect treatment comparisons and rank the interventions in order using WinBUGS 1.4.3 (Informer Technologies) based on R 3.6.2 software (The R Foundation) The Markov Chains Monte Carlo (MCMC) method was applied to calculate the pooled effect sizes expressed as MD with 95% CrI. The rank of interventions from each outcome was performed through the data consistency model that is based on 100,000 iterations for each 3 MCMC chains with a burn-in period of the initial 50,000 iterations. Analyses of residual deviance were conducted to evaluate global consistency by comparing the parameters and deviance information criterion difference value between a "consistency" model and an "inconsistency" model (33). The statistical heterogeneity in the entire network was assessed based on the value of the heterogeneity parameter (I^2). According to the rank order of the treatment method in each iteration of the Markov chain, each outcome was assessed with the probability of which is the best (superior to all other interventions), second best, and third best.

Subgroup analysis was conducted to explore the short-term, intermediate-term, and long-term effects after injection. The postinjection follow-ups were divided into short-term (≤ 3 months) and intermediate-term (> 3 months to ≤ 12 months).

Results

Study Characteristics

A total of 4,943 studies from searching databases and 47 studies from other sources were searched at first. After eliminating duplicated studies, 2,643 studies were screened for titles and abstracts. Then, 2,625 studies were excluded for one or more of the following reasons: not an RCT, only an abstract, an animal study, or aconference study. Eighteen remained for full text reviewing. Next, these 18 articles were examined and 11 were eliminated for one or more of the following reasons: lack of comparative data or different doses or injection numbers between different groups in the same study. Ultimately, 7 studies were enrolled in this NMA (Fig. 1) (9,15,21,34-37).

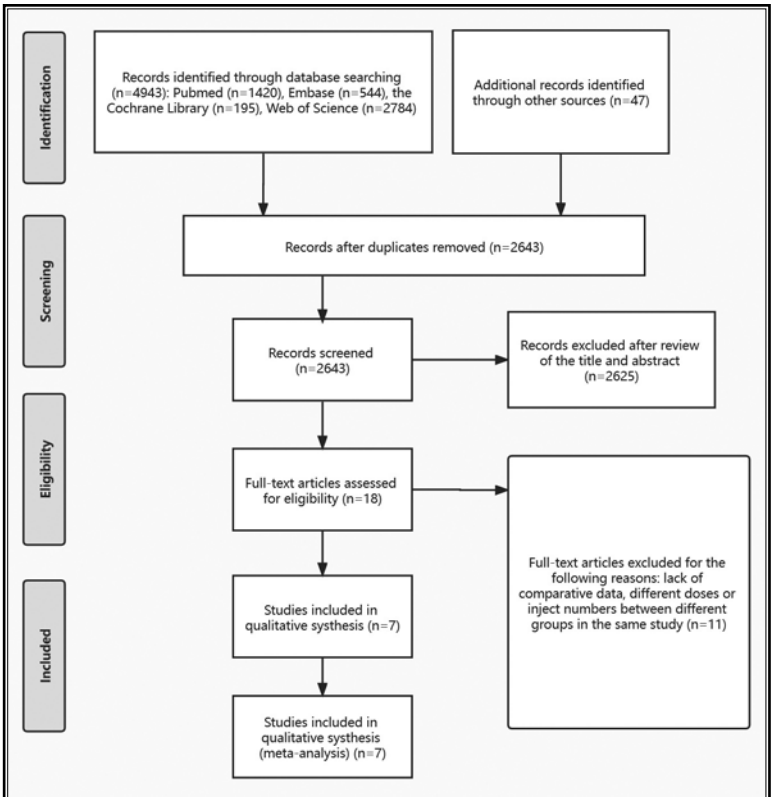

Fig. 1. *Flow chart of the selection process for relative studies in meta-analysis.*

Pain intensity was measured using the Visual Analog Scale (VAS) or the Numeric Rating Scale (NRS-11). The Oswestry Disability Index (ODI) measured a patient's level of function in these selected studies. Table 1 summarizes the main characteristics of the included studies.

Table 1. *Characteristics of included randomized trials.*

Study	Year	Design	Method	Medication	Sample size	Age(Mean±SD, Mean and Range)	Outcome	Follow-up
Candido(36)	2008	RCT	TF	80mg of methylprednisolone acetate 1 mL of normal saline 1 mL of 1% lidocaine	28	51.96(47.05-56.88)	VAS	3m, 6m
			PIL	80mg of methylprednisolone acetate 1 mL of normal saline 1 mL of 1% lidocaine	29	52.31 (46.29–58.32)		
Gharibo(35)	2011	RCT	MIL	80 mg of triamcinolone 2 mL of 0.25% bupivacaine	18	51.2±17.09	VAS, ODI	2 weeks
			TF	40 mg of triamcinolone (40 mg/ mL) 1 mL of 0.25% bupivacaine	20	48±12.61		
Makkar(9)	2019	RCT	MIL	80 mg of methylprednisolone acetate with 2 mL of 1% lidocaine	21	42.71±7.47	VAS, ODI	3m, 6m
			TF	80 mg of methylprednisolone acetate with 2 mL of 1% lidocaine	20	37.65±6.72		
			PIL	80 mg of methylprednisolone acetate with 2 mL of 1% lidocaine	20	41.15±7.38		
Thomas(37)	2003	RCT	MIL	5mg/2ml dexamethasone acetate solution	16	51.3±17	VAS	1m, 6m
			TF	5mg/2ml dexamethasone acetate solution	15	49.8±13.9		
Kamble(15)	2016	RCT	C	40mg of triamcinolone acetate 1 mL of bupivacaine 2 mL of lignocaine 10 mL of normal saline	30	49.6445	VAS, ODI	1m,6m
			MIL	40mg of triamcinolone acetate 1 mL of bupivacaine 1 mL of lignocaine 10 mL of normal saline	30			
			TF	40mg of triamcinolone acetate 1 mL of bupivacaine 2 mL of lignocaine	30			
Ackerman(21)	2007	RCT	C	40 mg of triamcinolone 19 mL of normal saline	30	36.4±4	VAS, ODI	6m
			MIL	40 mg of triamcinolone 4 mL of normal saline	30	39.2±6		
			TF	40 mg of triamcinolone 4 mL of normal saline	30	34±5		
Hong(34)	2017	RCT	PIL	5mg dexamethasone 3ml 0.2% rapivacaine	41	60.2±12.0	VAS, ODI	2 weeks
			TF	5mg dexamethasone 3ml 0.2% rapivacaine	31	59.9±13.1		

C, caudal steroids injection; MIL, midline interlaminar steroids injection; PIL, parasagittal interlaminar steroids injection; TF, transforaminal steroids injection; VAS, visual analog scale; ODI, the Oswestry Disability Index.

Methodological Quality Assessment

Details about the Cochrane review bias analysis of the 7 included studies are shown in Table 2. All 7 had a Cochrane bias score of at least 5 and were included. Details about the IPM-QRB analysis of the 7 included studies are shown in Table 3. All 7 had a score of at least 25 and were included.

Pairwise Meta-analysis

We conducted a pairwise meta-analysis comparing the effectiveness of each intervention with other interventions in the short-term (≤ 3 months) and intermediate-term (3-12 months).

VAS

In the pairwise meta-analysis, a significant treatment difference as measured by the VAS was reported for MIL vs TF (MD, 1.05; 95% CI, 0.69-1.40; $P < 0.00001$; $I^2 = 0\%$) for short-term; MIL vs TF (MD, 1.29; 95% CI, 0.95-1.64; $P < 0.00001$; $I^2 = 76\%$) and C vs TF (MD, 1.80; 95% CI, 1.36-2.24; $P < 0.00001$; $I^2 = 97\%$) for intermediate-term. These results suggest that TF is superior to MIL at short-term follow-up and MIL or C at intermediate-term follow-up in pain relief. No significant difference was found for TF vs PIL (MD, 0.14; 95%CI, -0.28-0.56; $P = 0.51$; $I^2 = 23\%$) for short-term and TF vs PIL (MD, 0.29; 95%CI, -0.21-0.78; $P = 0.26$; $I^2 = 21\%$), C vs MIL (MD, 0.01; 95%CI, -0.56-0.57; $P = 0.98$; $I^2 = 0\%$) for intermediate-term (Supplementary Fig. 1).

ODI

In the pairwise meta-analysis, a significant treatment difference as measured by the ODI was reported for MIL vs TF (MD, 7.28; 95% CI, 5.52-9.04; $P < 0.00001$; $I^2 = 76\%$) for short-term; MIL vs TF (MD, 5.38; 95% CI, 3.85-6.91; $P < 0.00001$; $I^2 = 97\%$) and C vs TF (MD, 3.14; 95% CI, 1.76-4.52; $P < 0.00001$; $I^2 = 96\%$) for intermediate-term. These results suggest that TF is superior to MIL at short-term follow-up and MIL or C at intermediate-term follow-up for functional improvement. No significant difference was found for TF vs PIL (MD,0.52; 95%CI, -2.32-3.36; $P = 0.72$; $I^2 = 0\%$) for short-term and C vs MIL (MD, -1.57; 95%CI, -3.38-0.23; $P = 0.09$; $I^2 = 12\%$) for intermediate-term (Supplementary Fig. 2).

Network Meta-analysis

Figure 2 shows the network maps and treatment rank probabilities for pain relief and functional improvement for short-term (≤ 3 months) and intermediate-term (> 3 months to ≤ 12 months) follow-up.

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

Source of Bias	Hong 2017 (34)	Thoms 2003 (37)	Ackerman 2007 (21)	Gharibo 2011 (35)	Candido 2008 (36)	Kamble 2016 (15)	Makkar 2019 (9)
(1) Was the method of randomization adequate?	Y	Y	N	N	Y	Y	Y
(2) Was the treatment allocation concealed?	N	N	N	N	U	Y	Y
(3) Was the patient blinded to the intervention?	Y	Y	N	Y	Y	Y	Y
(4) Was the care provider blinded to the intervention?	U	U	N	Y	Y	N	Y
(5) Was the outcome assessor blinded to the intervention?	Y	Y	N	U	U	Y	Y
(6) Was the drop-out rate described and acceptable?	Y	N	Y	Y	Y	N	Y
(7) Were all randomized participants analyzed in the group to which they were allocated?	Y	Y	Y	Y	Y	N	Y
(8) Are reports of the study free of suggestion of selective outcome reporting?	Y	U	Y	Y	Y	Y	Y
(9) Were the groups similar at baseline regarding the most important prognostic indicators?	Y	Y	Y	Y	Y	Y	Y
(10) Were cointerventions avoided or similar?	Y	Y	Y	Y	Y	Y	Y
(11) Was the compliance acceptable in all groups?	Y	Y	Y	Y	Y	U	Y
(12) Was the timing of the outcome assessment similar in all groups?	Y	Y	Y	Y	Y	Y	Y
(13) Are other sources of potential bias unlikely?	Y	Y	Y	Y	Y	Y	Y
SCORES	11(13)	9(13)	8(13)	10(13)	11(13)	9(13)	13(13)

Table 3. *Methodologic quality assessment of randomized trials of epidural injections utilizing IPM-QRB.*

		Hong 2017 (34)	Thomas 2003 (37)	Candido 2008 (36)	Kamble 2016 (15)	Makkar 2019 (9)	Ackerman 2007 (21)	Gharibo 2011 (35)
I.	TRIAL DESIGN AND GUIDANCE REPORTING							
1	CONSORT OR SPIRIT	3	1	1	0	3	0	1
II.	DESIGN F ACTORS							
2	Type and Design of Trial	2	3	3	2	2	2	3
3	Setting/Physician	2	2	2	2	2	2	1
4	Imaging	3	3	3	2	3	3	3
5	Sample Size	2	1	2	2	2	1	1
6	Statistical Methodology	1	1	1	1	1	1	1
III.	PATIENT F ACTORS							
7	Inclusiveness of Population	2	2	2	2	2	2	2
8	Duration of Pain	1	1	1	1	1	1	0
9	Previous Treatments	2	0	0	2	2	0	2
10	Duration of Follow-up with Appropriate Interventions	0	1	1	1	1	2	0
IV.	OUTCOMES							
11	Outcomes Assessment Criteria for Significant Improvement	0	0	1	2	2	1	4
12	Analysis of all Randomized Participants in the Groups	2	2	2	2	2	2	2
13	Description of Drop Out Rate	1	1	1	0	1	2	1
14	Similarity of Groups at Baseline for Important Prognostic Indicators	1	2	2	1	2	1	2
15	Role of Co-Interventions	1	1	1	1	1	1	1
V.	RANDOMIZATION							
16	Method of Randomization	2	2	2	2	2	0	0
VI.	ALLOCATION CONCEALMENT							
17	Concealed Treatment Allocation	2	2	1	2	2	0	0
VII.	BLINDING							
18	Patient Blinding	1	1	1	1	1	0	1
19	Care Provider Blinding	0	1	1	0	0	0	1
20	Outcome Assessor Blinding	1	1	0	1	1	0	0
VIII.	CONFLICTS OF INTEREST							
21	Funding and Sponsorship	2	2	2	2	2	0	2
22	Conflicts of Interest	3	0	0	3	3	0	3
TOTAL		34	31	30	32	38	25	31

Short-term Follow-up

VAS

Six studies measured patient VAS scores at short-term follow-up. Two studies consisted of a total of 69 patients and compared MIL vs TF; 2 studies consisted of a total of 129 patients and compared TF vs PIL; one study consisted of 61 patients and compared MIL, TF and PIL; and one study consisted of 90 patients and compared C, MIL, and TF. (Fig. 2A)

A statistically significant difference for pain relief was reported for MIL vs PIL (MD, 1.16; 95% CrI: 0.31-2.06), MIL vs TF (MD, 1.12; 95% CrI, 0.51-1.85) and C vs TF (MD, 1.07; 95% CrI, 0.01-2.18). Based on the treatment ranking, PIL had the highest probability (54.72%) of being the most effective treatment for pain relief. TF had

the highest probability (54.93%) of being the second most effective. C had the highest probability (49.90%) of being the third most effective. MIL (53.76%) was the least effective treatment (Table 4, Fig. 3A).

ODI

Three studies measured patient ODI scores at short-term follow-up. One study consisted of 72 patients and compared TF vs PIL; one study consisted of 61 patients and compared MIL, TF and PIL; and one study consisted of 90 patients and compared C, MIL, and TF (Fig. 2C).

A statistically significant difference for ODI was reported for MIL vs PIL (MD, 9.9; 95% CrI, 0.64-19.94) and MIL vs TF (MD, 1.08; 95% CrI, 1.08-17.08). Based on treatment ranking, PIL had the highest probability (66.43%) of being the most effective treatment for functional improvement. TF had the highest probability (65.42%) of being the second most effective. C had the highest probability (66.1%) of being the third most effective. MIL (73.8%) was the least effective treatment (Table 5, Fig. 3C).

Intermediate-term Follow-up

VAS

Four studies measured patient VAS scores at intermediate-term follow-up. One study consisted of 31 patients and reported MIL vs TF; one study consisted of 57 patients and reported TF vs PIL; one study consisted of 61 patients and compared MIL, TF, and PIL; and 2 studies consisted of a total of 180 patients and compared C, MIL, and TF (Fig. 2B).

A statistically significant difference for VAS was reported for MIL vs TF (MD, 1.8; 95% CrI, 0.3-3.48). PIL had the highest probability (64.15%) of being the most effective treatment for pain relief. TF had the highest probability (63.24%) of being the second most effective. MIL had the highest probability (58.77%) of being the third most effective. C (59.95%) was the least effective treatment (Table 6, Fig. 3B).

ODI

Three studies measured patient ODI scores at intermediate-term follow-up. One study consisted of 61 patients and compared MIL, TF, and PIL; 2 studies consisted of a total of 180 patients and compared C, MIL, and TF (Fig. 2D).

No statistically significant difference was obeserved in ODI among the 4 approaches. Based on treatment ranking, PIL had the highest probability (65.67%) of being the most effective treatment for functional improvement. TF had he highest probability (46.03%) of being the second most effective. C had the highest probability (34.12%) of being the third most effective. MIL (62.09%) was the least effective treatment (Table 7, Fig. 3D).

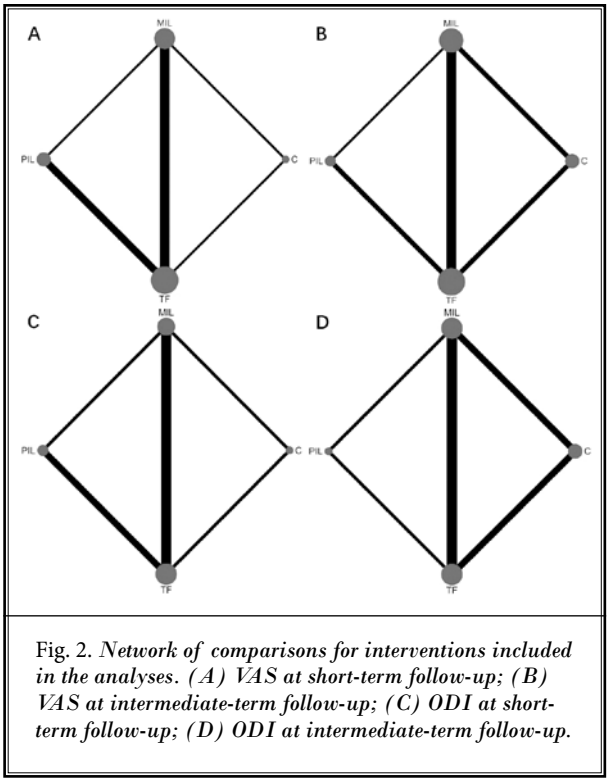

Fig. 2. *Network of comparisons for interventions included in the analyses. (A) VAS at short-term follow-up; (B) VAS at intermediate-term follow-up; (C) ODI at short-term follow-up; (D) ODI at intermediate-term follow-up.*

Table 4. *Results for VAS score from NMA in short-term follow-up.*

C			
-0.04 (-1.18, 1.01)	MIL		
1.11 (-0.16, 2.36)	1.16 (0.31, 2.06)	PIL	
1.07 (0.01, 2.18)	1.12 (0.51, 1.85)	-0.04 (-0.74, 0.72)	TF

MIL, midline interlaminar steroids injection; PIL, parasagittal interlaminar steroids injection; TF, transforaminal steroids injection.

Consistency Test and Heterogeneity Analysis

In order to evaluate the consistency or inconsistency for the interested outcomes, global consistency analyses were performed. The differences in values of the parameters and deviance information criterion in both "consistency" and "inconsistency" models were used to evaluate the global consistency. The results of the consistency model were similar to the inconsistency model, which indicates a good level of global consis-

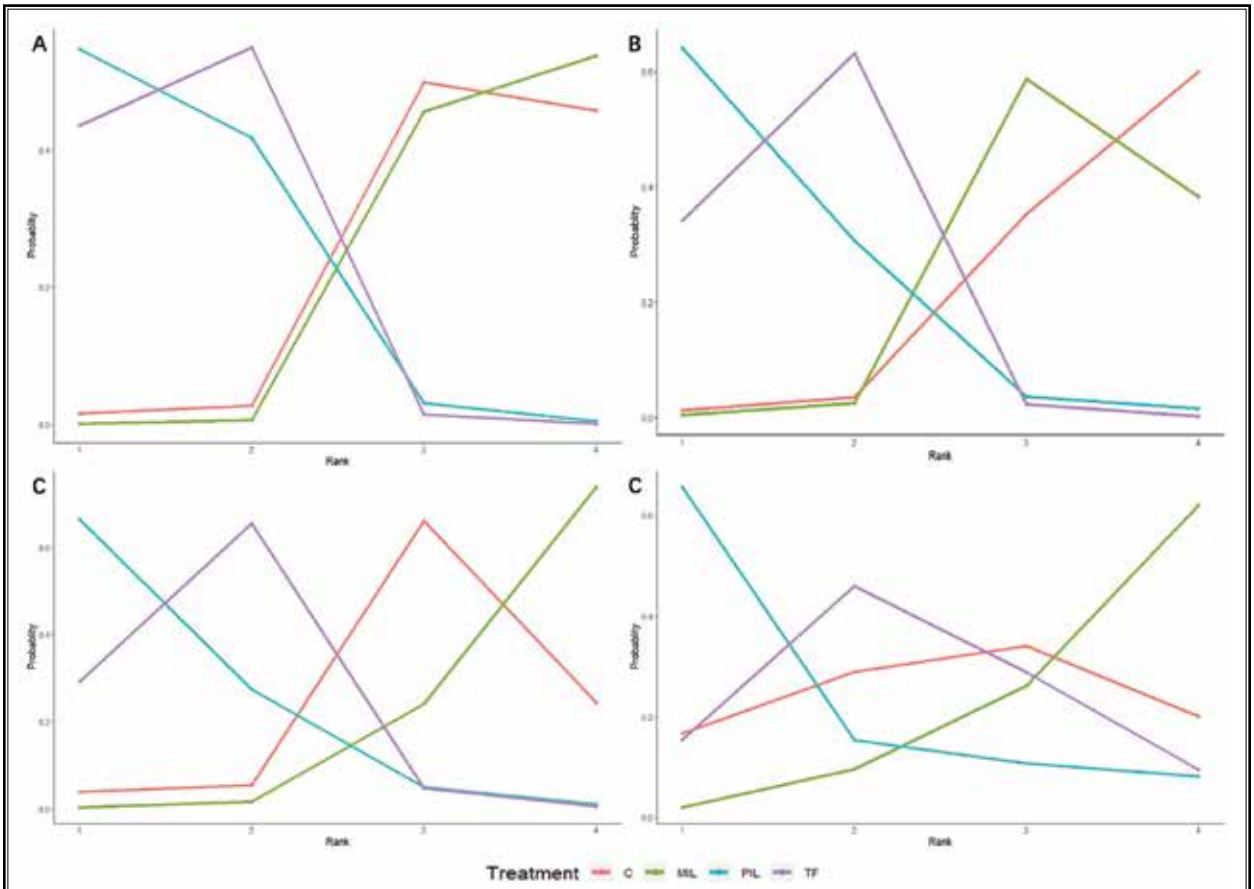

Fig. 3. *Treatment rank probabilities for pain relief in short-term (A) and intermediate-term (B) follow-up, and functional improvement in short-term (C) and intermediate-term (D) follow-up.*

Table 5. *Results for VAS score from NMA in intermediate-term follow-up.*

C			
0.23 (-1.92, 2.24)	MIL		
2.35 (-0.45, 5.24)	2.12 (-0.14, 4.59)	PIL	
2.02 (-0.01, 4.12)	1.8 (0.3, 3.48)	-0.33 (-2.47, 1.8)	TF

C, caudal steroids injection; MIL, midline interlaminar steroids injection; PIL, parasagittal interlaminar steroids injection; TF, transforaminal steroids injection.

Table 6. *Results for ODI from NMA in short-term follow-up.*

C			
-2.09 (-13, 8.3)	MIL		
7.77 (-4.8, 20.52)	9.9 (0.64, 19.94)	PIL	
6.38 (-3.89, 17.4)	8.53 (1.08, 17.08)	-1.34 (-9.35, 7.06)	TF

C, caudal steroids injection; MIL, midline interlaminar steroids injection; PIL, parasagittal interlaminar steroids injection; TF, transforaminal steroids injection.

Table 7. *Results for ODI from NMA in intermediate-term follow-up.*

C			
-4.07 (-17.72, 9.34)	MIL		
6.38 (-14.77, 27.43)	10.45 (-7.72, 28.68)	PIL	
1.14 (-12.52, 14.51)	5.2 (-6.28, 16.69)	-5.23 (-23.4, 12.96)	TF

C, caudal steroids injection; MIL, midline interlaminar steroids injection; PIL, parasagittal interlaminar steroids injection; TF, transforaminal steroids injection.

tency. Global I^2 was used to evaluate heterogeneity which was 0% for short-term VAS, 7% for intermediate-term VAS, 13% for short-term ODI, and 12% for intermediate-term ODI (Supplementary Table 4).

Discussion

Many systematic reviews have evaluated the effec-

tiveness and safety of epidural injections, but there has never been an NMA comparing the effectiveness of different epidural injection approaches (1,17,22,23,38-55). Comprehensive evidence-based guidelines for epidural interventions from the American Society of Interventional Pain Physicians (ASIPP) give the same recommendation level for epidural steriod injections of C, IL, and TF in the treatment of LDH (56). In our NMA, we attempted to obtain the relative pain relief and functional improvement of epidural injections in LDH patients through a Bayesian NMA, which makes it possible to perform indirect comparisons of multiple treatments in studies that lack direct comparisons. A total of 7 RCTs comparing 4 epidural injection approaches were included in our NMA.

For pain relief and functional improvement, our NMA showed that PIL and TF were ranked in the top 2 for both short-term and intermediate-term follow-up. Since radicular pain originates from the chemical stimulation around the nerve root sheath or dorsal root ganglion, the degree of perineural drug diffusion is a key factor in reducing radicular pain effectively (23,57-59). Compared with MIL, PIL is closer to the lesion and can deliver drugs to the lateral and ventral epidural space, which is like the TF approach (9,27,28). Therefore, PIL can achieve similar effects as TF in terms of the effectiveness of pain relief while the limited diffusion of drugs in the ventral epidural space leads to poor effectiveness of the MIL approach (21,25). Makkar et al (9) and Candido et al (36) compared PIL and TF epidural steroids injection; the PIL route was equivalent to TF in terms of effective pain relief. The study reported by Ghai et al (25) found that the effective pain relief rate of PIL (68.4%) was much higher than that of MIL (16.7%). The research of Furman et al (60) showed that PIL can significantly manage pain. It was not included in this study because it was a single arm pilot study. Gharibo et al (35) and Rados et al (61) compared the effectiveness of TF and MIL approaches in patients with low back pain and radiculopathy. They found that MIL is as effective as TF, but the patients in their study were not administered equal doses in either route. The previous meta-analysis conducted by Lee et al (23) investigated the effectiveness of TF and IL. TF showed significantly better short-term and long-term analgesia effect, but the quality of evidence for these results were low;in addition, the authors did not conduct a subgroup analysis of PIL and MIL.

Our NMA shows that PIL and TF provided better pain relief than C in the short-term and intermediate-term, but the results were not statistically significant except for short-term C vs TF. On the contrary, our NMA shows that TF is significantly superior to C in the intermediate-term, but the result had higher heterogeneity, which may be caused by only including 2 articles. In the C approach, the drug is administered through a caudal hiatus that is far from the diseased area. This is an indirect method that results in most of the drug reaching the target area through diffusion (62). Due to the large sacral epidural space, it is difficult for the medication to reach the target area.

The study by Kim et al (63) showed that cephalad spread was limited by anterior injectate leakage through the anterior sacral foramen, and even repeated injections could not improve the cephalad level of spread. Unlike other literature, Singh et al (64) reported that C epidural steroid injection was superior to TF in pain relief because they utilized 3 C epidural injections compared to one TF epidural injection. Thus, our NMA did not include it. The meta-analysis reported by Lee et al (22) showed that TF epidural steroid injection presented favorable results in reducing pain compared with C, which was consistent with our NMA result despite lacking in significance. The study by Singh et al (64) was included in them, which made their results unreliable.

In this NMA, long-term follow-up results beyond 12 months were not analyzed because epidural injections can be administered annually as long as the treatment interval is 2.5 to 3 months or longer, with a frequency of no more than 4 treatments per year (56).

One of the advantages of our NMA is that we include RCTs of epidural steriod injection for the treatment of lumbosacral radicular pain caused by LDH, which reduced the heterogeneity and inconsistency of the test, and provided a relatively high-quality NMA. In addition, IL was divided into PIL and MIL for further analyzing the best approach of epidural steroid injection to treat the disease. This NMA may provide clinicians with recommendations for the treatment of lumbosacral radicular pain and may be more appropriate for providing epidural approach options for the design of RCTs later.

Limitations

This NMA has several limitations: 1) the number of studies included was small; 2) some treatments lacked direct comparisons; 3) and only the VAS and ODI were included in the result. In addition, important outcomes, such as complications, were not included.

Conclusion

This NMA demonstrates that epidural steriod injection for the treatment of lumbosacral radicular pain caused by LDH, the PIL approach has the highest probability of pain relief and functional improvement, but there was no significant difference with the TF approach. Therefore, more high-quality direct comparison RCTs with larger sample sizes and longer trial periods are required to confirm and update these results.

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Supplementary material available at www.painphysicianjournal.com

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Supplementary Table 1. *Search string used for PubMed, adjusted for other electronic databases*.

No.	Search Strategy	Number of Hits
1	((((((((("Intervertebral Disc Displacement"[Mesh]) OR (((((((Disc Displacement, Intervertebral[Title/Abstract]) OR (Disc Displacements, Intervertebral[Title/Abstract])) OR (Disk, Herniated[Title/Abstract])) OR (Slipped Disk[Title/Abstract])) OR (Disk Prolapse[Title/Abstract])) OR (Herniated Disc[Title/Abstract])) OR (Intervertebral Disk Displacement[Title/Abstract]))) OR ("Radiculopathy"[Mesh])) OR (("Radiculopathies"[Title/Abstract] OR "nerve root disorder"[Title/Abstract] OR "Radiculitis"[Title/Abstract] OR "Radiculitides"[Title/Abstract] OR "nerve root inflammation"[Title/Abstract] OR "nerve root compression"[Title/Abstract]) OR "pinched nerve"[Title/Abstract])) OR ("Spinal Nerve Roots"[Mesh])) OR ((((Spinal Nerve Root[Title/Abstract]) OR (Spinal Root[Title/Abstract])) OR (Ventral Root[Title/Abstract])) OR (Dorsal Root[Title/Abstract]))) OR (Prolapsed Disc[Title/Abstract])) OR (Prolapsed Discs[Title/Abstract])) AND ((((((("Lumbosacral Region"[Mesh]) OR ((Lumbosacral Region[Title/Abstract]) OR (Lumbar Region[Title/Abstract]))) OR ("Lumbar Vertebrae"[Mesh])) OR (Vertebrae, Lumbar[Title/Abstract])) OR (Lumbar[Title/Abstract])) OR (lumbosacral[Title/Abstract])) OR (lower back[Title/Abstract]))) OR ((((("Sciatica"[Mesh]) OR ((((Sciatic Neuralgia[Title/Abstract]) OR (Bilateral Sciatica[Title/Abstract])) OR (Sciatica[Title/Abstract])) OR (Sciatic neuropathy[Title/Abstract]))) OR ("Sciatic Neuropathy"[Mesh])) OR ("Low Back Pain"[Mesh])) OR (((((((((((Back Pain, Low[Title/Abstract]) OR (Low Back Pains[Title/Abstract])) OR (Low Back Pain[Title/Abstract])) OR (Lumbago[Title/Abstract])) OR (Lower Back Pain[Title/Abstract])) OR (Lower Back Pains[Title/Abstract])) OR (Low Back Ache[Title/Abstract])) OR (Low Back Aches[Title/Abstract])) OR (Low Backache[Title/Abstract])) OR (Low Backaches[Title/Abstract])) OR (Low Back Pain, Recurrent[Title/Abstract])))	62,655
2	(((((((((Adrenal Cortex Hormones[MeSH Terms]) OR (Glucocorticoids[MeSH Terms])) OR (Triamcinolone[MeSH Terms])) OR (Dexamethasone[MeSH Terms])) OR (Steroids[MeSH Terms])) OR (Lidocaine[MeSH Terms])) OR (Anesthetics, Local[MeSH Terms])) OR (Anti-Inflammatory Agents[MeSH Terms])) OR (Bupivacaine[MeSH Terms])) OR ((Hormones, Adrenal Cortex[Title/Abstract]) OR (Adrenal Cortex Hormone[Title/Abstract])) OR (Cortex Hormone, Adrenal[Title/Abstract])) OR (Hormone, Adrenal Cortex[Title/Abstract])) OR (Corticosteroids[Title/Abstract])) OR (Corticosteroid[Title/Abstract])) OR (Corticoids[Title/Abstract])) OR (Corticoid[Title/Abstract])) OR (Glucocorticoid[Title/Abstract])) OR (Glucocorticoid Effect[Title/Abstract])) OR (Effect, Glucocorticoid[Title/Abstract])) OR (Glucorticoid Effects[Title/Abstract])) OR (Effects, Glucorticoid[Title/Abstract])) OR (Volon[Title/Abstract])) OR (Aristocort[Title/Abstract])) OR (Methylfluorprednisolone[Title/Abstract])) OR (Hexadecadrol[Title/Abstract])) OR (Decameth[Title/Abstract])) OR (Decaspray[Title/Abstract])) OR (Dexasone[Title/Abstract])) OR (Dexpak[Title/Abstract])) OR (Maxidex[Title/Abstract])) OR (Millicorten[Title/Abstract])) OR (Oradexon[Title/Abstract])) OR (Decaject[Title/Abstract])) OR (Hexadrol[Title/Abstract])) OR (Steroid[Title/Abstract])) OR (Catatoxic Steroids[Title/Abstract])) OR (Steroids, Catatoxic[Title/Abstract])) OR (Lignocaine[Title/Abstract])) OR (Lidocaine Carbonate[Title/Abstract])) OR (Lidocaine Hydrocarbonate[Title/Abstract])) OR (Lidocaine Hydrochloride[Title/Abstract])) OR (Lidocaine Monohydrochloride[Title/Abstract])) OR (Lidocaine Monoacetate[Title/Abstract])) OR (Xyloneural[Title/Abstract])) OR (Octocaine[Title/Abstract])) OR (Xylesthesin[Title/Abstract])) OR (Xylocaine[Title/Abstract])) OR (Xylocitin[Title/Abstract])) OR (Dalcaine[Title/Abstract])) OR (Lidocaine Monohydrochloride, Monohydrate[Title/Abstract])) OR (Local Anesthetics[Title/Abstract])) OR (Anesthetics, Conduction-Blocking[Title/Abstract])) OR (Anesthetics, Conduction Blocking[Title/Abstract])) OR (Conduction-Blocking Anesthetics[Title/Abstract])) OR (Conduction Blocking Anesthetics[Title/Abstract])) OR (Local Anesthetic[Title/Abstract])) OR (Anesthetic, Local[Title/Abstract])) OR (Anesthetics, Topical[Title/Abstract])) OR (Topical Anesthetics[Title/Abstract])) OR (Anti Inflammatory Agents[Title/Abstract])) OR (Antiinflammatory Agent[Title/Abstract])) OR (Agent, Antiinflammatory[Title/Abstract])) OR (Antiinflammatory Agents[Title/Abstract])) OR (Agents, Antiinflammatory[Title/Abstract])) OR (Anti-Inflammatories[Title/Abstract])) OR (Anti Inflammatories[Title/Abstract])) OR (Antiinflammatories[Title/Abstract])) OR (Anti-Inflammatory Agent[Title/Abstract])) OR (Agent, Anti-Inflammatory[Title/Abstract])) OR (Anti Inflammatory Agent[Title/Abstract])) OR (Agents, Anti-Inflammatory[Title/Abstract])) OR (Agents, Anti Inflammatory[Title/Abstract])) OR (Marcain[Title/Abstract])) OR (Bupivacain Janapharm[Title/Abstract])) OR (Bupivacain-RPR[Title/Abstract])) OR (Bupivacain RPR[Title/Abstract])) OR (Bupivacaina Braun[Title/Abstract])) OR (Carbostesin[Title/Abstract])) OR (Bupivacaine Carbonate[Title/Abstract])) OR (Bupivacaine Hydrochloride[Title/Abstract])) OR (Bupivacaine Monohydrochloride, Monohydrate[Title/Abstract])) OR (Buvacaina[Title/Abstract])) OR (Dolanaest[Title/Abstract])) OR (Sensorcaine[Title/Abstract])) OR (Svedocain Sin Vasoconstr[Title/Abstract])) OR (Marcaine[Title/Abstract])) OR (Bupivacaine Anhydrous[Title/Abstract]))	1,298,297
3	(((("Injections, Epidural"[Mesh]) OR (((((Extradural Injections[Title/Abstract]) OR (Peridural Injections[Title/Abstract])) OR (Peridural Injection[Title/Abstract])) OR (Extradural Injection[Title/Abstract])) OR (Epidural Injection[Title/Abstract]))) OR ("Nerve Block"[Mesh])) OR ((((((Block, Nerve[Title/Abstract]) OR (Nerve Blocks[Title/Abstract])) OR (Nerve Blockade[Title/Abstract])) OR (Blockade, Nerve[Title/Abstract])) OR (Nerve Blockades[Title/Abstract])) OR (Chemical Neurolysis[Title/Abstract]))) OR ((((((Injections[MeSH Terms]) OR (Injection[Title/Abstract])) OR (Injectables[Title/Abstract])) OR (Injectable[Title/Abstract])) OR (Block[Title/Abstract])) AND ((((((epidural[Title/Abstract]) OR (interlaminar[Title/Abstract])) OR (transforaminal[Title/Abstract])) OR (caudal[Title/Abstract])) OR (((spinal[Title/Abstract]) OR (dorsal[Title/Abstract])) AND (((root[Title/Abstract]) OR (nerve[Title/Abstract])) OR (ganglia[Title/Abstract]))))) OR (("Ganglia, Spinal"[Mesh]) OR (((((((Dorsal Root Ganglia[Title/Abstract]) OR (Ganglia, Dorsal Root[Title/Abstract])) OR (Spinal Ganglia[Title/Abstract])) OR (Dorsal Root Ganglion[Title/Abstract])) OR (Ganglion, Dorsal Root[Title/Abstract])) OR (Ganglion, Spinal[Title/Abstract])) OR (Spinal Ganglion[Title/Abstract])))))	48,844
4	1&2&3	1,420

Supplementary Table 2. *Sources of risk of bias from Cochrane Review collaboration.*

Bias Domain	Source of Bias	Possible Answers
Selection	(1) Was the method of randomization adequate?	Yes/No/Unsure
Selection	(2) Was the treatment allocation concealed?	Yes/No/Unsure
Performance	(3) Was the patient blinded to the intervention?	Yes/No/Unsure
Performance	(4) Was the care provider blinded to the intervention?	Yes/No/Unsure
Detection	(5) Was the outcome assessor blinded to the intervention?	Yes/No/Unsure
Attrition	(6) Was the drop-out rate described and acceptable?	Yes/No/Unsure
Attrition	(7) Were all randomized participants analyzed in the group to which they were allocated?	Yes/No/Unsure
Reporting	(8) Are reports of the study free of suggestion of selective outcome reporting?	Yes/No/Unsure
Selection	(9) Were the groups similar at baseline regarding the most important prognostic indicators?	Yes/No/Unsure
Performance	(10) Were cointerventions avoided or similar?	Yes/No/Unsure
Performance	(11) Was the compliance acceptable in all groups?	Yes/No/Unsure
Detection	(12) Was the timing of the outcome assessment similar in all groups?	Yes/No/Unsure
Other	(13) Are other sources of potential bias unlikely?	Yes/No/Unsure

Supplementary Table 3. *Item checklist for assessment of randomized controlled trials of IPM techniques utilizing IPM – QRB.*

		Scoring
I.	CONSORT OR SPIRIT	
1	Trial Design Guidance and Reporting	
	Trial designed and reported without any guidance	0
	Trial designed and reported utilizing minimum criteria other than CONSORT or SPIRIT criteria or trial was conducted prior to 2005	1
	Trial implies it was based on CONSORT or SPIRIT without clear description with moderately significant criteria for randomized trials or the trial was conducted before 2005	2
	Explicit use of CONSORT or SPIRIT with identification of criteria or trial conducted with high level reporting and criteria or conducted before 2005	3
II.	DESIGN F ACTORS	
2	Type and Design of Trial	
	Poorly designed control group (quasi selection, convenient sampling)	0
	Proper active-control or sham procedure with injection of active agent	2
	Proper placebo control (no active solutions into active structures)	3
3	Setting/Physician	
	General setting with no specialty affiliation and general physician	0
	Specialty of anesthesia/PMR/neurology/radiology/ortho, etc.	1
	Interventional pain management with interventional pain management physician	2
4	Imaging	
	Blind procedures	0
	Ultrasound	1
	CT	2
	Fluoro	3
5	Sample Size	
	Less than 50 participants in the study without appropriate sample size determination	0
	Sample size calculation with less than 25 patients in each group	1
	Appropriate sample size calculation with at least 25 patients in each group	2
	Appropriate sample size calculation with 50 patients in each group	3

Supplementary Table 3 (continued). ***Item checklist for assessment of randomized controlled trials of IPM techniques utilizing IPM – QRB.***

		Scoring
6	Statistical Methodology	
	None or inappropriate	0
	Appropriate	1
III.	PATIENT F ACTORS	
7	Inclusiveness of Population	
7a.	For epidural procedures:	
	Poorly identified mixed population	0
	Clearly identified mixed population	1
	Disorders specific trials (i.e. well defined spinal stenosis and disc herniation, disorder specific, disc herniation or spinal stenosis or post surgery syndrome)	2
7b.	For facet or sacroiliac joint interventions:	
	No diagnostic blocks	0
	Selection with single diagnostic blocks	1
	Selection with placebo or dual diagnostic blocks	2
8	Duration of Pain	
	Less than 3 months	0
	3 to 6 months	1
	> 6 months	2
9	Previous Treatments	
	Conservative management including drug therapy, exercise therapy, physical therapy, etc.	
	Were not utilized	0
	Were utilized sporadically in some patients	1
	Were utilized in all patients	2
10	Duration of Follow-up with Appropriate Interventions	
	Less than 3 months or 12 weeks for epidural or facet joint procedures, etc. and 6 months for intradiscal procedures and implantables	0
	3 to 6 months for epidural or facet joint procedures, etc., or 1 year for intradiscal procedures or implantables	1
	6 months to 17 months for epidurals or facet joint procedures, etc., and 2 years or longer for discal procedures and implantables	2
	18 months or longer for epidurals and facet joint procedures, etc., or 5 years or longer for discal procedures and implantables	3
IV.	OUTCOMES	
11	Outcomes Assessment Criteria for Significant Improvement	
	No descriptions of outcomes OR < 20% change in pain rating or functional status	0
	Pain rating with a decrease of 2 or more points or more than 20% reduction OR functional status improvement of more than 20%	1
	Pain rating with decrease of ≥ 2 points AND ≥ 20% change or functional status improvement of ≥ 20%	2
	Pain rating with a decrease of 3 or more points or more than 50% reduction OR functional status improvement with a 50% or 40% reduction in disability score	2
	Significant improvement with pain and function ≥ 50% or 3 points and 40% reduction in disability scores	4

Supplementary Table 3 (continued). ***Item checklist for assessment of randomized controlled trials of IPM techniques utilizing IPM – QRB.***

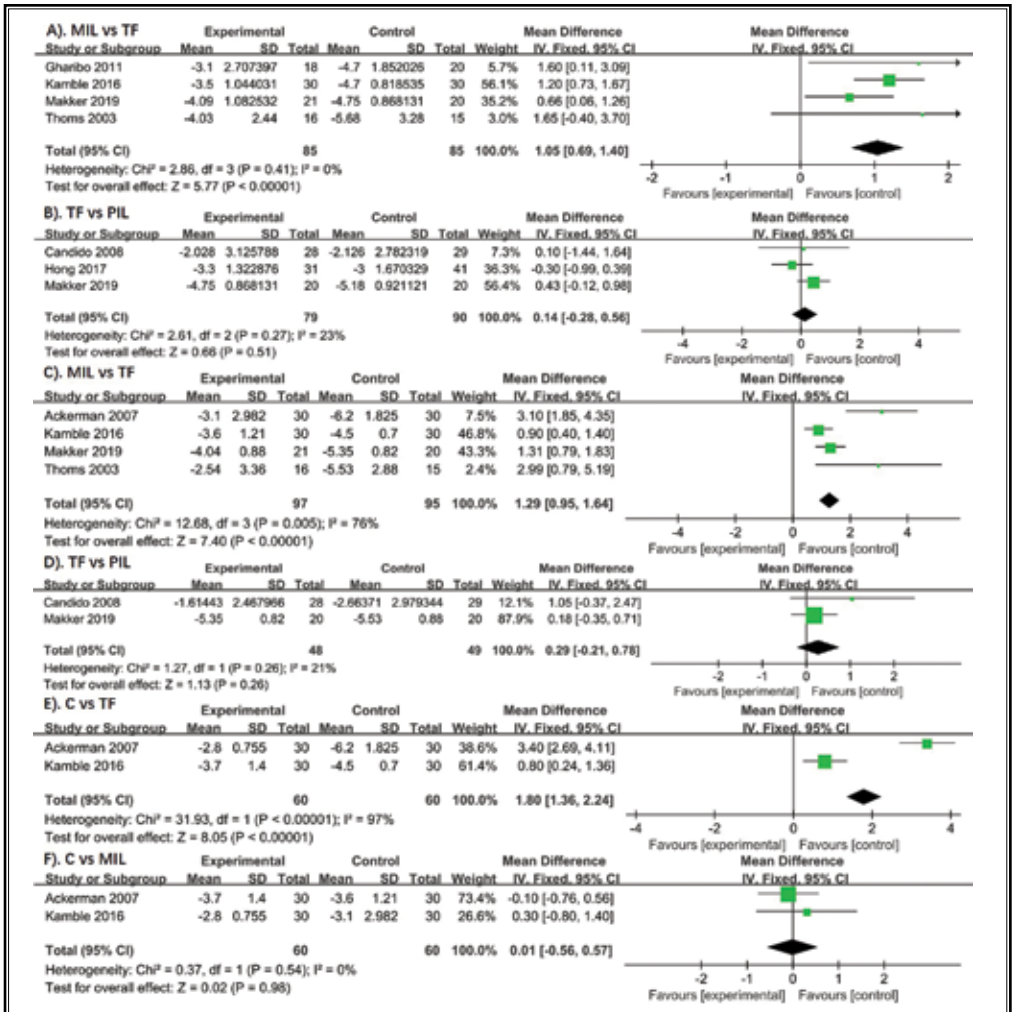
		Scoring
12	Analysis of all Randomized Participants in the Groups	
	Not performed	0
	Performed without intent-to-treat analysis without inclusion of all randomized participants	1
	All participants included with or without intent-to-treat analysis	2
13	Description of Drop Out Rate	
	No description of dropouts, despite reporting of incomplete data or ≥ 20% withdrawal	0
	Less than 20% withdrawal in one year in any group	1
	Less than 30% withdrawal at 2 years in any group	2
14	Similarity of Groups at Baseline for Important Prognostic Indicators	
	Groups dissimilar with significant influence on outcomes with or without appropriate randomization and allocation	0
	Groups dissimilar without influence on outcomes despite appropriate randomization and allocation	1
	Groups similar with appropriate randomization and allocation	2
15	Role of Co-Interventions	
	Co-interventions were provided but were not similar in the majority of participants	0
	No co-interventions or similar co-interventions were provided in the majority of the participants	1
V.	RANDOMIZATION	
16	Method of Randomization	
	Quasi randomized or poorly randomized or not described	0
	Adequate randomization (coin toss, drawing of balls of different colors, drawing of ballots)	1
	High quality randomization (computer generated random sequence, pre-ordered sealed envelopes, sequentially ordered vials, telephone call, pre-ordered list of treatment assignments, etc.)	2
VI.	ALLOCATION CONCEALMENT	
17	Concealed Treatment Allocation	
	Poor concealment of allocation (open enrollment) or inadequate description of concealment	0
	Concealment of allocation with borderline or good description of the process with probability of failure of concealment	1
	High quality concealment with strict controls (independent assignment without influence on the assignment sequence)	2
VII.	BLINDING	
18	Patient Blinding	
	Patients not blinded	0
	Patients blinded adequately	1
19	Care Provider Blinding	
	Care provider not blinded	0
	Care provider blinded adequately	1
20	Outcome Assessor Blinding	
	Outcome assessor not blinded or was able to identify the groups	0
	Performed by a blinded independent assessor with inability to identify the assignment-based provider intervention (i.e., subcutaneous injection, intramuscular distant injection, difference in preparation or equipment use, numbness and weakness, etc.)	1
VIII.	CONFLICTS OF INTEREST	
21	Funding and Sponsorship	
	Trial included industry employees	-3
	Industry employees involved; high levels of funding with remunerations by industry or an organization funded with conflicts	-3
	Industry or organizational funding with reimbursement of expenses with some involvement	0

Supplementary Table 3 (continued). *Item checklist for assessment of randomized controlled trials of IPM techniques utilizing IPM – QRB.*

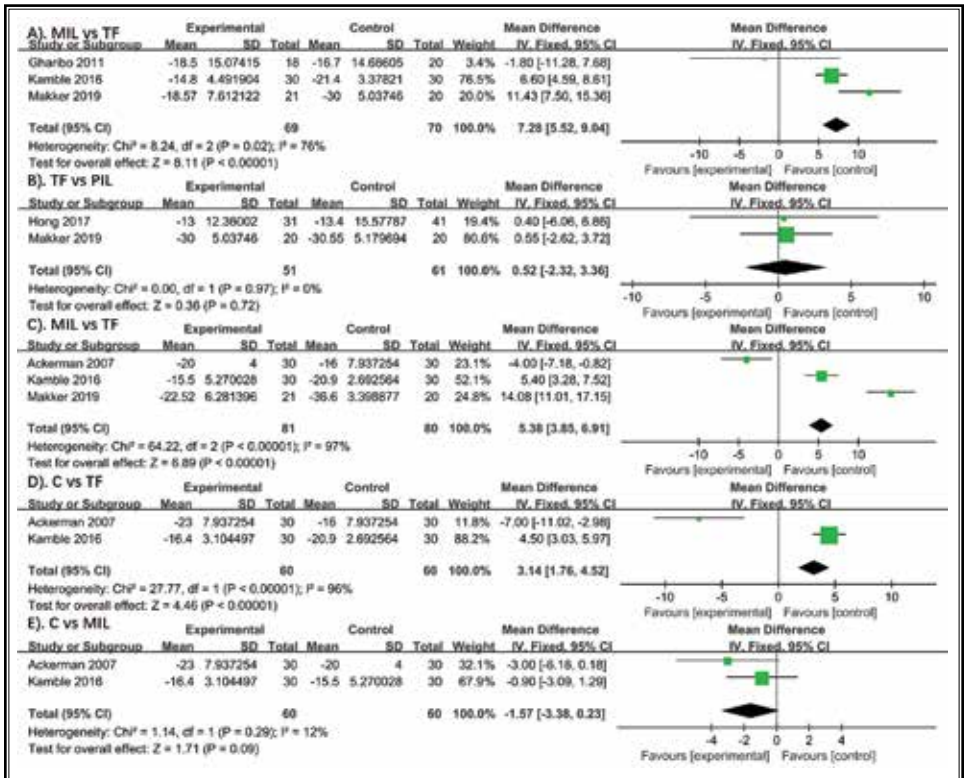
		Scoring
	Industry or organization funding of expenses without involvement	1
	Funding by internal resources only with supporting entity unrelated to industry	2
	Governmental funding without conflict such as NIH, NHS, AHRQ	3
22	Conflicts of Interest	
	None disclosed with potential implied conflict	0
	Marginally disclosed with potential conflict	1
	Well disclosed with minor conflicts	2
	Well disclosed with no conflicts	3
	Hidden conflicts with poor disclosure	-1
	Misleading disclosure with conflicts	-2
	Major impact related to conflicts	-3
TOTAL MAXIMUM		48

Supplementary Table 4. *Assessment of model fit. If the difference of DIC value in 2 modes is within 5, it means that the data is consistent. DIC, deviance information criterion.*

Outcome	**Consistency Model**			**Inconsistency Model**		
	pD	**DIC**	**I^2**	**pD**	**DIC**	**I^2**
Short-term VAS	11.06	23.53	0%	12.25	25.22	0%
Intermediate-term VAS	12.30	25.23	7%	12.74	25.73	8%
Short-term ODI	7.65	15.66	13%	7.99	15.98	12%
Intermediate-term ODI	8.96	18.05	12%	8.97	18.04	12%



Supplementary Fig. 1. *Results of pairwise meta-analyses with mean differences for VAS in short-term (A,B) and intermediate-term (C-F) follow-up.*



Supplementary Fig. 2. ***Results of pairwise meta-analyses with mean differences for ODI in short-term (A,B) and intermediate-term (C-F) follow-up.***
C, caudal steroid injection; MIL, midline interlaminar steroid injection; PIL, parasagittal interlaminar steroid injection; TF, transforaminal steroid injection; VAS, visual analog scale; ODI, the Oswestry Disability Index.