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Systematic Review

Comparison of Clinical Efficacy Between Transforaminal and Interlaminar Epidural Injections in Lumbosacral Disc Herniation: A Systematic Review and Meta-Analysis

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Background: Epidural injection (EI) is used to treat back or radicular pain from lumbosacral disc herniation (LDH). Although several reports have stated that the transforaminal approach in EI (TFEI) has an advantage in target specificity and yields better clinical efficacy than the interlaminar approach in EI (ILEI), other studies have indicated that the clinical efficacy of ILEI was not inferior to that of TFEI and that ILEI also has the ability to spread medication into the ventral space to a degree similar to that of TFEI. There has been controversy about whether TFEI is superior to ILEI in clinical efficacy.

Objectives: This systematic review and meta-analysis aimed to investigate whether TFEI is more useful than ILEI for achieving clinical outcomes in patients with LDH.

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

Methods: A literature search was performed in MEDLINE, EMBASE, Cochrane review, and KoreaMed for studies published from January 1996 until July 2017. From those found fulfilling the search criteria, manuscripts 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. After reviewing titles, abstracts, and the full text of 6,711 studies; 12 studies were included in the qualitative synthesis. Data including pain scores, functional scores, and follow-up period were extracted from 10 studies and analyzed using a random effects model to obtain effect size and its statistical significance. The quality and level of evidence were analyzed in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Results: In terms of pain control, TFEI showed significantly better short-term (2 weeks to 1 month) outcomes and slightly favorable long-term (4 - 6 month) outcomes, but without significance, in comparison with ILEI. In terms of functional improvement, TFEI also showed favorable short- and long-term outcomes, but without significance, in comparison with ILEI. TFEI had target specificity, required no additional cost and resources, and had equal applicability to ILEI. However, TFEI was more associated with a higher frequency of discomfort or adverse events during the procedure. Overall, better results were reported with TFEI over ILEI, but with low-grade evidence due to the inconsistency and imprecision of the selected studies.

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

Conclusions: Based on low-grade evidence, TFEI showed significantly better short-term pain control and slightly favorable outcomes in long-term pain reduction and short- and long-term functional improvement in comparison with ILEI.

Key words: Epidural injection, interlaminar, transforaminal, meta-analysis, systemic review, pain, function

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Lumbar epidural injections (EI) have been used to treat low back and lower extremity pain from lumbosacral disc herniation (LDH) (1,2). The epidural administration of the drugs provides targeted delivery of the medications and supresses inflammatory mediators that irritate nervous tissues. Three types of techniques such as interlaminar (ILEI), caudal, and transforaminal epidural injection (TFEI) have been utilized in clinical practice. Because axial back or radicular leg pain is mainly generated from sinuvertebral nerves existing in the ventral epidural space, the nerve root sheath and the dorsal root ganglion, the main target of drug administration is logically considered the ventral epidural spread rather than the dorsal epidural space (3,4). Hence, TFEI is preferred by some physicians because it delivers the medication directly into the ventral epidural space (5-8), whereas, ILEI delivers the medication into the posterior epidural spaces under the expectation that the administered medication ideally spreads to the ventral spaces afterward (9-12).

Even though several reports have stated that TFEI obtained better clinical efficacy than ILEI in patients with LDH (9,13-16), conflicting studies have indicated that the clinical efficacy of ILEI was not inferior to that of TFEI and that it also had the ability to spread the medication into the ventral space to a degree similar to that of TFEI (16-20). Furthermore, one study found that ILEI involved less pain or discomfort, and that it was less likely than TFEI to penetrate vascular structures during needle insertion (18).

One systemic review compared the clinical efficacy between TFEI and ILEI. This review concluded that there was no significant difference found between the 2 methods (16). Another systemic review comparing caudal, lumbar interlaminar, and transforaminal approach techniques indicated that all methods conducted under fluoroscopic guidance were effective at managing lumbar disc herniation in terms of pain relief and functional improvement (21). However, the authors did not perform a meta-analysis comparing TFEI and ILEI. Identifying which method is more clinically useful could help physicians choose appropriate treatments for patients with LDH. Thus, this systematic review and meta-analysis investigates whether TFEI is more useful than ILEI in terms of pain control and functional improvement during short- and long-term follow-up in the treatment of patients with LDH during short- and long-term follow up periods.

Methods

Study Selection Criteria

We included articles with human subjects written in Korean or English that met the following criteria: patients aged ≥ 18 years, clinical presentation of low back and radicular leg pain, diagnosis of LDH on a radiological evaluation such as computed tomography or magnetic resonance imaging. Exclusion criteria included a previous history of lumbosacral surgery, nonspecific low back pain without a definite diagnosis of LDH on radiological evaluation, spinal stenosis, severe disc degeneration, intradiscal disc derangement or a bulging disc, or prominent spinal instability. Of the studies fulfilling these criteria, those that compared the clinical efficacy of TFEI and ILEI in terms of pain control and functional improvement under C-arm fluoroscopy were included in the present study.

Database Search and Study Extraction

The MEDLINE (Pubmed), EMBASE, Cochrane review, and KoreaMed databases were searched for articles published up to July 2017. We established individual search terms in each database's search engine (Appendix). The search was not restricted to randomized controlled studies (RCT) and was extended to original articles, including non-RCT. The decision to include an article was primarily made based on title and abstract review, followed by full-text screening. 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, 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 were extracted for the estimation of relative risk ratio and 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.

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 (22). The bias assessment for each RCT was conducted by method of risk of bias (ROB), 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 by Risk of Bias Assessment tool for Non-randomized Study (RoBANs), domains of which were 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 with "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.

The components of inconsistency, indirectness, imprecision, and publication bias were comprehensively examined in addition to the risk of bias of all studies. Evidence level was determined as high, moderate, low, or very low grades. The strength of recommendation was determined as strong or weak by comprehensively assessing not only evidence level, but also other factors such as balancing benefits and harms, resources required, values and preferences, and acceptability/feasibility (22). The level of evidence and strength of recommendation were determined by discussion by the entire research group.

Quality assessment was performed using the Cochrane review criteria and Interventional Pain Management techniques Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB). Studies meeting the inclusion criteria with a Cochrane review score of 8-12 were considered high quality with respect to the Cochrane criteria; those with a score of 4-7 were considered moderate-quality; and those with a score less than 4 were considered low-quality. Studies meeting the inclusion criteria with an IPM-QRB score of 32-48 were considered high quality with respect to the IPM-QRB criteria; those with a score of 16-31 were considered moderate quality; and those with a score less than 16 were considered low-quality (23-26). Only high- and moderate-quality studies were included in the present review.

Meta-analysis

Review Manager software (RevMan version 5.3; The Cochrane Collaboration 2014) was used for data analysis. The analysis was done in 4 categories of pain control and functional improvement at short- and long-term follow-up period. Tests of heterogeneity were performed using I2 statistics. The category with I2 values of 50% or more was considered to have a high degree of heterogeneity and was assessed again by subgroup analysis. A random effect model was applied to obtain effect size and its statistical significance because it was assumed that the subjects and methods of included studies performed by independent researchers could not be entirely equivalent and, therefore, could not have a common effect size. A probability of $P < 0.05$ was considered statistically significant. The results were expressed as mean difference and 95% confidence interval (95% CI) for continuous outcome data and in the form of relative risk ratio and 95% CI for dichotomous outcome data.

Results

Search Results

Our database search initially yielded 9,088 articles. 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 292 were subsequently excluded because they were irrelevant to this study. Ultimately, 10 RCT and 2 non-RCT (prospective observational studies) were included in this study. The pain intensity measures used in the selected studies were the visual analog scale (VAS) or the numerical rating scale (NRS). Both scores were considered the same in the meta-analysis because they were highly correlated and, when transformed, could be used interchangeably (27). The most frequently used functional measurement tool used in the selected studies was the Oswestry Disability Index (ODI). However, one study (15) provided only the Japan Orthopedic Association score as a functional evaluation that could not be correlated with ODI; thus, it was excluded from the meta-analysis. Because another RCT did not provide available data for the meta-analysis (28), 10 studies (7 RCTs and 3 non-RCTs) were ultimately included in the meta-analysis.

Figure 1 demonstrates a flowchart of the study selection process. The follow-up period was variable across the studies ranging from 1 day to 1 year. The short-term follow-up period was 2 weeks to 1 month, while the long-term follow-up period was 4 to 6 months because pain and functional data in this period could be most abundantly obtained and clinically meaningful. Clinical data after 6 months was not considered due to clinical effects from previously performed ESI deteriorating substantially by this time (2,29).

Quality Assessment

The risk of bias of all selected studies is illustrated in Fig. 2 (a: RCT, b: non-RCT). Except for one RCT that was assessed as high risk, all RCTs were assessed as low risk in the random sequence domain (30). The domain that was most frequently biased was allocation concealment, of which 5 RCTs were rated as unclear because they did not adequately describe the procedure for allocation concealment (3,13,20,30,31), and 2 RCTs were graded as high risk because they showed flaws in the

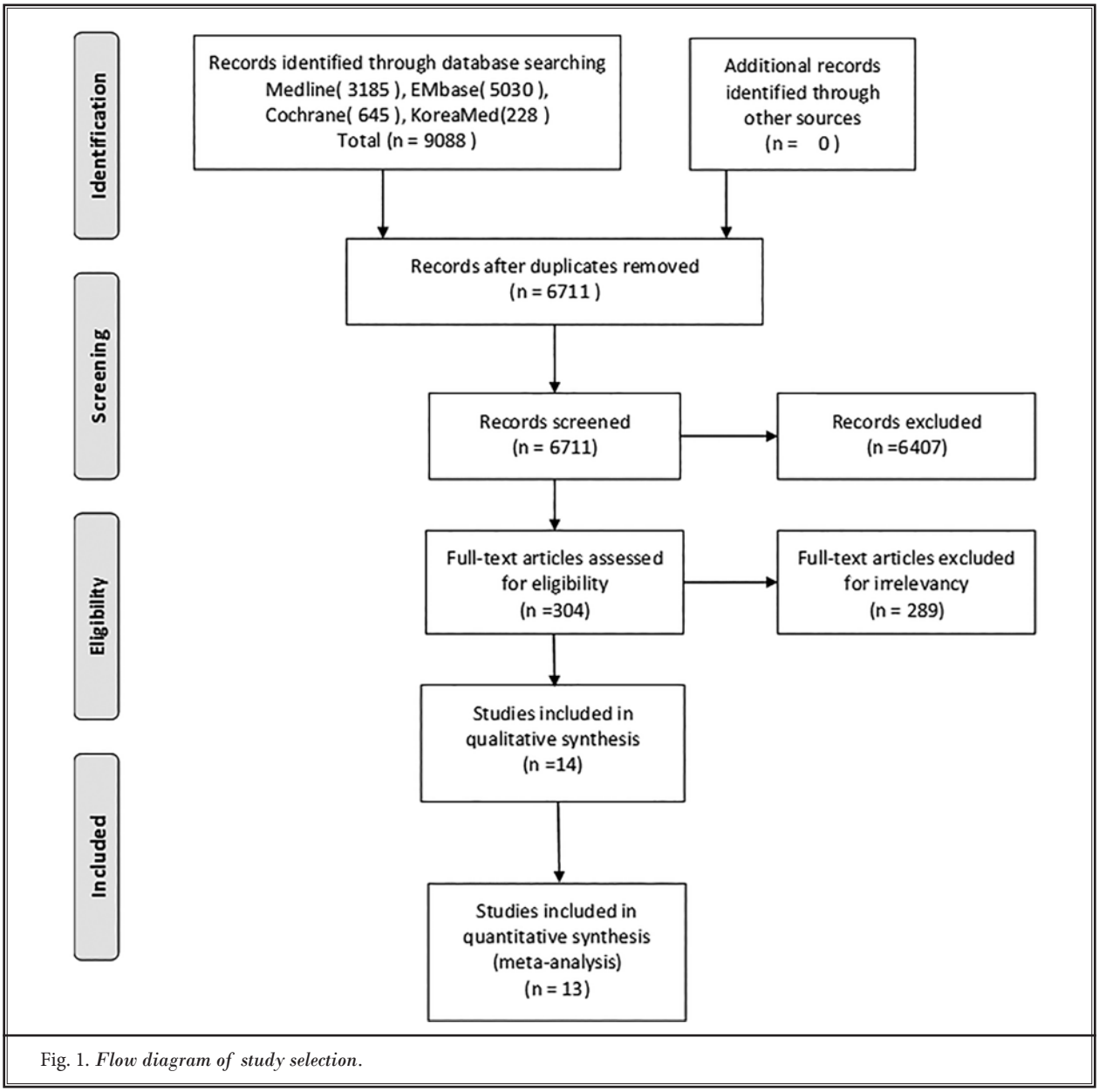


Fig. 1. *Flow diagram of study selection.*

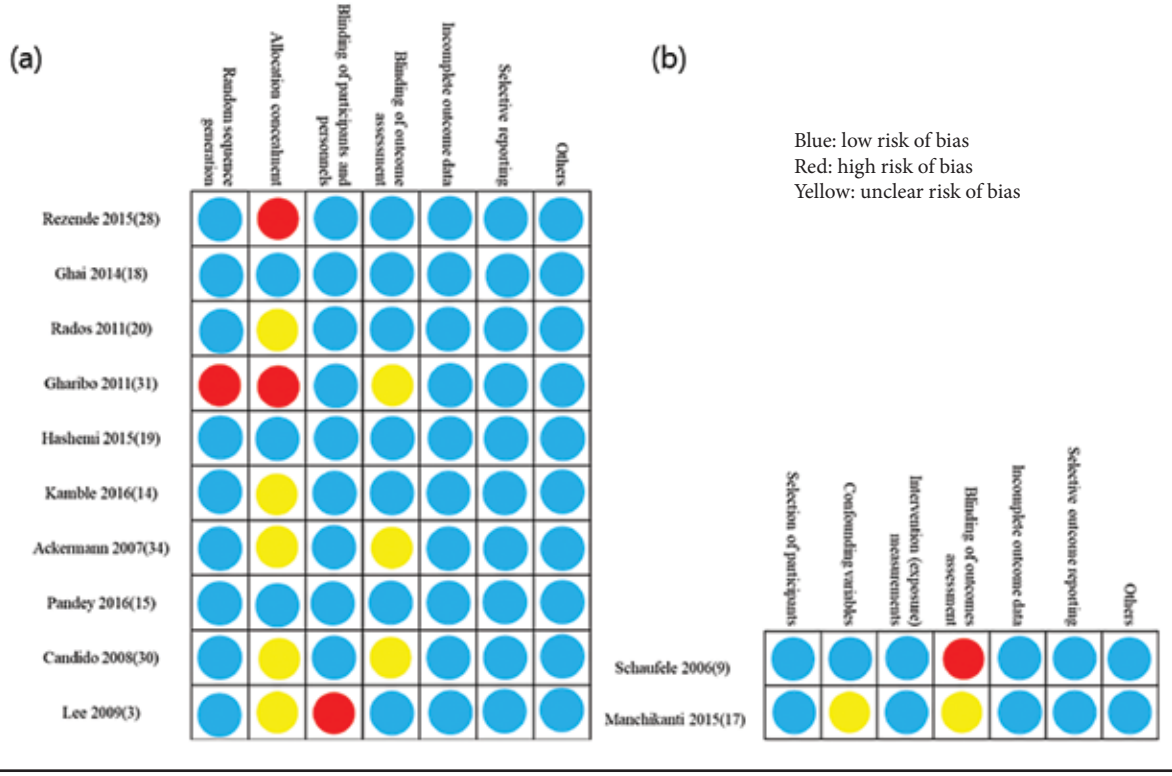


Fig. 2. *Quality assessment for extracted studies a) risk of bias(ROB) for randomized controlled study, b) Risk of Bias Assessment tool for Non-randomized Study (RoBANs) for non-randomized study.*

allocation process (15,28). One of the non-RCTs was rated as unclear in the domain of confounding variables because it did not clearly present the procedures of excluding the confounding factors (17,32,33). Of 84 domains across all studies, 69 domains (82.1%) were determined as low risk; thus, the overall risk of bias was considered low.

Clinical Outcome Analysis

Among the 10 RCTs ultimately selected, no significant difference of clinical efficacy was found between TFEI and ILEI in 5 studies (3,18-20,31), another 4 reported (14,15,28,34) that TFEI obtained significantly better clinical effects than ILEI during 3-12 months follow-up periods, and 1 article (30) noted that TFEI was more effective in the short term but the superiority was diminished after 2 weeks. Between the 2 non-RCTs, one study (17) showed no significant difference between the 2 techniques, and the other study (9) stated that TFEI demonstrated better clinical efficacy than ILEI). Comprehensively, TFEI was non-inferior or superior to ILEI in the treatment of patients with LDH (Table 1).

Quality assessment results of the Cochrane review criteria and IPM-QRB for RCTs and IPM-QRBNR for non-RCTs are presented in Tables 2, 3 and 4 respectively. All RCTs were rated as high quality for Cochrane review criteria, with 7 RCTs determined as high and 3 RCTs as moderate quality according to IPM-QRB. One non-RCT was rated as high quality and the other non-RCT was rated as moderate.

Pain Control in the Short-Term Period (2 Weeks to 1 Month)

Three studies (3,18,19) reported the number of patients with successful pain reduction in the short-term period after TFEI, thus enabling the measurement of effect size by the relative risk ratio of successful pain control in the short-term period. Overall, 83 of 121 cases treated with TFEI and 71 of 98 cases treated with ILEI accomplished successful pain reduction. Although no statistically significant difference between TFEI and ILEI was found (P = 0.60), the data showed slightly

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

1st author	TFESI	ILESI	Evaluation	Follow up	outcomes
RCT					
Rezende 2015 (28)	N=20 3 mL of betamethasone phosphate (40 mg/mL) 2 mL of 0.25% neo-bupivacaine 5 mL of distilled water	N=20 3 mL of betamethasone phosphate (40 mg/mL) 2 mL of 0.25% neo-bupivacaine 5 mL of distilled water	VAS	1 day to 3 months	TFESI>>ILESI
Ghai 2014 (18)	N=30 2 mL of methylprednisolone acetate (40mg/mL) 2 mL of sterile normal saline	N=32 2 mL of methylprednisolone acetate (40mg/mL), 2 mL of sterile normal saline	VAS, MODQ	2 weeks to 12 months	no significant difference
Rados 2011 (20)	N = 32 40 mg of methylprednisolone, 3 mL of 0.5% lidocaine	N = 32 80 mg of methylprednisolone 8 mL of 0.5% lidocaine	VAS, ODI	6 months	no significant difference
Gharibo 2011 (31)	N= 20 40 mg of triamcinolone (40 mg/mL) 1 mL of 0.25% bupivacaine	N = 18 80 mg of triamcinolone 2 mL of 0.25% bupivacaine	NRS,ODI depression scale walking tolerance	2-3 weeks	TFESI>>ILESI at initial stage, but no significant difference at subacute stage
Hashemi 2015 (19)	N=32 2 mL of triamcinolone 2 mL of bupivacaine 6 mL of sterile normal saline	N=32 2 mL of triamcinolone 2 mL of bupivacaine 6 mL of sterile normal saline	NRS,ODI	4 weeks	no significant difference
Kamble 2016 (14)	N=30 40mg of triamcinolone acetate 1 mL of bupivacaine 2 mL of lignocaine	N=30 40mg of triamcinolone acetate 1 mL of bupivacaine 1 mL of lignocaine 10 mL of normal saline	VAS, ODI	1, 6 months	TFESI > ILESI
Ackermann 2007 (34)	N= 30 40 mg of triamcinolone 4 mL of normal saline	n = 30 40 mg of triamcinolone 4 mL of normal saline	VAS OLBPS BDI, NPIS	6 months	TFESI > ILESI
Pandey 2016 (15)	N=40 1mL of 2% xylocaine 40mg of methylprednisolone .	N=18 4mL of 2% xylocaine 40mg of methylprednisolone	JOA	6 months, 1 year	TFESI > ILESI
Candido 2008 (30)	N=28 80mg of methylprednisolone acetate 1 mL of normal saline 1 mL of 1% lidocaine	N=29 80mg of methylprednisolone acetate 1 mL of normal saline 1 mL of 1% lidocaine	VAS	2 weeks to 6 months	no significant difference
Lee 2009 (3)	N=59 40 mg of triamcinolone 8 mL of 0.5% lidocaine	N=34 40mg of triamcinolone 8mL of 0.5% lidocaine	NRS, PSI Roland 5 points scale	2 weeks to 4 months	no significant difference
Non RCT					
Manchikanti 2015 (17)	N=120 1.5 mL of 1% lidocaine with 0.5 mL of sodium chloride solution or 3 mg of betamethasone	N=120 6mL of 0.5% lidocaine or 5 ml of lidocaine with 1 mL of steroid	NRS, ODI	3 to 24 months	no significant difference
Schaufele 2006 (9)	N=20 80 mg of methylprednisolone 1-2 mL of 2% lidocaine	N=20 80 mg of methylprednisolone 2-3 mL of 2% lidocaine	NRS	1 hours to 2-3 weeks	TFESI > ILESI

TFESI : transforaminal epidural steroid injection, ILESI : interlaminar epidural steroid injection
VAS : visual analogue scale, MODQ : modified oswestry disability questionnaire, ODI : oswestry disability score
NRS : numeric rating scale, OLBPS : Oswestry low back pain scale, BDI : Back depression index,
NPIS : Numeric pain intensity score, JOA : Japanese Orthopaedic Association

favorable trends toward ILEI with an estimated relative risk ratio of 0.95 (95% CI: 0.80-1.14) (Fig. 3a). No heterogeneity was observed in dichotomous data analysis (I^2 = 0%).

Four studies presented the continuous pain score data and were included in the analysis of effect size by mean difference (9,14,30,31). The overall mean difference was measured as 1.04 (95% CI: 0.39-1.70) that supported the superiority of TFEI with statistical significance (P = 0.002) (Fig. 3b). A low degree of heterogeneity was observed in continuous data analysis (I^2 = 29%).

Pain Control in the Long-Term Period (4 to 6 Months)

Five studies provided the number of patients with a successful pain score reduction at 4-6 months thus allowing for an estimate of relative risk ratio (3,17,18,20,34). Successful pain reduction was found in 183 of the 273 patients who underwent TFEI versus 154 of the 250 patients who underwent ILEI. TFEI achieved a higher proportion of successful pain control than ILEI with an overall estimated effect size of 1.13 (95% CI, 0.91-1.40) with no statistical significance (P = 0.29). A high degree of heterogeneity was found to be present (I^2 = 58%).

A subgroup analysis was conducted after the division of the studies into 2 subgroups depending on whether ILEI used a higher steroid dosage or equal dosage of steroid to TFEI. Two studies (17,20) in which ILEI used a higher steroid dose were included in the ILEI higher steroid dose group, while the 3 studies (3,18,34) in which ILEI used an equal dose were included in the equal steroid dose subgroup. The equal steroid dose subgroup showed that TFEI had a better result than ILEI with an effect size of 1.43 (95% CI 1.02-1.99) with no degree of statistical significance but with a degree of clinical improvement (P = 0.09) (3,13,35). The level of heterogeneity was I^2 = 58%.

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

	Rezende 2015 (28)	Ghai 2014 (18)	Rados 2011 (20)	Gharibo 2011 (30)	Hashemi 2015 (19)	Kamble 2016 (14)	Ackermann 2007 (34)	Pandey 2016 (15)	Candido 2008 (31)	Lee 2009 (3)
Randomization adequate	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Concealed treatment allocation	N	Y	U	N	Y	U	U	Y	U	U
Patient blinded	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Care provider blinded	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Outcome assessor blinded	Y	Y	Y	U	Y	Y	U	Y	U	Y
Drop-out rate described	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
Reports of the study free of suggestion of selective outcome reporting	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
Co-interventions avoided or similar	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
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Score	11	12	11	9	12	11	10	12	12	9

Y : yes. N : no U : unclear

Table 3. *Methodological quality assessment utilizing IPM-QRB for randomized studies.*

	Rezende 2015 (28)	Ghai 2014 (18)	Rados 2011 (20)	Gharibo 2011 (31)	Hashemi 2015 (19)	Kamble 2016 (14)	Ackermann 2007 (34)	Pandey 2016 (15)	Candido 2008 (30)	Lee 2009 (3)
I. TRIAL DESIGN AND GUIDANCE REPORTING										
1. CONSORT or SPIRIT	3	3	3	1	1	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. Setting/Physician	1	2	2	1	2	2	2	1	2	3
4. Imaging	3	3	3	3	3	3	3	3	3	3
5. Sample Size	1	2	1	1	2	2	2	2	2	2
6. Statistical Methodology	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
8. Duration of Pain	0	1	1	0	2	0	0	1	1	1
9. Previous Treatments	2	2	2	2	2	0	2	2	0	0
10. Duration of Follow-up with Appropriate Interventions	1	2	0	0	0	1	1	1	1	1
IV. OUTCOMES										
11. Outcomes Assessment Criteria for Significant Improvement	4	4	4	4	4	2	4	4	1	1
12. Analysis of all Randomized Participants in the Groups	2	2	2	2	2	2	2	2	2	2
13. Description of Drop Out Rate	1	1	1	1	0	1	1	1	1	2
14. Similarity of Groups at Baseline for Important Prognostic Indicators	2	2	2	2	2	2	2	2	2	2
15. Role of Co-Interventions	1	1	1	1	1	1	1	1	1	1
V. RANDOMIZATION										
16. Method of Randomization	2	2	2	0	2	2	2	2	2	2
VI. ALLOCATION CONCEALMENT										
17. Concealed Treatment Allocation	1	2	1	0	2	1	1	2	1	0

Table 3m (cont). *Methodological quality assessment utilizing IPM-QRB for randomized studies.*

	Rezende 2015 (28)	Ghai 2014 (18)	Rados 2011 (20)	Gharibo 2011 (31)	Hashemi 2015 (19)	Kamble 2016 (14)	Ackermann 2007 (34)	Pandey 2016 (15)	Candido 2008 (30)	Lee 2009 (3)
VII. BLINDING										
18. Patient Blinding	1	1	1	1	1	1	1	1	1	0
19. Care Provider Blinding	1	1	1	1	1	1	1	1	1	0
20. Outcome Assessor Blinding	1	1	1	0	1	1	0	1	0	1
VIII. CONFLICTS OF INTEREST										
21. Funding and Sponsorship	1	2	2	2	2	2	2	2	2	2
22. Conflicts of interest	3	3	3	3	0	0	0	3	0	3
Score	37	43	39	31	36	31	34	39	30	33

Table 4. *Methodological quality assessment utilizing IPM-QRBNR for non-randomized studies.*

	Schaufele 2006 (9)	Manchikanti 2015 (17)
1. Study Design Guidance and Reporting	2	4
2. Study Design and Type	1	4
3. Setting/Physician	2	2
4. Imaging	3	3
5. Sample Size	0	4
6. Statistical Methodology	2	2
7. Inclusiveness of Population	4	4
8. Duration of Pain	0	2
9. Previous Treatments	2	0
10. Duration of Follow-up with Appropriate Interventions	1	4
11. Outcomes Assessment Criteria for Significant Improvement	1	0
12. Description of Drop Out Rate	0	2
13. Similarity of Groups at Baseline for Important Prognostic Indicators	2	2
14. Role of Co-Interventions	2	2
15. Method of Assignment of Participants	3	4
16. Funding and Sponsorship	2	2
Score	27	41

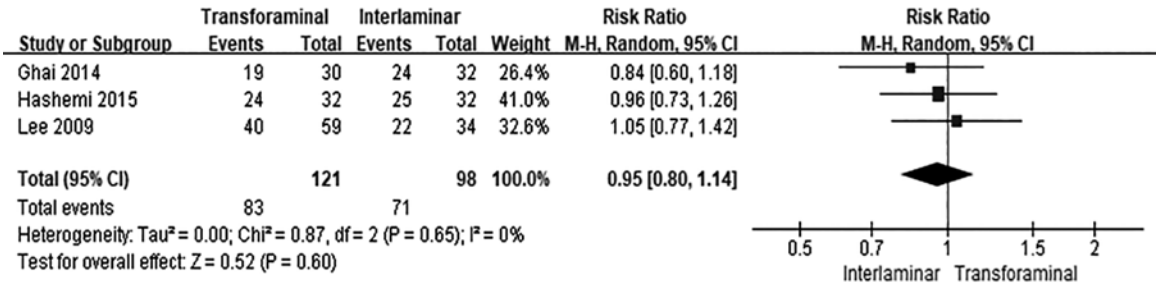
The ILEI higher steroid dose subgroup, showed results supporting ILEI without statistical significance (P = 0.26) (17,20). Heterogeneity was reduced to I^2 = 22 %.

Continuous data of pain measurement scores were available in 4 studies (14,17,20,31). The overall mean difference was calculated as 0.13 (95% CI : -0.50-0,77) which favored TFEI, but this did not show statistical significance (P = 0.68). A high degree of heterogeneity was found (I^2 = 70%) (Fig. 3d).

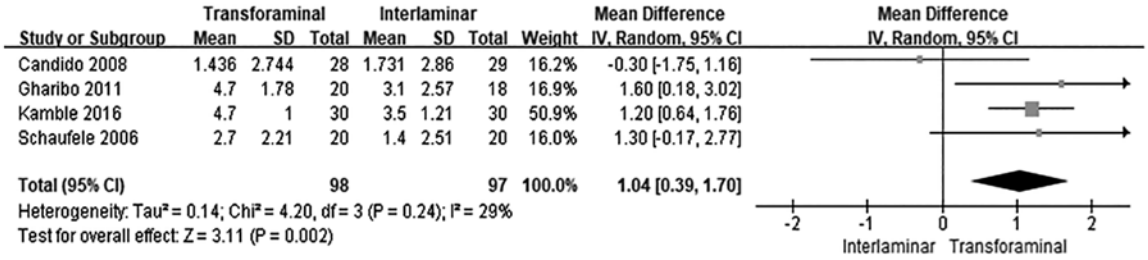
The subgroup analysis was conducted in the same way as the estimate of relative risk ratio. Two studies included in the ILEI higher steroid dose subgroup showed results that slightly favored ILEI by a mean difference of -0.13 (95% CI -0.43-0.16) with no statistical significance (P = 0.38). No heterogeneity was observed in this subgroup (I^2 = 0%) (17,20). The equal steroid dose subgroup showed that TFEI showed better result than ILEI with an effect size of 0.66 (95% CI -0.15-1.47) that was without significance (P = 0.11). The level of heterogeneity was reduced to I^2 = 31% (14,31).

Functional Improvement in the Short-Term Period (2 weeks to 1 month)

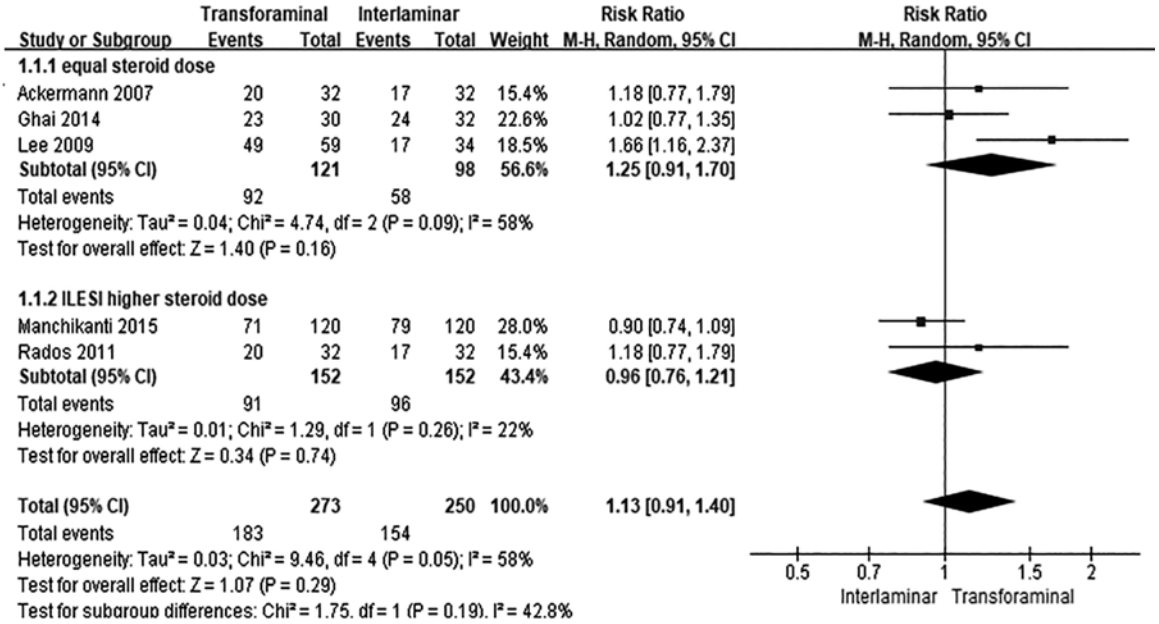
Only 2 studies (14,30) presented continuous data consisting of functional scores at less than 1 month and were available in the analysis of effect size by mean difference. Although 2 studies



(a) Comparison of pain reduction as relative risk ratio at short term b



(b) Comparison of pain reduction as mean difference at short term



(C) Comparison of pain reduction as relative risk ratio at long term.

Fig. 3. *Forest plot of a) comparison of pain reduction as relative risk ratio at short term b) comparison of pain reduction as mean difference at short term c) comparison of pain reduction as relative risk ratio at long term.*

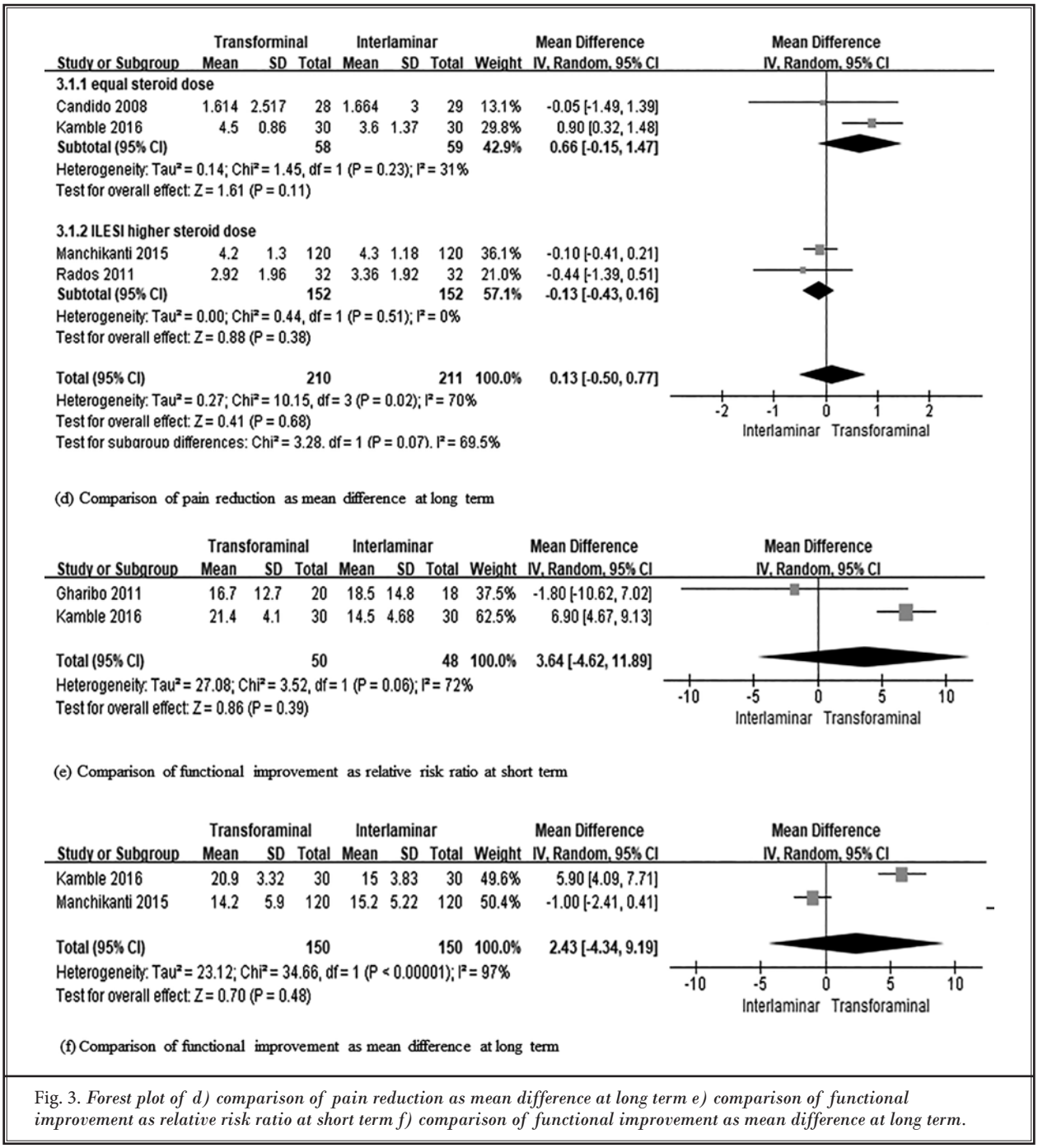


Fig. 3. *Forest plot of d) comparison of pain reduction as mean difference at long term e) comparison of functional improvement as relative risk ratio at short term f) comparison of functional improvement as mean difference at long term.*

showed contradictory results, the overall mean difference was estimated as 3.64 (95% CI: -4.62-11.89), which favored TFEI although without statistical significance (P = 0.39). A high degree of heterogeneity was revealed (I2 = 72%), but a subgroup analysis could not be performed because only 2 studies were included (Fig. 3e).

Functional Improvement in the Long-Term Period (4-6 Months)

Only 2 studies (14,17) were available in the analysis of effect size by the mean difference for functional improvement at 4-6 months after treatment. The estimated overall mean difference was calculated as 2.43

(95% CI: -4.34-9.19), which favored TFEI, but again without statistical significance (P = 0.48). The degree of heterogeneity was high (I2 = 97%), but the subgroup analysis could not be performed because only 2 studies were included (Fig. 3f).

Level of Evidence and Strength of Recommendation

The risk of bias was evaluated as low as previously mentioned. Directness was not considered problematic because all included studies directly compared TFEI with ILEI. Publication bias was not assessed because fewer than 10 studies were included in each meta-analysis. However, the level of evidence was considered low due to inconsistency and imprecision. The consistency was considered to have serious problems because some extent of diversity in type of steroid used or treatment protocols existed across studies, and considerable heterogeneity was found in meta-analysis. The degree of precision was also considered serious because most of the studies included fewer than 100 subjects.

All reviewers agreed that TFEI achieved superior clinical outcomes to ILEI as was supported by selected studies with a modest degree. TFEI did not require higher cost, greater resources, or additional devices than ILEI. Thus, TFEI could be applicable to patients with LDH with the same accessibility as ILEI in the clinical setting. However, pain or discomfort occurred more frequently during TFEI than during ILEI due to the needle trajectory approaching near the nerve root (4,18). There was greater concern about serious adverse effects associated with TFEI than ILEI including radicular artery embolism and consequent spinal cord infarction. However, this complication was also related to the steroid type (particulate steroid) that could produce thrombosis after intravasation (36,37). TFEI could be more recommendable than ILEI; however, with low grade evidence due to inconsistency and imprecision of selected studies. The strength of recommendation was determined as weak by discussion of all reviewers.

Discussion

While TFEI had the advantage of targeting the ventral epidural space which was considered the main source of pain and has been believed to be a more effective method than ILEI (13-15,28,38), conflicting opinions or results also showed that ILEI was not inferior in clinical efficacy and had comparable ability to deliver the medication into the ventral epidural spaces (16,20,35,39). Studies have identified that the proportion of ventral epidural spread after ILEI is comparable to that of TFEI (18,40).

A number of concerns have been raised regarding the side effects of TFEI such as lower-limb paraplegia resulting from intravascular penetration or embolic infarct (41). The incidence of pain or discomfort related to nerve root damage and intradiscal penetrations was also higher in TFEI than in ILEI, probably because of the needle approach (4,18,42). Taken together, ILEI could be a suitable alternative to TFEI or the first choice of treatment.

A slightly favorable result toward ILEI was observed in the relative risk ratio in the short-term follow up period, despite no significant difference. This was because that 2 studies (18,19) that supported ILEI used the parasagittal approach, a more lateral approach than the usual ILEI, and thus succeeded in delivering injectate into the lateral and ventral epidural spaces than just using the usual ILEI. In the subgroup analysis for long-term pain control, if ILEI used a higher steroid dose than the usual ILEI, it achieved greater pain reduction, while if it used a dose equal to that of TFEI, TFEI showed greater pain reduction than in the pre-subgroup analysis of ILEI. This finding suggested that a more lateral approach or higher steroid dose should be required for ILEI to achieve pain control comparable to or slightly better than that for TFEI.

Despite several controversial points and the slight positivity of ILEI observed in some categories mentioned above, the current meta-analysis advocated TFEI because it generally showed trends toward better pain reduction and functional improvement than ILEI in the short term and long term. TFEI obtained significantly greater pain reduction than ILEI in the short term. The deterioration of the superiority of TFEI in the long-term period could be explained by the fact that the efficacy of EI was not usually maintained over the long term, so the difference in the clinical efficacy between TFEI and ILEI also diminished over time (29,43). In addition, 6 of the 12 selected studies (9,14,15,28,30,34) including RCTs and non-RCTs were significantly favorable to TFEI, while the rest also demonstrated comparable results between the 2 techniques, but none showed a favorable outcome toward ILEI.

Although ILEI successfully delivered the medication in the ventral epidural space to a degree comparable to that of TFEI, the degree of perineural spread was significantly higher after TFEI than after ILEI (18). Because the radicular pain originated from chemical irritation around the nerve root sheath or dorsal root ganglion, the degree of perineural spread was a key

factor in effectively reducing radicular pain (4,44-46). This property of TFEI gave it the advantage over ILEI of controlling radicular pain. Most of the studies included in this analysis chose the subjects complaining of radicular leg pain with or without axial back pain. Lee's study (33) distinctively selected the patients with axial back pain without radicular pain and showed no significant difference in mean pain scores between TFEI and ILEI in subjects with LDH. However, interestingly, TFEI achieved significantly better pain control than ILEI in patients with spinal stenosis in that study. This was explained by the fact that a prominent barrier such as a hypertrophied bone or ligament kept the medication from spreading around the nerve root sheath or ventral epidural space in spinal stenosis, whereas this barrier in patients with LDH was not so prominent as in stenosis; thus, posteriorly administered medication spread more easily into the ventral epidural space in cases of LDH (3). This could support the importance of the targeted delivery of medication around the ventral epidural space or nerve root sheath.

The number of injections required for appropriate pain control could be another measurement of treatment effects. One study (47) examining repeat ILEI, showed that 21% of 120 total participants received only 1 injection, 32% received 2 injections, and 47% received 3 injections. Even 56 of 95 patients (59%) who underwent a second injection required a third injection. Another study examining repeat TFEI showed that only 32.4% of patients who underwent 2 injections required a third injection to accomplish satisfactory pain reduction (33). This might be because ILEI was less efficient at providing pain relief than TFEI and required an increased number of injections.

Serious adverse effects such as neurologic deficits of the lower limb were concerns related to TFEI (48). An intravascular particulate steroid injection or needle penetration could produce radicular artery occlusions by embolus formation and further cause a spinal cord infarction (41,49). TFEI has been more frequently associated with these adverse effects than ILEI because the former approach positioned the needle closer to the radicular artery (41). But these adverse effects occurred mainly in cases in which particulate steroid was administered, and its replacement with a non-particulate steroid could reduce serious side effects (50-53). A Soluble non-particulate steroid reportedly showed comparable and non-inferior clinical outcomes to those of particulate steroid (50,54,55). Thus injection of soluble non-particulate steroid could reduce the fear or concerns of serious side effects and consequently prevent unnecessary avoidance of TFEI (36,37).

This study has several limitations. First, few studies have provided data about functional evaluations; thus, meta-analysis for functional improvement analysis was performed with only 2 articles. Although a high degree of heterogeneity was found in this analysis, the subgroup analysis could not be performed. Second, the supportive strength of this study was weak mainly because the level of evidence was low due to inconsistency from diversities across the studies and imprecision induced by the relatively small number of subjects.

Conclusion

In conclusion, TFEI showed significantly better short-term pain control and modestly favorable outcomes in long-term pain reduction and short- and long-term functional improvement compared with ILEI. However, the evidence level was determined to be low grade. TFEI required no additional cost and resources to ILEI and had equal accessibility or applicability as ILEI. TFEI was preferred to ILEI due to its target specificity, although discomfort during the needle approach more frequently occurred in TFEI. Without the use of particulate steroid, serious side effects could be considerably avoidable. As a result, TFEI could be recommended more frequently than ILEI, but based on low grade evidence, and was weakly recommended.

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Appendix

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