Systematic Review

Comparison of Clinical Efficacy of Transforaminal and Interlaminar Epidural Steroid Injection in Radicular Pain due to Cervical Diseases: A Systematic Review and Meta-analysis

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Background: Cervical epidural steroid injection (ESI) has been used to alleviate axial or radicular pain incurred from various cervical pathologies, including herniated intervertebral disc (HIVD) and spinal stenosis (SS). However, the superiority of the transforaminal ESI (TFESI) method over the interlaminar ESI (ILESI) in terms of clinical effectiveness for the radicular pain is still controversial.

Objectives: This study has compared TFESI and ILESI in terms of clinical effectiveness, such as pain control and functional improvement, as well as the incidence of adverse events in patients with radicular pain secondary to cervical HIVD or SS.

Study Design: A systematic review and meta-analysis.

Setting: Primary clinic and tertiary referral center.

Methods: A literature search was performed using Medline (PubMed), Embase, Cochrane Review, and KoreaMed databases from the studies published until March 2022. After reviewing titles, abstracts, and full texts of 371 studies during the initial database search, 6 studies were included in a qualitative and quantitative synthesis. Data, including pain score, functional score, and adverse events were extracted from 6 studies and were analyzed using a random-effects model to obtain effect size and its statistical significance. Quality assessment and evidence level were established in accordance with the Grading of Recommendations Assessment, Development and Evaluation methodology.

Results: Among 6 studies, including 4 randomized controlled trials (RCTs), only 1 RCT showed that TFESI achieved a significant lower Numeric Rating Scale (NRS-11) at 1 month than ILESI, but no advantage in the NRS-11 at 3 months and the Neck Disability Index at 1 month and 3 months, respectively. Another RCT indicated that ILESI achieved significantly more neck NRS-11 reduction at 1 month and 3 months than TFESI. The other 4 studies revealed no significant difference between the 2 groups. A meta-analysis showed no significance in clinical outcomes, except that ultrasound-guided TFESI featured less intravascular leakage of contrast than ILESI. The level of evidence was low because of inconsistency and imprecision.

Limitations: The feasible clinical heterogeneity from the relatively small number of patients included as well as differences in methodology across the studies.

Conclusions: Comprehensive reviews of selected articles revealed TFESI could not be recommended over ILESI for the sake of a preferential cervical radiculopathy control due to the weak evidential strength.

Key words: Cervical vertebrae, epidural steroid injection, transforaminal, interlaminar, systematic review, meta-analysis

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Cervical epidural steroid injection (ESI) has been used to subside the axial or radicular pain incurred from various cervical pathologies, including herniated intervertebral disc disease (HIVD) and spinal stenosis (SS). This procedure might properly deliver the medications that eliminate inflammatory mediators that irritate the nervous tissues inside the epidural spaces (1-3).

Percutaneous cervical injection techniques, such as interlaminar (ILESI) or transforaminal ESI (TFESI), have been implemented for the treatment of axial and/or radicular pain from various cervical pathologies. Among the nervous tissues contained inside the epidural spaces, the nerve root sheath and the dorsal root ganglion, the optimal target of drug administration for radicular pain alleviation, are generally regarded as the main upper extremity pain generators (2). Hence, TFESI has been conventionally preferred over ILESI (1,3) due to its more direct accessibility closer to these arm pain generators.

However, TFESI methodology has also been fraught with serious complications, such as brainstem or spinal cord embolic infarction, incurred from the intravascular needle or injectate violation or minor adverse events, such as pain or discomfort during the needle access (4-6). While ILESI, a potential substitute, might be vulnerable to a shortcoming of less specific anatomical regional coverage inside the epidural space than TFESI (7).

To the best of our knowledge, there has been no systematic review with meta-analysis that compares clinical effectiveness between TFESI and ILESI in patients with cervical radicular pain. This study has investigated whether TFESI might offer a greater clinical effectiveness, such as more effective pain control or functional improvement than ILESI. It also has compared the proportion of adverse events, such as inadvertent vascular drug uptake and transient pain exacerbation during and after the injection between the 2 techniques.

Methods

Study Selection Criteria

The authors have recruited articles described in Korean or English language that have primarily met the following criteria: patients aged ≥ 18 years, clinical manifestation with upper extremity radicular pain, and the confirmative diagnosis of cervical pathologies, such as HIVD and SS, supported by computed tomography (CT) or magnetic resonance imaging (MRI). Exclusion criteria were a previous history of cervical spinal surgery, inflammatory cervical spinal diseases, cervical myelopathy, tumor, or infectious disease. Among the studies fulfilling these criteria, those that have included the contents regarding the clinical effectiveness or adverse effects after TFESI or ILESI and have provided the comparative results between the 2 procedures were finally selected.

Database Search and Study Extraction

The Medline (PubMed), Embase, Cochrane Review, and KoreaMed databases were searched for articles published until March 2022. We established individual search terms in each database's search engine (Appendix). The search was not restricted to randomized controlled studies (RCTs) and was extended to original articles, including non-RCT and case reports. The decision for an article selection was primarily based on the title and abstract review, followed by full-text screening. Irrelevant studies not fulfilling selection criteria or case reports were excluded. The study screening and data extraction were independently performed by the 2 reviewers (Lee JH and Lee Y), and any discrepancies were resolved by discussion between the 2 reviewers (Lee JH and Lee Y) or with the entire research group. Flow chart demonstrating the process of study selection was illustrated in Fig. 1.

Data Collection

Reference data, such as the diagnosis and number of patients, regimen and dosage of injection, clinical evaluation tools, follow-up period, and comparative results of the clinical outcomes or adverse effects, were extracted from the selected articles. Dichotomous variables, such as the number of patients with pain and functional scores or adverse events, were extracted for the estimation of relative risk ratio. Continuous variables, such as mean and standard deviation of clinical scores, were extracted for the estimation of mean differences. If the standard deviations were not reported, they were calculated from the confidence interval (CI), 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 methodology (8,9). 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 patients and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases (10). The bias for each non-RCT was assessed with the ROB Assessment Tool for Nonrandomized Study (RoBANs); domains were selection of patients, confounding variables, measurement of intervention (exposure), blinding of outcome assessment, incomplete outcome data, and selective reporting (11). All the domains were evaluated as "low risk," "high risk," or "unclear." These evaluations were performed by 2 independent reviewers (Lee JH and Lee Y) and disagreements were resolved by discussion between the 2 reviewers (Lee JH and Lee Y) or with the entire research group.

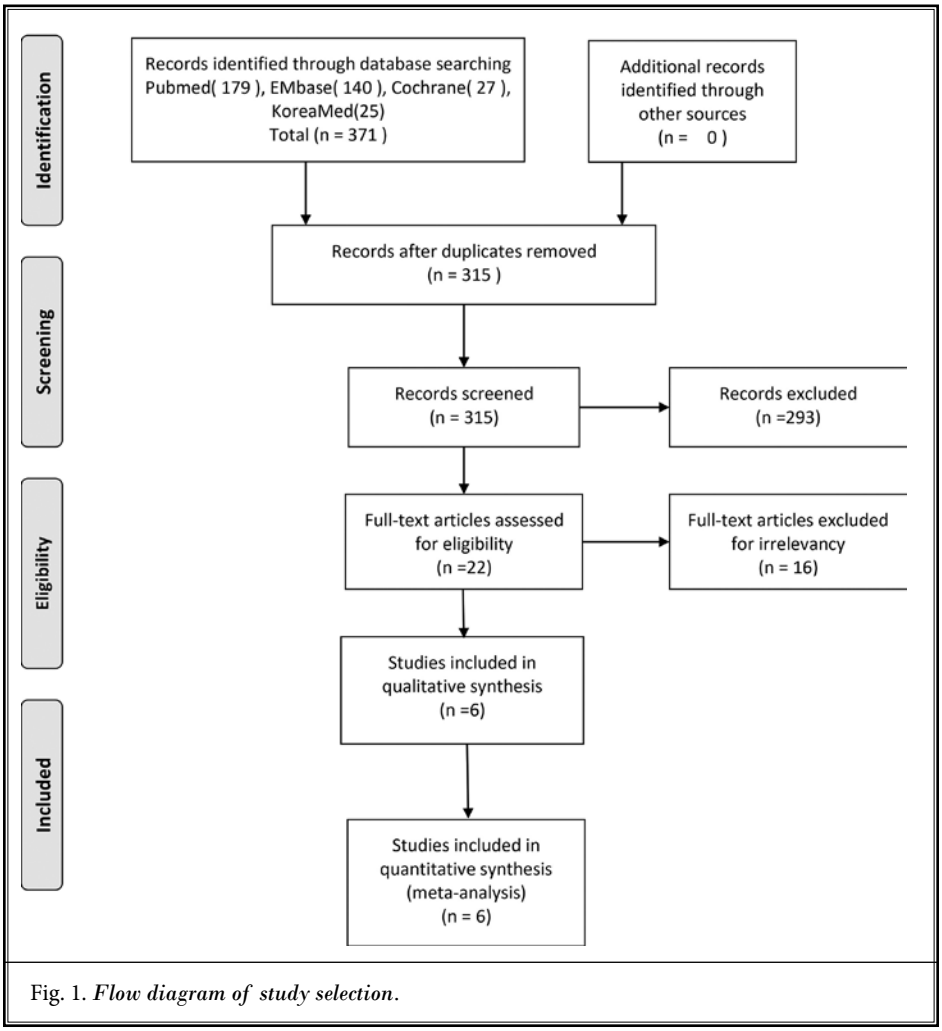

Fig. 1. *Flow diagram of study selection.*

Based on the comprehensive evaluation of inconsistency, indirectness, imprecision, and publication bias in addition to ROB in all studies, the evidence level was determined as high, moderate, low, or very low grade. Besides, the strength of recommendation was determined as strong or weak by comprehensively assessing not only evidence level, but also other factors, such as benefits, risks, burdens, and possibly cost (12). The level of evidence and strength of recommendation were determined by discussion involving the entire research group.

Quality assessment was performed using Interventional Pain Management Techniques –Quality Appraisal of Reliability and ROB Assessment (IPM-QRB) and Interventional Pain Management Techniques – Quality Appraisal of Reliability and ROB Assessment for Nonrandomized Studies (IPM-QRBNR) for RCTs and non-RCTs, respectively. Studies meeting the inclusion criteria with a score of 32-48 were considered as high quality, those with a score of 16-31 were considered as moderate quality, and those with a score < 16 were considered as low quality (13-16).

Meta-analysis

Review Manager software (RevMan version 5.3; The Cochrane Collaboration, Copenhagen, 2014) was used for data analysis. The analysis was performed in 2 categories of clinical outcomes, such as pain control and functional improvement, in 1, 3, and 6 months follow-up and adverse events, such as vascular contrast uptake during injection and transient pain exacerbation after injection. Tests of heterogeneity were performed using I^2 statistics. The category with I^2 values of 50% or more was considered to have a high

degree of heterogeneity. A random-effects model was applied to obtain effect size and its statistical significance because it was assumed that the patients and methods of the 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% 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 has initially recruited 371 articles. After the exclusion of the 56 duplicates, 315 potentially eligible articles have remained. After the title and abstract screening, 293 articles were excluded due to the lack of the inclusion criteria fulfillment. Thus, the remaining 22 articles were retrieved for full-text analysis, of which 16 were subsequently excluded because of the irrelevance to the scheme of this analysis.

Ultimately, 4 RCTs and 2 non-RCTs (retrospective comparative studies) (17-22) were included in this study. All 6 articles included patients with radicular upper limb pain who were diagnosed as cervical HIVD or SS by clinical and radiological evaluation, including CT or MRI. The pain intensity was measured in the selected studies using the Numeric Rating Scale (NRS-11) or the Verbal Numeric Scale (VNS). The functional measurement tool used in the selected studies was the Neck Disability Index (NDI). The Medication Quantification Scale (MQS), an evaluation tool for quantifying medication regimen use (23), was used to assess the requirement for pain medication after treatment in one study (20,22). Five-point Likert scale and Patient Global Impression of Change (PGIC) response was used to evaluate the degree of patients' satisfaction for treatment (17,18,20). The grade of the contrast flow was analyzed according to the extension area of contrast flow visualized by intraoperative fluoroscopy (C-arm) in one study (17). Four studies (17,19,21,22) indicated the number of adverse events, including vascular contrast uptake, transient pain exacerbation, vasovagal syncope, or headache. The follow-up period was variable across the studies ranging from 2 weeks to 12 months (Table 1).

Clinical Outcome Analysis

Among the 4 RCTs ultimately selected, 2 studies have implemented the parasagittal approach during ILESI. Choi et al (17) showed that although ventral contrast flow was more frequently obtained during the parasagittal ILESI than TFESI, there was lack of significance in serial clinical outcome differences, such as the NRS-11 and the 5-point Likert scale at 2 weeks, 1 month, and 3 months. Sim et al (22) showed that TFESI achieved significantly lower NRS-11 at 1 month, but no advantage in NRS-11 at 3 months and NDI and MQS at one month and 3 months. The other 2 studies used a catheter-induced approach during ILESI. McCormick et al (20) have indicated that ILESI accomplished better clinical result only in 50% or more neck NRS-11 reduction at one month and 3 months than TFESI. Otherwise, there was no significant difference in 50% or more neck NRS-11 reduction at 6 months, as well as 50% or more arm NRS-11 reduction, 30% or more NDI reduction, MQS, and PGIC at 1, 3 and 6 months between ILESI and TFESI (20). The other study (18) conducted using same design as McCormick et al (20) with the follow-up period extension up to 12 months found no significant different clinical results in all parameters .

In 2 non-RCTs, one study (19) compared ILESI under fluoroscopy with TFESI under fluoroscopy, as well as ultrasonography (US) in terms of NDI and VNS at 1, 3, and 6 months. The other study (21) compared NDI and VNS at 1, 3, and 6 months between ILESI under fluoroscopy with TFESI under US. Both studies concluded no significant different clinical results between the 2 techniques. Comprehensively, TFESI was neither significantly inferior nor superior to ILESI in the treatment of patients with cervical radicular pain (Table 1).

Quality Assessment

The ROB of all selected studies was illustrated in Fig. 2 (a: RCT, b: non-RCT). Except for one RCT (22) that was assessed as high risk, the other RCTs were assessed as low risk in random sequence generation domain. The most frequently biased domain was blinding of patients and personnel, in which all 4 RCTs (17,18,20,22) were rated as high risk because blinding was not possible given the inherent different characteristics of the 2 techniques. In allocation concealment, 3 RCTs (17,18,20) were rated as unclear because they did not adequately describe the procedure for allocation concealment. One RCT (17) (Fig. 2a) was rated as unclear in the domain of blinding of outcome assessment because they did not clarify whether the clinical evaluation was conducted by an assessor who was blind or not involved in the process of patient selection and treatment. Two non-RCTs (19,21)

Table 1. *Evidence table.*

Author (y)	Design	Patients	Intervention	Evaluation	Results	Complication
Choi et al (2015) (17)	RCT	HIVD SS	n = 31F-IL, 5 mL of 0.18% ropivacaine and dexamethasone 5 mg (modified paramedian approach) n = 31 F-TF, 2 mL of 0.18% ropivacaine and dexamethasone 5 mg	Contrast flow, NRS-11, 5-point Likert scale at 2 weeks, 1 mo and 3 mo	Contrast flow: F-IL > F-TF more ventral epidural space and more than 1 level than needle entry level NRS-11, 5- point Likert scale: no significant difference	Vascular uptake: 0 F-IL, 12 F-TF Discomfort : 7 F-IL < 21 F-TF
Sim et al (2021) (22)	RCT	Cervical Pathology	n = 35 F-IL (parasagittal approach), 5 mL mixture of 5 mg dexamethasone and 1% lidocaine n = 38 F-TF, 3 mL mixture of 5 mg of dexamethasone and 1% lidocaine	NRS-11, NDI, MQS, and successful responders at 1 and 3 mo	NRS-11 1 mo: F-TF > F-IL NRS-11 3 mo: no significant difference NDI & MQS at 1 & 3 mo: no significant difference	Vascular contrast uptake, 7 F-TF, 0 F-IL Temporary pain, 5 F-TF: 2 F-IL
McCormick et al (2020) (20)	RCT	Cervical Pathology	n = 57 F-IL, 1 mL of triamcinolone acetonide (40 mg) and 0.5 mL of 1% lidocaine (catheter induced approach) n = 60 F-TF, 1 mL of dexamethasone sodium phosphate (10 mg) and 0.5 mL of 1% preservative-free lidocaine	> 50% NRS-11 reduction, > 30% NDI reduction, MQS, PGIC response at 1, 3 & 6 mo	F-IL > F-TF: > 50% dominant NRS-11 reduction at 1 mo, > 50% neck NRS-11 reduction at 1 & 3 mo No significant difference in other parameters between 2 groups	
Conger et al (2021) (18)	RCT	Cervical Pathology	n = 57 F-IL, 1 mL of triamcinolone acetonide (40 mg) and 0.5 mL of 1% lidocaine (catheter induced approach) n = 60 F-TF, 1 mL of dexamethasone sodium phosphate (10 mg) and 0.5 mL of 1% preservative-free lidocaine	> 50% NRS-11 reduction, > 30% NDI reduction, MQS, PGIC response at 12 mo	No significant difference in all parameters between 2 groups	
Jang et al (2020) (19)	Retrospective Comparative Study	HIVD SS	n = 41, F-IL n = 37, F-TF n = 44, U-SNRB All groups were treated with 2 mL of dexamethasone (10 mg) and 1 mL of 0.5% lidocaine	NDI VNS at 1, 3, 6 mo	No significant difference among 3 groups	Vasovagal reactions : 5 U-SNRB, 3 F-IL, 4 F-TF, Transient headache 3 U-SNRB, 3 F-IL, 4 F-TF, Transient pain exacerbation 2 U-SNRB, 2 F-IL, 3 F-TF, Intravascular contrast spread 0 U-SNRB, 7 F-IL, 8 F-TF
Park et al (2019) (21)	Retrospective Comparative Study	HIVD SS	n = 61, F-IL n = 51, U-SNRB All groups were treated with 2 mL of dexamethasone (10 mg) and 1 mL of 0.5% lidocaine	NDI VNS at 1, 3, 6 mo	No significant difference between 2 groups	Vasovagal reactions : 4 U-SNRB, 3 F-IL Transient headache, 4 U-SNRB, 3 F-IL Transient pain exacerbation, 3 U-SNRB, 4 F-IL, 3 F-TF Intravascular contrast spread 0 U-SNRB, 7 F-IL

Abbreviations: RCT: randomized controlled trials; HIVD: herniated intervertebral disc; SS: spinal stenosis; F-IL, fluoroscopy-guided interlaminar; F-TF, fluoroscopy-guided transforaminal; NRS-11, Numeric Rating Scale; NDI, Neck Disability Index; MQS, Medication Qualification Scale; PGIC, Patient Global Impression of Change; U-SNRB, ultrasound-guided selective nerve root block; VNS, Verbal Numeric Scale.

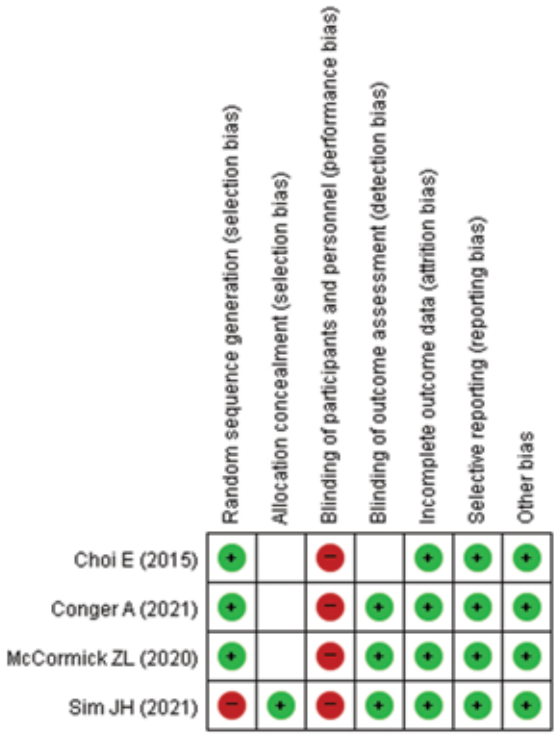

Fig. 2. *Quality assessment for extracted studies (a) ROB for randomized controlled study, and (b) RoBANs for nonrandomized study. (Green color: low ROB, red color: high risk, white color: unclear ROB.)*
ROB, risk of bias; RoBANs, ROB Assessment Tool for Non-randomized Study.

were all rated as high risk in the domain of selective reporting because they did not reveal the results of "patient satisfaction scores" using a 5-grade scale that were mentioned in the study method (Fig. 2b). Of 40 domains across all studies, 29 domains (72.5%) were determined as low risk; thus, the overall ROB was considered low. A discrepancy between reviewers was found in 8 of total 40 domains (20%) at first. After the discussion, all 8 discrepancies were resolved.

Quality assessment results of IPM-QRB for RCT and IPM-QRBNR for non-RCTs were presented in Tables 2 and 3, respectively. All RCTs and non-RCTs were rated as high quality because the scores of all studies were measured to be 32 or more.

Meta-analysis

Meta-analysis was mainly performed in terms of pain and functional score, sufficiently provided for analysis across the studies; whereas, other parameters including the 5-point Likert scale, MQS, and PGIC were frequently unavailable. Successful pain reduction or functional improvement for assessing effect size by relative risk ratio were defined in an individual study after the significant decrement of pain score, such as NRS-11 or VNS, or functional score, such as NDI, from the baseline after injection treatment. In addition, adverse events, such as the proportion of vascular uptake of contrast during injection and transient pain exacerbation after injection, were included in meta-analysis. From the study (19) comparing 3 groups, 2 comparisons between fluoroscopy-guided interlaminar (F-IL) approach vs fluoroscopy-guided transforaminal and US-guided transforaminal approaches were extracted and analyzed, respectively.

Pain Control at One Month

Two studies reported the number of patients with successful pain reduction at one month after ILESI and TFESI (19,21); thus, enabling the measurement of effect size by relative risk ratio. Overall, 55 among 98 cases treated with TFESI and 46 among 92 cases treated with ILESI accomplished successful pain reduction. While significant difference between TFESI and ILESI was not found (P = 0.47), the data showed slightly favorable trends toward TFESI with an estimated relative risk ratio of 0.87 (95% CI: 0.60-1.26). No significant heterogeneity was observed in dichotomous data analysis (I^2 = 47%) (Fig. 3a).

Four comparisons from 3 studies presented the continuous pain score data and were included in the analysis of effect size by mean difference (18,20,21). The overall mean difference was measured as 0.32 (95% CI: -0.33-0.97) that supported the superiority of ILESI, but not to the degree of statistical significance (P = 0.34). A high degree of heterogeneity was observed in continuous data analysis (I^2 = 86%) (Fig. 3b).

Pain Control at 3 Months

Two studies have provided the number of patients with a successful pain reduction at 3 months that could be available for an estimation of relative risk ratio(19,21). A successful pain reduction was found in 49 out of the 98 patients who underwent TFESI vs 51 out of the 92 for ILESI. ILESI achieved a higher portion of the effective pain control than TFESI with an overall estimated effect size of 1.10 (95% CI, 0.84-1.43) with no statistical significance (P = 0.50). No heterogeneity was found (I^2 = 0%) (Fig. 3c).

Continuous data of pain measurement scores were available in 4 comparisons from 3 studies (18,20,21).

Table 2. *Methodological quality assessment utilizing IPM-QRB for randomized studies.*

	Choi et al 2015 (17)	Conger et al 2021(18)	McCormick et al 2020 (20)	Sim JH 2021(22)
I. TRIAL DESIGN AND GUIDANCE REPORTING				
1. CONSORT or SPIRIT	3	3	3	3
II. DESIGN FACTORS				
2. Type and Design of Trial	2	2	2	2
3. Setting/Physician	2	2	2	1
4. Imaging	3	3	3	3
5. Sample Size	2	3	3	2
6. Statistical Methodology	1	1	1	1
III. PATIENT FACTORS				
7. Inclusiveness of Population	2	0	0	2
8. Duration of Pain	0	1	1	0
9. Previous Treatments	2	2	2	2
10. Duration of Follow-up With Appropriate Interventions	1	2	2	1
IV. OUTCOMES				
11. Outcomes Assessment Criteria for Significant Improvement	2	2	2	2
12. Analysis of all Randomized Patients in the Groups	2	1	1	2
13. Description of Drop-Out Rate	1	0	0	1
14. Similarity of Groups at Baseline for Important Prognostic Indicators	2	2	2	2
15. Role of Co-Interventions	1	1	1	1
V. RANDOMIZATION				
16. Method of Randomization	2	2	2	1
VI. ALLOCATION CONCEALMENT				
17. Concealed Treatment Allocation	0	0	0	2
VII. BLINDING				
18. Patient Blinding	0	0	0	0
19. Care Provider Blinding	0	0	0	0
20. Outcome Assessor Blinding	0	1	1	1
VIII. CONFLICTS OF INTEREST				
21. Funding and Sponsorship	2	1	1	2
22. Conflicts of Interest	3	3	3	3
Score	33	32	32	34

Abbreviation: IPM-QRB: Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment.

The overall mean difference was calculated as -0.02 (95% CI: -0.39-0.36), which favored TFESI, but this did not show statistical significance (P = 0.94). No heterogeneity was found (I^2 = 0%) (Fig. 3d).

Pain Control at 6 Months

Only continuous data were available as to pain measurement score at 6 months in 3 comparisons from 2 studies (18,20). The overall mean difference was calculated as -0.16 (95% CI: -0.49-0.16), which supported TFESI, but this did not show statistical significance (P = 0.33). No heterogeneity was found (I^2 = 0%) (Fig. 3e).

Functional Improvement at One Month

Two studies presented dichotomous data of functional score at 1 month and were available in the analysis of effect size by risk ratio (19,21). Although the 2 studies showed contradictory results, the overall mean difference was estimated as 0.97 (95% CI: 0.55-1.71), which slightly favored TFESI without statistical signifi-

Table 3. *Methodological quality assessment utilizing IPM-QRBNR for nonrandomized studies.*

	Jang et al 2020 (19)	Park et al 2019 (21)
1. Study Design Guidance and Reporting	4	4
2. Study Design and Type	1	1
3. Setting/Physician	2	2
4. Imaging	3	3
5. Sample Size	1	1
6. Statistical Methodology	2	2
7. Inclusiveness of Population	4	4
8. Duration of Pain	1	1
9. Previous Treatments	2	2
10. Duration of Follow-up With Appropriate Interventions	2	2
11. Outcomes Assessment Criteria for Significant Improvement	4	4
12. Description of Drop-Out Rate	1	1
13. Similarity of Groups at Baseline for Important Prognostic Indicators	2	2
14. Role of Co-Interventions	2	2
15. Method of Assignment of Patients	3	4
16. Funding and Sponsorship	2	2
Score	36	37

Abbreviation: IPM-QRBNR: Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment for Non-randomized Studies.

cance (P = 0.91). A high degree of heterogeneity was revealed (I^2 = 79%) (Fig. 4a).

Four comparisons from 3 studies were available in the analysis of effect size by the mean difference for functional improvement at 1 month (18,20,21). The estimated overall mean difference was calculated as 0.92 (95% CI: -0.63-2.47), which favored ILESI without statistical significance (P = 0.25). The degree of heterogeneity was low (I^2 = 36%) (Fig. 4b).

Functional Improvement at 3 Months

Two studies were available in the measurement of effect size by relative risk ratio of successful functional improvement at 3 months (19,21). The 59 among the 98 cases treated with TFESI and 51 among the 92 cases treated with ILESI accomplished successful functional improvement. While significant difference between TFESI and ILESI was not found (P = 0.51), the data showed slightly favorable trends toward TFESI with an estimated relative risk ratio of 0.90 (95% CI: 0.67-1.22). No significant heterogeneity was observed in dichotomous data analysis (I^2 = 36%) (Fig. 4c).

Four comparisons from 3 studies were available in the analysis of effect size by the mean difference for functional improvement at 3 months (18,20,21). The estimated overall mean difference was calculated as 0.62 (95% CI: -0.69-1.93), which favored ILESI without statistical significance (P = 0.36). The degree of heterogeneity was not to be significantly high (I^2 = 29%) (Fig. 4d).

Functional Improvement at 6 Months

Only continuous data were available in terms of functional measurement score at 6 months. Three comparative data from the 2 studies provided the value of 0.18 (95% CI: -0.70-1.06) (18,20), the effect size measured by the mean difference, which favored ILESI without statistical significance (P = 0.69). No heterogeneity was not found (I^2 = 0%) (Fig, 4e).

Pain Control and Functional Improvement at One Month

Four comparisons from 3 studies presented the dichotomous data for measurement of effect size by relative risk ratio about satisfying successful pain control and functional improvement simultaneously at 1 month (18,20,21). The 129 among the 170 cases treated with TFESI and 132 among the 178 cases treated with ILESI accomplished successful pain control and functional improvement simultaneously at 1 month. While the significant difference between TFESI and ILESI was not found (P = 0.68), the data showed slightly favorable trends toward TFESI with an estimated relative risk ratio of 0.98 (95% CI: 0.87-1.10). No heterogeneity was observed in dichotomous data analysis (I^2 = 0%) (Fig. 5a).

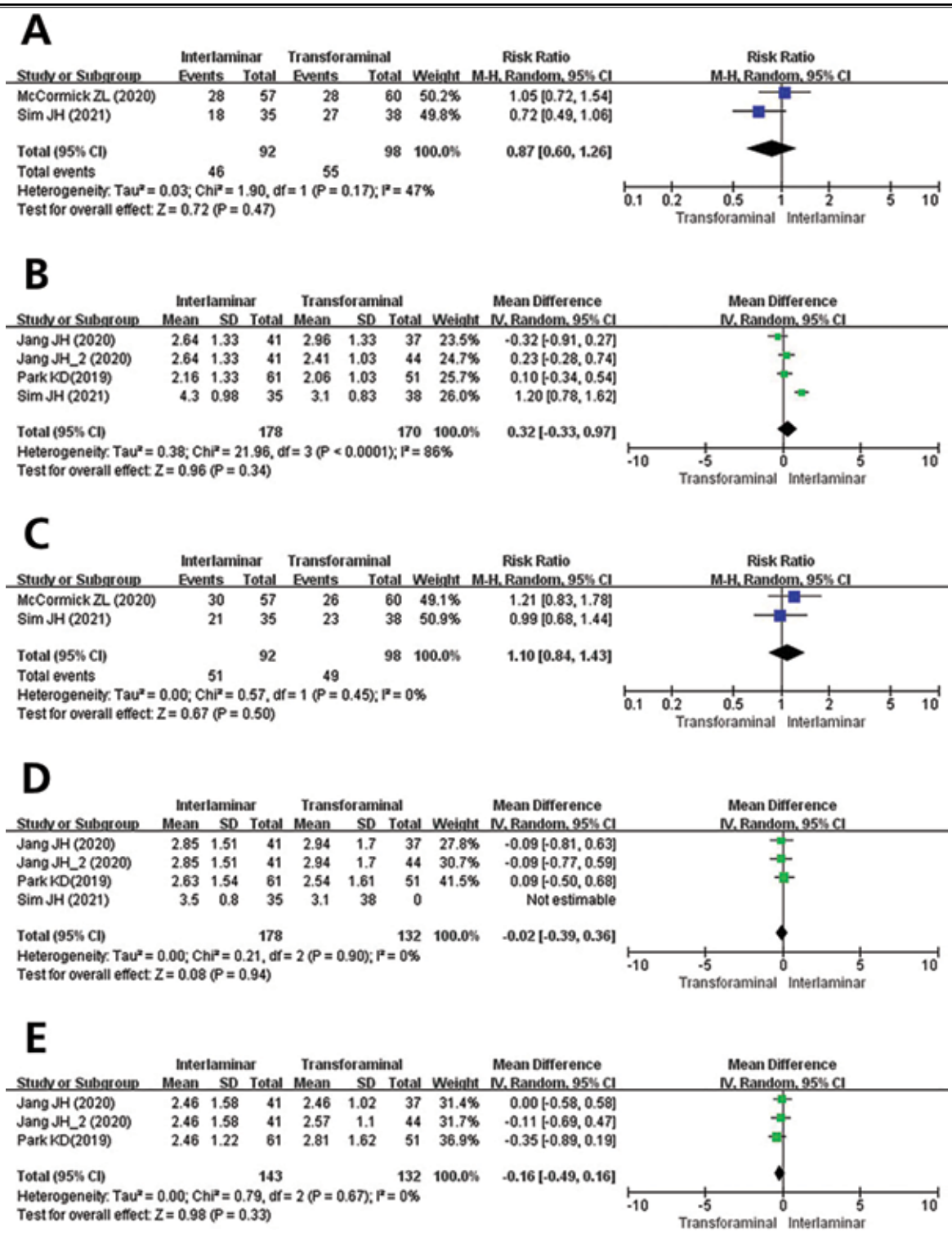

Fig. 3. *Forest plot of comparison (a) relative risk of pain control at 1 month, (b) mean difference of pain control at 1 month, (c) relative risk of pain control at 3 months, (d) mean difference of pain control at 3 months, and (e) mean difference of pain control at 6 months.*
JANG JH: comparison between fluoroscopy-guided TFESI and ILESI. JANG JH2: comparison between ultrasound-guided TFESI and fluoroscopy-guided ILESI. ESI, epidural steroid injection; TFESI, transforaminal ESI; ILESI, interlaminar ESI.

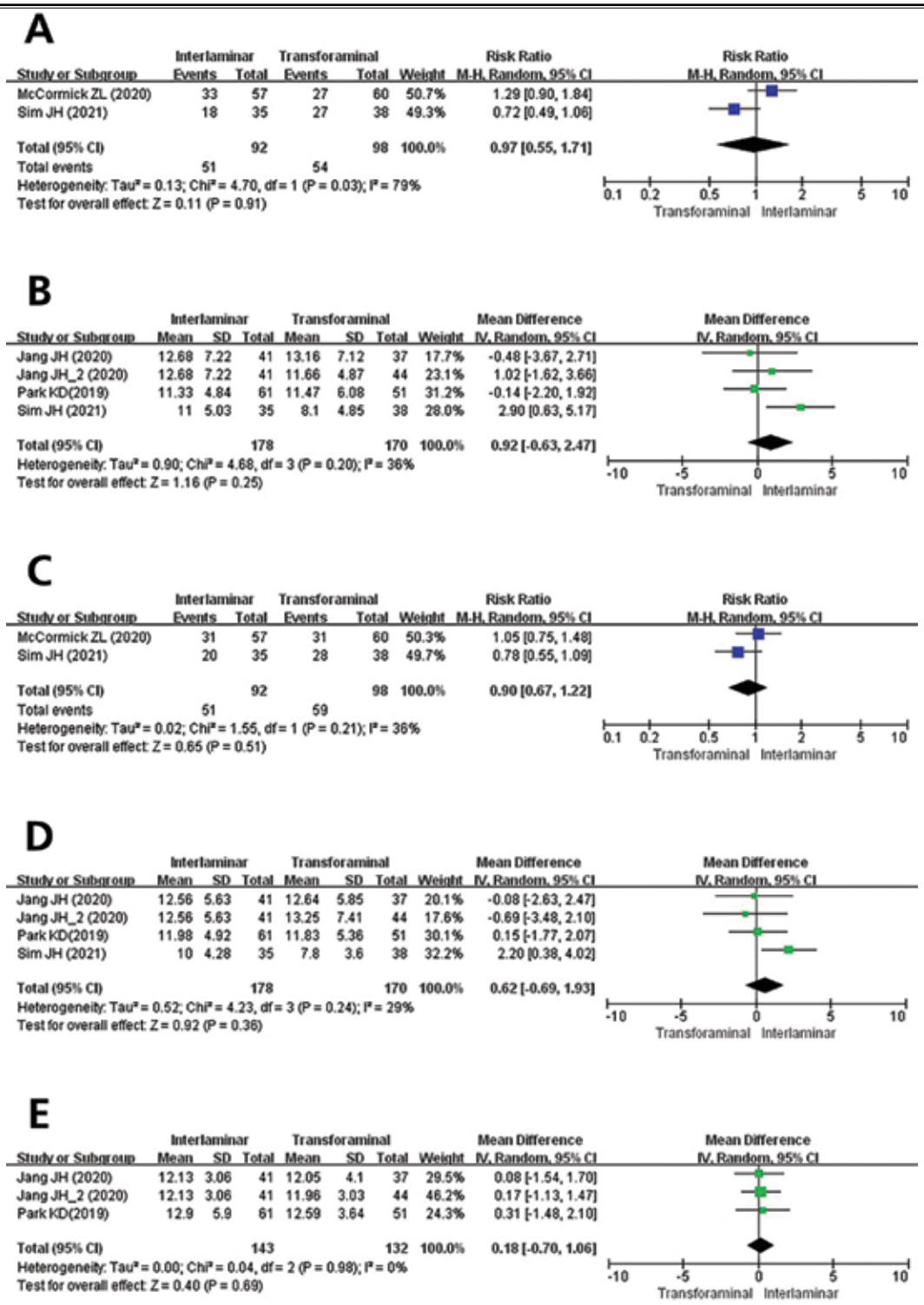

Fig. 4. *Forest plot of comparison (a) relative risk of functional improvement at 1 month, (b) mean difference of functional improvement at 1 month, (c) relative risk of functional improvement at 3 months, (d) mean difference of functional improvement at 3 months, and (e) mean difference of functional improvement at 6 months.*
JANG JH: comparison between fluoroscopy-guided TFESI and ILESI. JANG JH2: comparison between ultrasound-guided TFESI and fluoroscopy-guided ILESI. ESI, epidural steroid injection; TFESI, transforaminal ESI; ILESI, interlaminar ESI.

Pain Control and Functional Improvement at 3 Months

Four comparisons from 3 studies were available in the measurement of effect size by relative risk ratio of successful pain control and functional improvement at 3 months (18,20,21). These successful results were observed in 108 among the 170 cases in TFESI and 107 among the 178 cases in ILESI. This showed slightly favorable trends toward TFESI with an estimated relative risk ratio of 0.94 (95% CI: 0.80-1.11), but without statistical significance (P = 0.48). No heterogeneity was observed (I^2 = 0%) (Fig. 5b).

Pain Control and Functional Improvement at 6 Months

Three comparisons from 2 studies presented dichotomous data of successful pain control and functional improvement at 6 months and were available in the analysis of effect size by relative risk ratio (18,20). These successful results were achieved in 72 among the

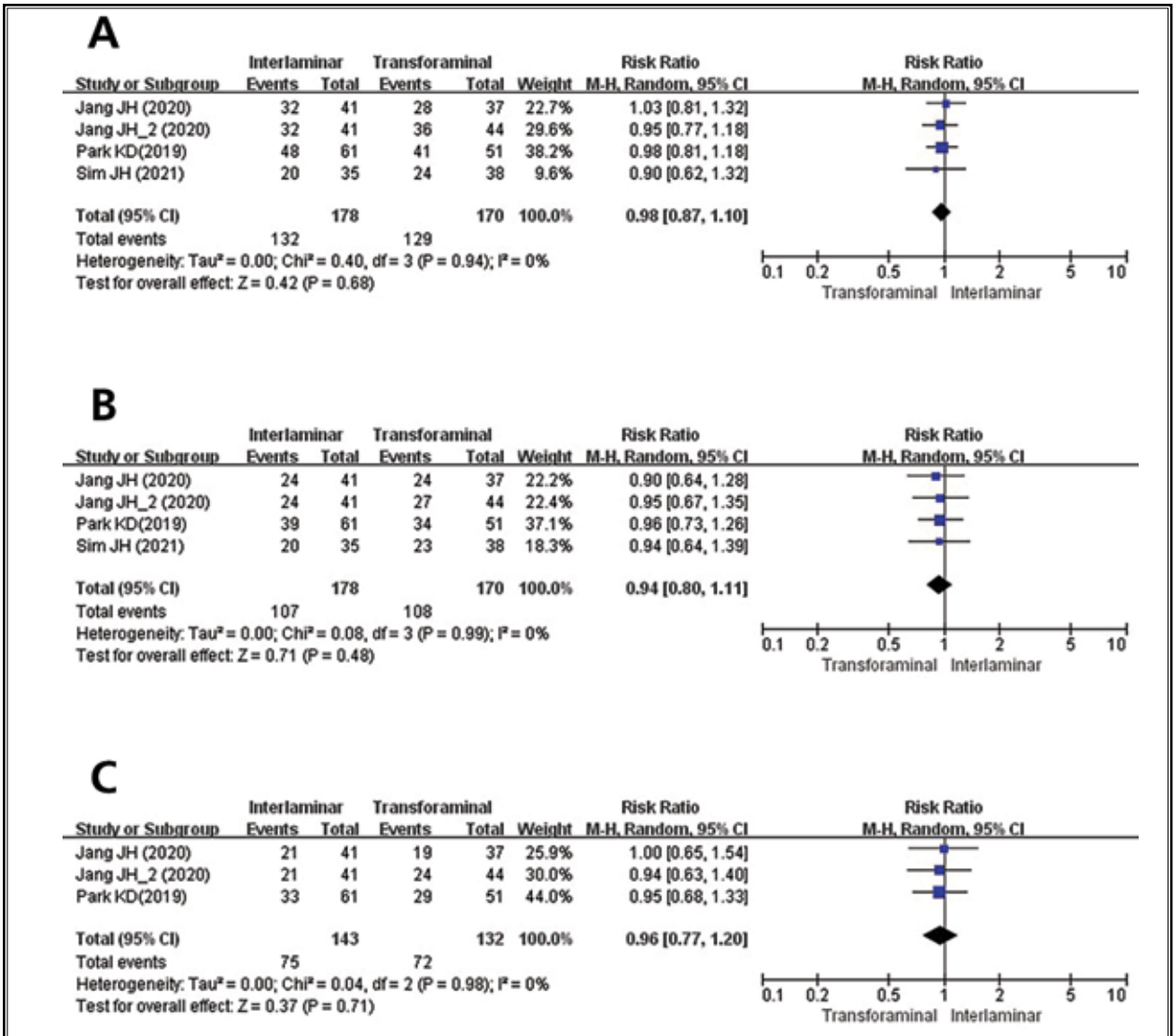

Fig. 5. *Forest plot of comparison (a) relative risk of pain control and functional improvement at 1 month, (b) relative risk of pain control and functional improvement at 3 months, and (c) relative risk of pain control and functional improvement at 6 months.* JANG JH: comparison between fluoroscopy -guided TFESI and ILESI. JANG JH2: comparison between ultrasound-guided TFESI and fluoroscopy-guided ILESI. ESI, epidural steroid injection; TFESI, transforaminal ESI; ILESI, interlaminar ESI.

132 cases in TFESI and 75 among the 143 cases in ILESI. This showed slightly favorable trends toward TFESI with an estimated relative risk ratio of 0.96 (95% CI: 0.77-1.20), but without statistical significance ($P = 0.71$). No heterogeneity was observed in dichotomous data analysis ($I^2 = 0\%$) (Fig, 5c).

Vascular Uptake of Contrast During Injection

The dichotomous data of intravascular contrast spread during the injection for the analysis of effect size by the relative risk ratio were available in 5 comparisons from 4 studies (16,18,20,21). An inadvertent intravasation of contrast was observed in 27 among the 201 cases in TFESI and 21 among the 209 cases in ILESI. This suggested the insignificant trends toward TFESI with an estimated relative risk ratio of 0.84 (95% CI: 0.12-6.12) ($P = 0.87$).

Contradictory result with high heterogeneity across the studies was found ($I^2 = 74\%$); therefore, subgroup analysis was conducted after division of the studies into 2 subgroups depending on whether TFESI was performed under the guidance of fluoroscopy or US. The 2 studies of US subgroup showed that no case of vascular uptake was observed among the 95 US-guided TFESI; whereas, 14 cases among the 102 fluoroscopy-guided ILESIs. US-guided TFESI showed significantly lower proportion of vascular uptake than fluoroscopy-guided ILESI with an effect size of 14.22 (95% CI: 1.92-105.61) with statistical significance ($P = 0.009$). The level of heterogeneity was $I^2 = 0\%$. The other fluoroscopy subgroup consisting of 3 studies revealed vascular uptake was found in 27 cases among the 106 TFESIs and 7 cases among the 107 ILESIs. Fluoroscopy-guided TFESI showed trends toward higher proportion of vascular uptake than ILESI with an effect size of 0.17 (95% CI: 0.01-1.99) without statistical significance ($P = 0.16$). A significant heterogeneity was observed ($I^2 = 75\ \%$) (Fig. 6a).

Transient Pain Exacerbation After Injection

Five comparisons from 4 studies reported the number of patients with transient pain exacerbation after ILESI and TFESI injections (16,18,20,21); thus, enabling the measurement of effect size by relative risk ratio. Overall, transient pain was found in 34 among the 201 cases treated with TFESI and 17 among the 209 cases treated with ILESI. While significant difference was not found ($P = 0.08$), the data showed considerable trends toward TFESI with an estimated relative risk ratio of 0.52 (95% CI: 0.25-1.07). No significant heterogeneity was observed in dichotomous data analysis ($I^2 = 24\%$) (Fig. 6b).

Level of Evidence and Strength of Recommendation

The ROB was considered low as previously mentioned. Directness was not considered problematic because all included studies directly compared TFESI with ILESI. Publication bias was not assessed because fewer than 10 studies were included in each meta-analysis. However, the level of evidence was considered as low grade due to inconsistency and imprecision. The consistency was validated to expose the serious problems of the decent degree of diversity prevalence inside the treatment protocols, such as different types or dose of steroid across the studies. Similarly, the degree of heterogeneity, in part, of results during this meta-analysis, reduced the level of consistency. The degree of precision was also evaluated to be serious because all studies included fewer than 150 patients and CIs of risk ratio were ranged beyond the range 0.75-1.0 or 1.0-1.25, in part, of this meta-analysis.

Conversely, TFESI showed no significant clinical beneficiary over ILESI in the treatment of cervical radicular pain from cervical pathologies, despite the assumptions of more anatomical accuracy or methodological specificity for TFESI performance, considering the higher predilection of nerve root involvement than epidural space during the cervical radiculopathy (2). Although TFESI under US had the advantage of reducing the possibility of intravascular spread over ILESI under fluoroscopy, TFESI under fluoroscopy showed no significant difference in intravascular uptake rate from ILESI and was more frequently involved with postinjective transient pain aggravation than ILESI, although without statistical significance. Even though TFESI did not require additional cost, resources, or devices compared to ILESI, there was another greater concern about more serious adverse effects associated with TFESI, including radicular artery embolism and consequent spinal cord or brainstem infarct (4-6).

After all these analyses and considerations, the authors have concluded that TFESI could not be preferentially recommended over ILESI for the sake of more optimal cervical radiculopathy control based on the weak evidential strength.

Discussion

Radicular pain might incur from the inflammation over the nerve root sheath or dorsal root ganglion rather than epidural space in the patients with cervical or lumbosacral disc diseases (24,25). Thus, in contrast to the axial neck or back painful condition, TFESI is

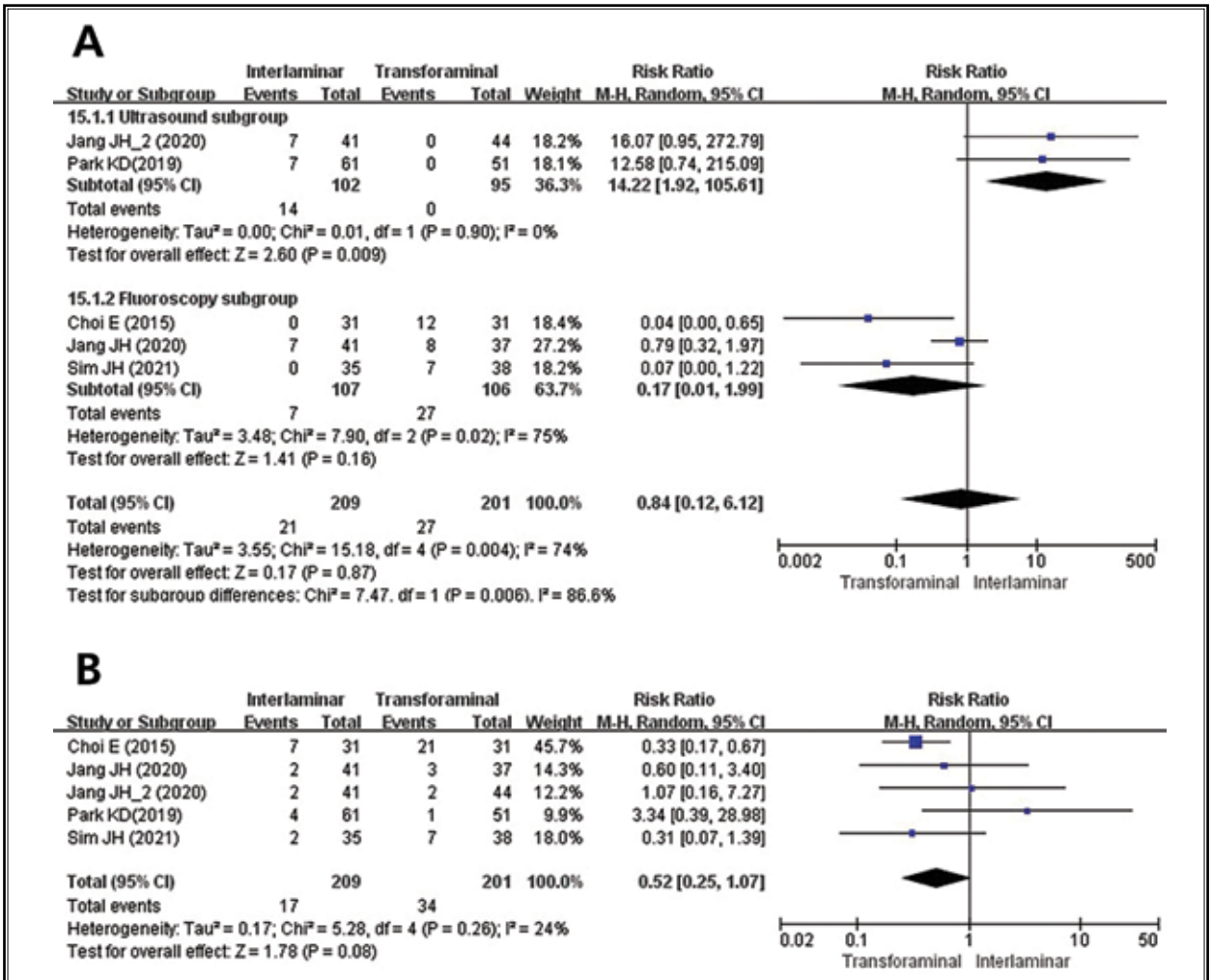

Fig. 6. *Forest plot of comparison (a) relative risk of vascular uptake of contrast during injection, and (b) relative risk of transient pain exacerbation after injection.*
JANG JH: comparison between fluoroscopy -guided TFESI and ILESI. JANG JH2: comparison between ultrasound-guided TFESI and fluoroscopy-guided ILESI. ESI, epidural steroid injection; TFESI, transforaminal ESI; ILESI, interlaminar ESI.

preferred by pain practitioners for the radicular pain situation due to the feasibility of more specific injective formula delivery onto the targeted pain generative region than ILESI (26).

For the lumbosacral radiculopathies, many reviews or comparative studies have reported that TFESI would be more advantageous over ILESI (25,27,28). But for the cervical radiculopathies, there is paucity of comparative studies or no systemic review with meta-analysis that might properly support the evidence that TFESI could still be preferred over ILESI for the sake of optimal radicular pain control as in lumbosacral series. Six articles (17-19,20-22) (Table 1) that have investigated the comparative clinical effectiveness of TFESI with ILESI from the patients with cervical radicular pain were discretely selected for review during this analysis. But the result showed no significant difference in terms of pain reduction or functional improvement between the 2 techniques (Table 1). Moreover, TFESI was not advantageous over ILESI in terms of adverse events incidence, such as intravasation and pain exacerbation. This systemic review with meta-analysis did not provide the clinically implicative evidence to support the superiority of TFESI over ILESI.

TFESI might be more vulnerable to the intravasation or vascular insult than ILESI by needle due to its

direct placement inside the neural foramen that is abundant with neurovascular structures. Despite the lack of statistical significance, fluoroscopy-guided TFESI showed trends toward higher proportion of vascular contrast leakage than fluoroscopy-guided ILESI. The US might be an alternative that provide the safer, alternative route to stay away from these neurovascular structures and subsequently to avoid intravascular injection during this TFESI by properly visualizing the crucial structures during needle advancement and injection. In addition, US might be advantageous both to the patients and physician from lacking the radiation exposure, as well as providing the real-time image projections of neurovascular structures during the procedure (19).

But US beam lacks the bony structure penetration capacity and offers a limited visualization to the underlying structures (29). Also, the mere capacity to project the cross-sectional imaging only might subsequently lead to a lower capacity to detect the actual intravascular leak for US. Consequently, the lowered incidence of intravasation after the implementation of the US instead of fluoroscopy in the past reference could merely have reflected the underestimated, but not the actual incidence (30,31). Moreover, US-guided injection was further criticized by the higher probability of the limited access before the neural foramen and subsequent lower portion of the drug delivery (about 30% of the injected drug) inside the neural foramen (30,32). Therefore, it is still controversial that US could still be implemented as a substitute for fluoroscopy or be applied as a first choice of procedural real-time guidance during TFESI.

The current analysis also demonstrated that TFESI preferentially incur the transient pain exacerbation after injection. This might be attributed to the inherent nerve root provocative, methodological glitch for TFESI due to its closer approximation of the needle trajectory underneath the exiting nerve root inside the neural foramen (17,33).

The proven lack of superiority for TFESI in terms of clinical effectiveness or radicular pain control over ILESI during this analysis might be assumed as a paradox, considering the technical aspect of TFESI at the closer proximity to the affected nerve root. Several hypotheses might back up this result.

Firstly, ILESI conducted in the selected articles have used parasagittal- or catheter-induced injection. Parasagittal ILESI had already been proven to be successful in concentrating the injected formula both over the ventral epidural space, as well as around the exiting nerve root as effectively TFESI for the patients with lumbosacral radicular pain, which subsequently had yielded the comparable or better clinical consequences (34-36). Also in cervical radiculopathy, it was reported that the parasagittal approach produced more effective drug delivery onto the ipsilateral ventral epidural spaces and around nerve root than midline ILESI and TFESI (17,37,38). This characteristic of more target specific ILESI helped to overcome the limitation of conventional midline approach of ILESI and consequently produced compatible clinical outcomes to TFESI.

Secondly, the reported "radicular pain" or "radiculopathy" from the cited references might be the simple reflection of patients' subjective description, a radiating pain dominantly spreading down to distal part of the upper limb, instead of the genuine, pathologically defined radiating pain resulted from nerve root compression or irritation. But a referred pain from sinuvertebral nerves innervating disc, dura mater, epidural space, or even muscle could also be manifested as distal arm spread, mimicking the radicular nature (39-43). Moreover, this radicular pain might not obey the typically expected, geographical pattern that is specifically innervated by the affected, correspondent nerve root due to the feasible significant variabilities and interconnections between the nerve roots dermatomes (44-46). Therefore, the isolation of the genuine radiculopathy from this obscure, referred pain is frequently unfeasible. This phenomena sometimes enables ILESI to be more efficient than TFESI in terms of the unintended, but turned out to be a referred pain management instead of originally misdiagnosed radiculopathy.

Thirdly, the HIVD or SS main pathology, which caused radicular pain by compressing or irritating the nerve root, might also have another pain generating mechanism, such as annular tear, dura irritation, and epidural inflammation, which lead to axial referred pain (42,43,47,48). Thus, the patients with radicular pain might be comorbid with axial neck and/or interscapular discomforts that have originated from the pain sources other than the nerve root (2). In this regard, ILESI, which enables the injected formula delivery onto a more extensive area inside the epidural space and nerve roots, might be more advantageous than TFESI. The ability to cover the nonspecific, but wider pain, susceptible region could overcome the disadvantage of ILESI if patients shared axial pain components in addition to the radicular pain.

However, TFESI should not be considered to be a valueless treatment strategy in the patients with cervical radicular pain simply based on these meta-analysis results. TFESI could be a more useful method in more obvious radicular pain from foraminal pathology (49). Aside from therapeutic utility, TFESI has been used as diagnostic injection as additives to clinical and radiological findings to help for preoperative investigation (7).

This study has several limitations. First, RCT and non-RCT were included in this analysis. Second, there were differences in methodology across the studies, which might produce clinical heterogeneity. Third, the follow-up period for the clinical effectiveness in included studies was relatively short so that meta-analysis was restricted to short term. Fourth, the number of studies included in the analysis was small, as well as the number of patients in studies was relatively small. Fifth, CIs of risk ratio in some studies were too widely ranged for achieving precision. All these aspects lowered the evidence level to low, consequently weakening the strength of meta-analysis.

Conclusions

Through the authors' discreet reviews and thorough analysis, TFESI lacked to produce clinically significant preferential outcomes over ILESI. It also showed no advantage over ILESI in terms of procedural-related intravasation or transient pain exacerbation incidence associated with injection as proven to be statistically insignificant during this analysis. Thus, despite the general belief that the more targeted, nerve root specific TFESI might superiorly control the cervical radiculopathies, the authors have concluded that TFESI could not be preferentially recommended over ILESI based on the weak evidential strength.

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