Systematic Review

Comparison of Intercostal Block and Epidural Analgesia for Post-thoracotomy: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Background: Thoracotomy is associated with severe postoperative pain. Effective management of acute pain after thoracotomy may reduce complications and chronic pain. Epidural analgesia (EPI) is considered the gold standard for postthoracotomy analgesia; however, it is associated with complications and limitations. Emerging evidence suggests that an intercostal nerve block (ICB) has a low risk of severe complications. Anesthetists will benefit from a review that assesses the advantages and disadvantages associated with ICB and EPI in thoracotomy.

Objectives: This meta-analysis aimed to evaluate the analgesic efficacy and adverse effects of ICB and EPI for pain treatment after thoracotomy.

Study Design: Systematic review.

Methods: This study was registered in the International Prospective Register of Systematic Reviews (CRD42021255127). Relevant studies were searched for in PubMed, Embase, Cochrane, and Ovid databases. Primary (postoperative pain at rest and during cough) and secondary (nausea and vomiting, morphine consumption, and length of hospital stay) outcomes were analyzed. The standard mean difference for continuous variables and the risk ratio for dichotomous variables were calculated.

Results: Nine randomized controlled studies with a total of 498 patients who underwent thoracotomy were included. The results of the meta-analysis demonstrated no statistically significant differences between the 2 methods in terms of the Visual Analog Scale scores for pain at 6-8, 12-15, 24-25, and 48-50 hours at rest and at 24 hours during coughing after surgery. There were no significant differences in nausea and vomiting, morphine consumption, or length of hospital stay between the ICB and EPI groups.

Limitations: The number of included studies was small, and the quality of evidence was low.

Conclusions: ICB may be as effective as EPI for pain relief after thoracotomy.

Key words: Thoracic surgery, intercostal nerve block, epidural analgesia, postthoracotomy pain, postoperative pain, randomized controlled trial, meta-analysis, systematic review

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Thoracotomy, which may cause severe trauma involving rib cage incisions, pleural and muscular damage, and adhesive fibrous disconnection in the ribs (1), is associated with severe postoperative pain (2). It markedly depresses respiratory function, which might lead to pneumonia, hypoxemia, respiratory failure, delayed recovery, and increased morbidity and mortality (3,4). Acute postoperative pain can cause chronic postthoracotomy pain (5). The rate of persistent postthoracotomy pain is reported to be 26% to 67%, and 61% of patients may experience mild pain one year after surgery (6). Adequate control of acute pain following thoracotomy may reduce complications and chronic pain. Regional nerve blocks may decrease the incidence of chronic pain after operation (7).Various techniques, including epidural analgesia (EPI), systemic opioids, and nerve blocks, have been used in thoracotomy or video-assisted thoracoscopic surgery (VATS) (8). EPI is considered the gold standard for postoperative pain control in thoracic surgery (9). However, the epidural puncture must be performed by a skilled anesthesiologist, and it may cause serious complications, such as epidural hematoma, neurological disorders, hypotension, and urinary retention (10). One study (11) questioned the superiority of EPI during lobectomy via VATS, because it leads to respiratory depression, hypotension, nausea and vomiting, and other adverse effects. Moreover, postthoracotomy EPI management in the ward is not convenient in some hospitals. These limitations have prompted the search for alternatives to EPI.

For enhanced recovery after surgery, a multimodal approach to analgesia is currently used by anesthetists, which combines regional anesthetic blockade and systemic opioid medications with nonsteroidal anti-inflammatory drugs (12.31). Several regional nerve blocks are available for the management of thoracotomy. Intercostal nerve block (ICB) and paravertebral blockade are the 2 most widely used postoperative analgesia methods in thoracic surgery. Some studies (13,14) claimed that thoracic paravertebral blockade might be as effective as EPI for thoracic surgery pain relief and with fewer complications. Some of the rare complications associated with paravertebral blockade include Harlequin syndrome and hypotension (15,16).With advantages, such as simple operation, increased safety, and a good analgesic effect with few complications, the use of ICB in thoracotomy, especially in VATS, has substantially increased. An ICB can be administered as a single, repeated, or continuous injection with short- or long-acting local anesthetics in the intercostal space (9,13). Richardson et al (17) demonstrated that the analgesic effect was the same between the ICB and EPI groups, but vomiting and urinary retention occurred in the EPI group; thus, ICB may be preferable to EPI.

Many studies described different regional analgesic techniques for postthoracotomy pain control. However, no unequivocal conclusions or guidelines for analgesia after thoracotomy, especially in VATS, have been proposed (18-26). This systematic review and meta-analysis aimed to compare the analgesic efficacy and side effects of ICB and EPI in managing postthoracotomy pain and guide future clinical research.

Methods

We performed a systematic review of the literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol, including the following elements: systematic literature search, critical standard for inclusion and exclusion of articles, assessment of outcome variables, and statistical analysis of data. The full details of the search protocol are shown in Fig. 1, and the characteristics of the relevant studies are outlined in Table 1. The quality of the included studies varied (Fig. 2).

Search Strategy

A literature search was performed using PubMed, Embase, Cochrane, and Ovid. The search strategy included free text words and medical subject headings terms: "nerve block," "epidural anesthesia," "intercostal nerve block," "thoracic surgery," "thoracotomy," and "cardio-thoracic." In addition, the terms used varied in the search databases. We checked for duplicates in different databases. Two reviewers (authors ZGZ, XZ) independently scanned eligible studies to find those that met the predefined inclusion criteria. Disagreements were resolved through discussion with a third reviewer (JFS).

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: 1) study population diagnosed with lung cancer and underwent thoracic surgery; 2) study design included a randomized controlled trial; and 3) interventions included EPI or ICB.

The exclusion criteria were as follows: 1) non-English language articles; and 2) nonrandomized controlled clinical trials.

Data Extraction and Quality Assessment

The following data were extracted from each eligible study: name of the first author, publication date, type of study, number of patients, and analgesic interventions of the ICB and EPI groups.

The primary outcome was the postoperative pain scores at different time points (6-8, 12-15, 24-25, and 48-

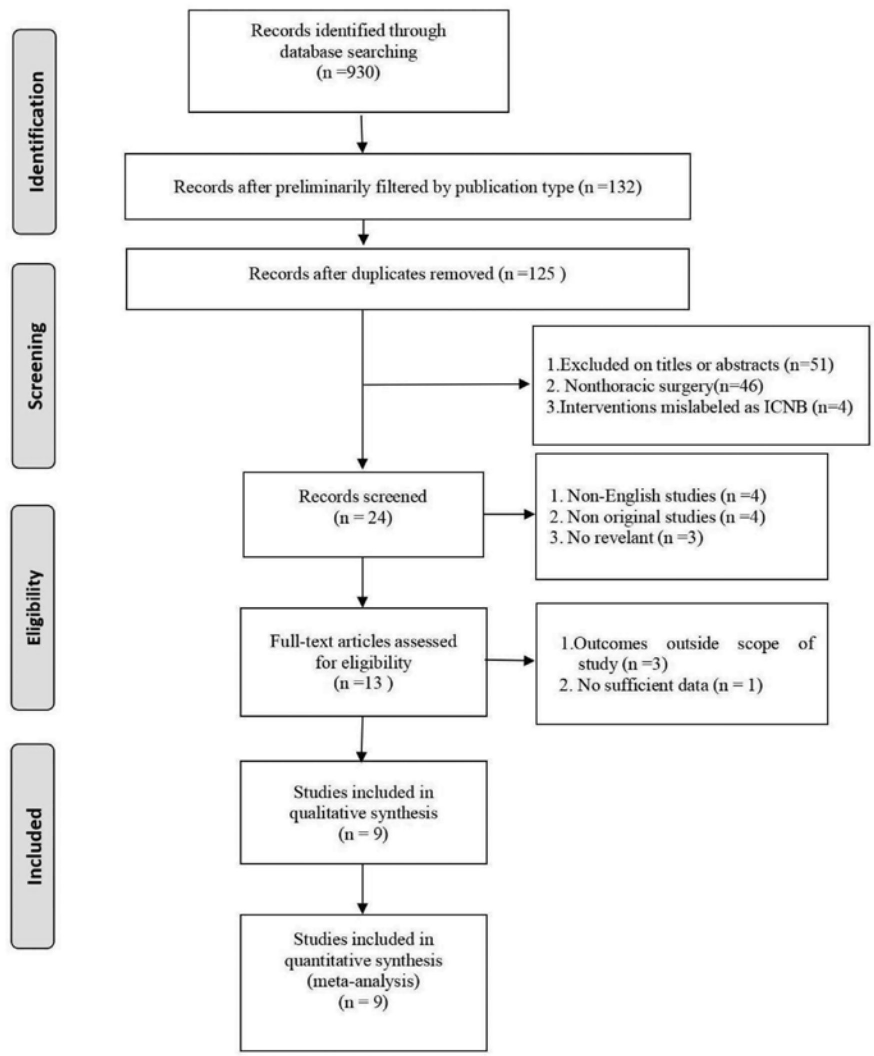

Fig. 1. *Flow chart of studies included and excluded according to PRISMA procotol.*

50 hours at rest and 24 hours during coughing). The secondary outcomes were frequency of nausea and vomiting, morphine consumption, and length of hospital stay. The Visual Analog Scale (VAS) scores are expressed as the mean and standard deviation (SD). The pain scores shown as medians were converted to means (27). The standard mean difference (SMD) was calculated as interquartile range/1.35, as reported by Hayduk et al (28). We digitally extracted the pain score shown in graphic form using GetData Graph Digitizer version 2 program (GetData Pty Ltd, Kogarah, Australia) if data were not obtained by email from the corresponding author. Since there were only 9 randomized controlled trials in our study, publication bias was not analyzed.

Data were independently extracted by 2 authors (XFJ, LPZ), and any disagreement was resolved through discussion or consultation with a senior author (SLL).

The quality of the included studies was assessed using the Cochrane criteria (29), and the relevant information was graded as randomization, allocation concealment, blinding, explanation of withdrawal, reporting bias, and other bias. All variables were graded as having a "low, unclear, or high" risk of bias.

Statistical Analyses

Review Manager computer software (RevMan Version 5.4, The Nordic Cochrane Centre, Copenhagen,

Table 1. *Characteristics of studies included in analysis.*

Authors	Publication	Type of Surgery	No of Patients	Intercoastal Group (ICB)	Epidural Group (EPI)	Additional Analgesia
Debreceni et al (18)	2003	Thoracotomy	47 (22/25)	0.2 mL/kg of 0.25% bupivacaine 5 mL/h 20 h	0.2 mL/kg of 0.25% bupivacaine 5 mL/h	None
Ueda et al (19)	2019	VATS	43 (21/22)	4,5,6 intercoastal nerve 7 mL 3.7 mg/mL ropivacaine hydrochloride hydrate single	T4/T5 or T5/T6 5 ML 3.7mg/mL, following 200 mL 2.0 mg/mL ropivacaine hydrochloride hydrate + 10 mL fentanyl; 4 mL/h, 2 d	OR celecoxib
Vilvanathan et al (20)	2020	Thoracotomy	50 (25/25)	3~8 intercoastal space 0.25% bupivacaine 20 mL + intravenous morphine 0.015%~0.02% mg/kg/h 24 h	T5/T6 0.25% bupivacaine 5~10 bolus + 0.1% bupivacaine with 5~8 mL/h fentanyl 2 μg/mL	None
Dauphin et al (21)	1997	Thorcotomy	49 (24/25)	0.3 mL/kg of 0.5% bupivacaine following 0.1 mL/kg/h continous for 3 d	L2~4 epidural catheter inserted 4 mL 0.25% bupivacaine with bolus epidural morphine 70 g/kg, 7 g/kg/h 3 d	None
Luketich et al (22)	2005	Thorcotomy	91 (44/47)	10 mL 0.5% bupivacaine during operation room + 0.25% 1 mL/kg/h 72 h	0.1%lidocaine + 0.125%bupivacaine + 0.05 mg/mL morphine 4~6 mL/h	Nonprotocol narcotic and nonnarcotic pain medication
Hotta et al (23)	2011	VATS	40 (20/20)	Extrapleural space catheterization 5 mL 0.75% ropivacaine + 5 mL 0.75% ropivacaine 5 mL + 0.2% ropivacaine 4 mL/h 60 h	T5/T6 or T6/T7 5 mL 0.75% ropivacaine + 5 mL 0.75% ropivacaine 5 mL+ 0.2% ropivacaine 4 mL/h 60 h	Intravenous flurbiprofen or oral loxoprofen
M Kaiser et al (24)	1998	Thoracotomy	30 (51/15)	20 mL 0.5% bupivacaine during 20 min, 0.5% 0.1/ mL/kg/h + ornipressin for 5 d	T5/T6 0.5% bupivacaine 4~6 mL/h during operation + 0.25%~0.375% bupivacaine + fentanyl 2 μg/mL	None
Sagiroglu et al (25)	2013	Thoractomy	60 (30/30)	T5/7.0. 25% bupivacaine 5 mL/h 24 h	T5/7 0.25% bupivacaine 5 mL/h 24 h	Morphine
Meierhenrich et al (26)	2011	Thoracotomy	88 (43/45)	0.75% ropivacaine 4 mL+ 0.75% ropivacaine 5 mL + ropivacaine 5 mL single + PCIA	T6/8 1% mepivacaine + 1% ropivacaine 8 mL + ropivacaine 5 mL repeated every 60 min	Mophine diclofenac orally metamizole orally

Abbreviations: ICB, intercostal nerve block; EPI, epidural analgesia; VATS, video-assisted thoracoscopic surgery; PCIA, interscalene analgesia.

Denmark) was used for the meta-analysis. Statistical heterogeneity was evaluated using the I^2 statistic and chi-square test. The SMD for continuous data and risk ratio (RR) for dichotomous data with their corresponding 95% confidence intervals (CIs) were calculated. A fixed-effects model was used if the heterogeneity test did not detect statistical significance ($I^2 < 50\%$, $P > 0.1$), and a random-effects model was used if statistically significant heterogeneity was found. To identify potential heterogeneity, subgroup and sensitivity analyses were conducted. The following subgroup analyses were performed: 1) different types of epidurals (local anesthetics with or without opioids); 2) different types of surgery (thoracic surgery or VATS); and 3) different methods of ICB (with or without a catheter). We chose to use only the primary outcome (regarding 24- to 25-hour VAS scores after surgery) in the subgroup analyses.

This meta-analysis was prospectively registered in the International Prospective Register of Systematic Reviews database (CRD42021255127).

Results

A total of 930 records were retrieved from the search of PubMed, Embase, Cochrane, and Ovid databases. After filtering by publication type, there were 132 randomized controlled trial articles relevant to the research question. After removing 7 duplicates, we had 125 unique manuscripts. After reviewing titles and abstracts, we excluded 51 studies. Of the 74 remaining articles, 50 were excluded (46 examined nonthoracic surgery and 4 included interventions mislabeled as ICB). The remaining 24 full-text randomized controlled trials were assessed for eligibility. Four articles were not written in English. Four reports were not original studies, and 3 articles were unrelated to this meta-analysis. Of the remaining 13 articles, the outcomes of 3 articles were outside the scope of study; one study was excluded because it only reported the mean without the SD for pain scores. Finally, 9 relevant full-text studies were included in the meta-analysis (18-26).

There were no statistically significant differences in the postoperative pain scores between the ICB and EPI groups at 6-8, 12-15, 24-25, and 48-50 hours (SMD = 0.22, 95% CI = -0.06, 0.50; SMD = 0.25, 95% CI = -0.04, 0.54; SMD = 0.06, 95% CI = -0.36, 0.47; SMD = -0.25, 95% CI = -0.99, 0.50, respectively) (Figs. 3-6). Pain during coughing may be the most important parameter for thoracotomy analgesia (30), and only 3 studies reported the VAS score during coughing (Fig. 7). There was also no statistically significant difference in pain scores during coughing at 24 hours after the operation (SMD = 0.12; 95% CI = -0.84, 1.08) (Fig. 7).

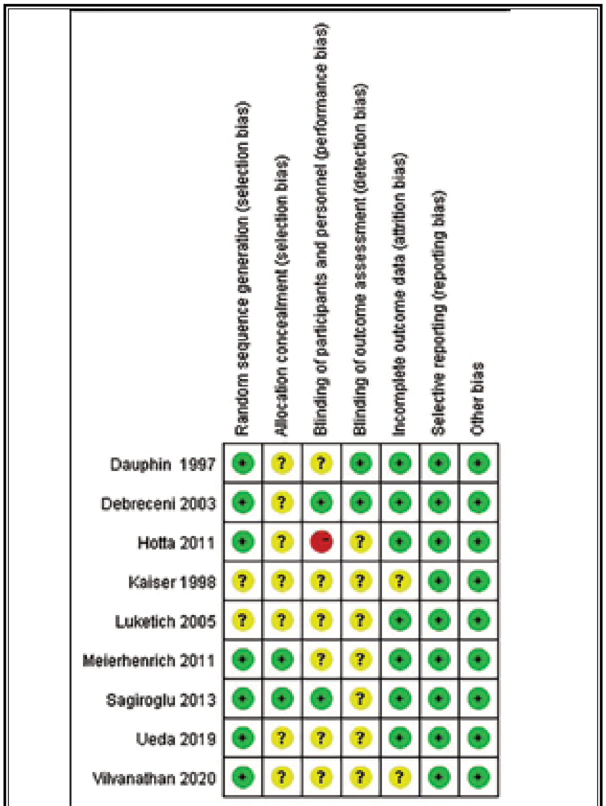

Fig. 2. *Risk of bias summary: review authors' judgments about each risk of bias item for each included study.*

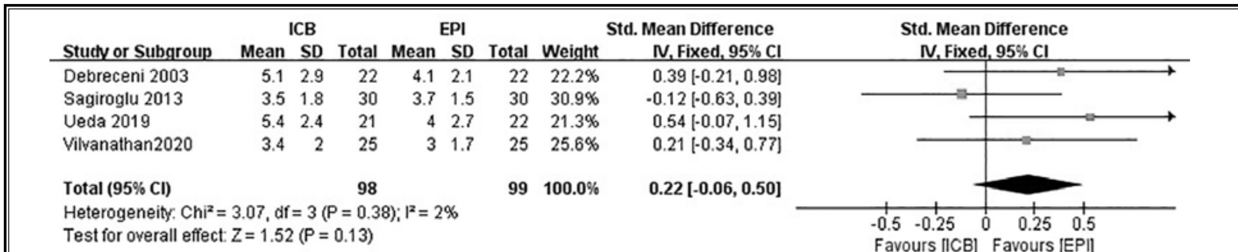

Fig. 3. *Meta-analysis of postthoracotomy analgesic efficacy of ICB compared with that of EPI VAS scores 6h~8h.*

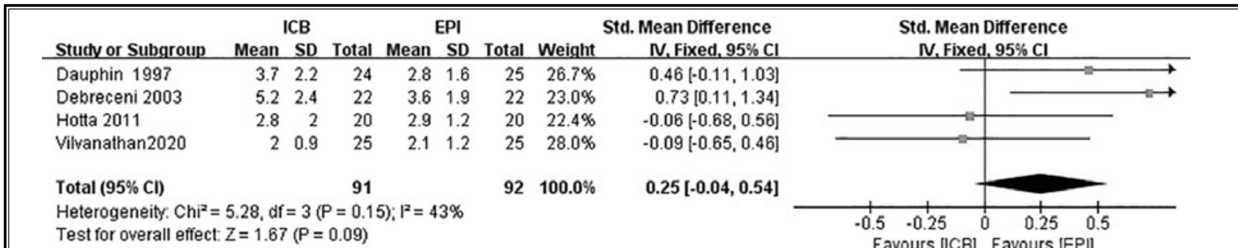

Fig. 4. *Meta-analysis of postthoracotomy analgesic efficacy of ICB compared with that of EPI VAS scores 12h~15h.*

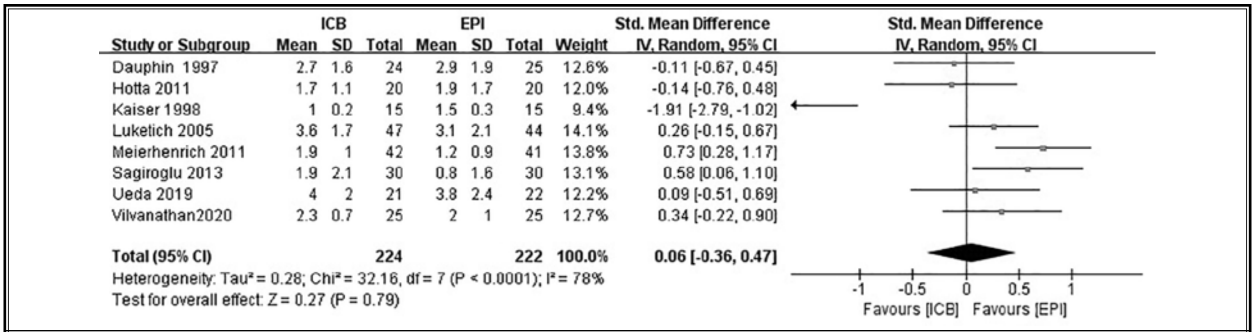

Fig. 5. *Meta-analysis of postthoracotomy analgesic efficacy of ICB compared with that of EPI VAS scores 24h~25h.*

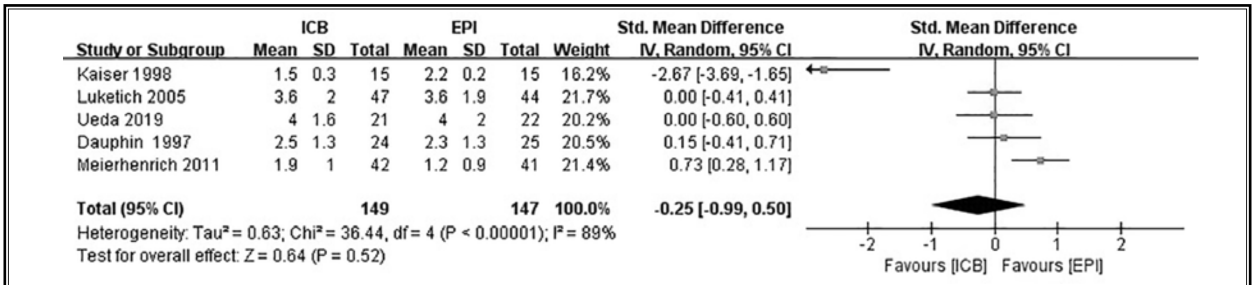

Fig. 6. *Meta-analysis of postthoracotomy analgesic efficacy of ICB compared with that of EPI VAS scores 48h~50h.*

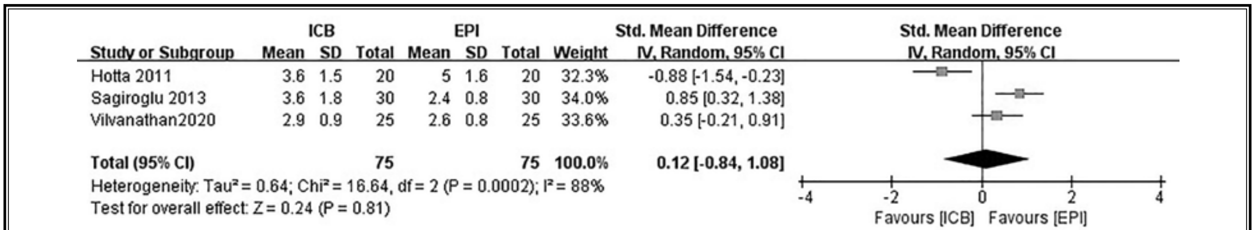

Fig. 7. *Meta-analysis of postthoracotomy analgesic efficacy of ICB compared with that of EPI on coughing 24h~25h.*

We performed a subgroup analysis of the VAS scores at 24-25 hours according to epidural type (local anesthetics with or without an added opioid), type of surgery (thoracic surgery or VATS), and method of ICB (with or without catheter). Heterogeneity decreased distinctly as the results demonstrated that postoperative VAS scores were higher for a single ICB than for EPI at rest at 24-25 hours. The postoperative VAS scores for continuous ICB were similar to those for EPI at 24-25 hours. This subgroup analysis indicated that single or continuous ICB might have been a source of heterogeneity (Fig. 8). There were no statistically significant differences in postoperative pain scores between the ICB and EPI groups at 24-25 hours with or without adjuvant drugs (Fig. 8). No significant differences were observed between ICB and EPI in the thoracotomy (Fig. 9) or thoracoscopy subgroups (Fig. 10).

We performed a sensitivity analysis of VAS scores after surgery at 48-50 hours at rest because evident heterogeneity was found ($I^2 > 50\%$ or $P < 0.1$). When the study by Kaiser et al (24) was excluded, the heterogeneity for postoperative VAS scores at 48-50 hours was resolved, and the results did not change (SMD = 0.23; 95% CI= -0.13, 0.60; $I^2 = 55\%$; $P = 0.08$) (Fig. 11).

Five studies reported nausea and vomiting; there were no statistically significant differences in nausea and vomiting (RR, 1.18; 95% CI = 0.66-2.09) (Fig. 12). There were no statistically significant differences in morphine consumption between the ICB and EPI groups (SMD = -0.05; 95% CI = -0.99-0.90) (Fig. 13). Four articles described the length of hospital stay; there was no significant difference in the length of hospital stay between the ICB and EPI groups (SMD = 0.11; 95% CI = -0.19-0.40) (Fig. 14).

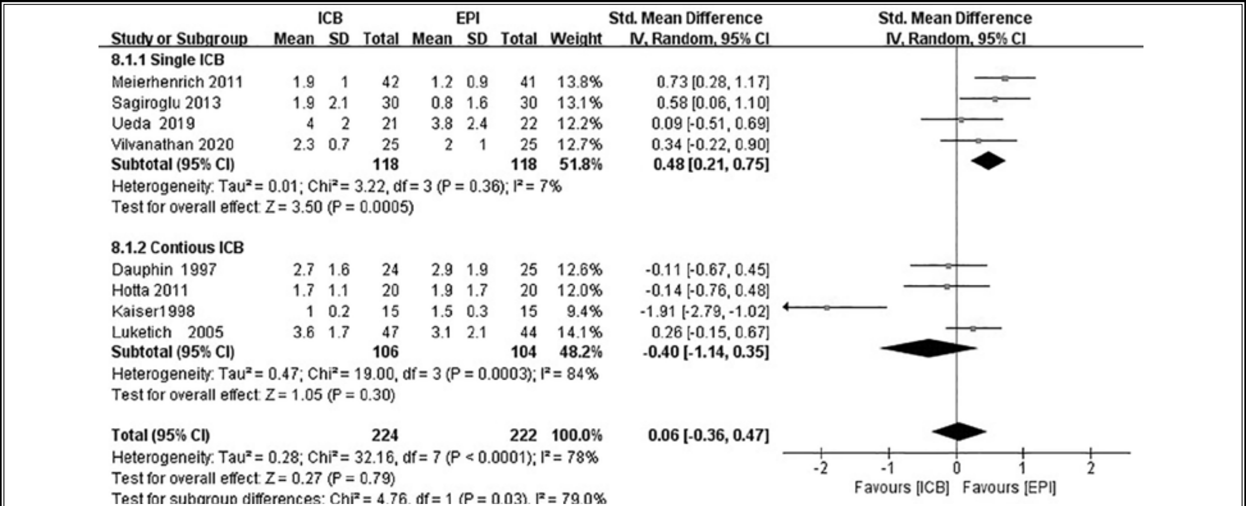

Fig. 8. *Subgroup analysis of the VAS score at 24h~25h between ICB and EPI groups according to different methods of ICB.*

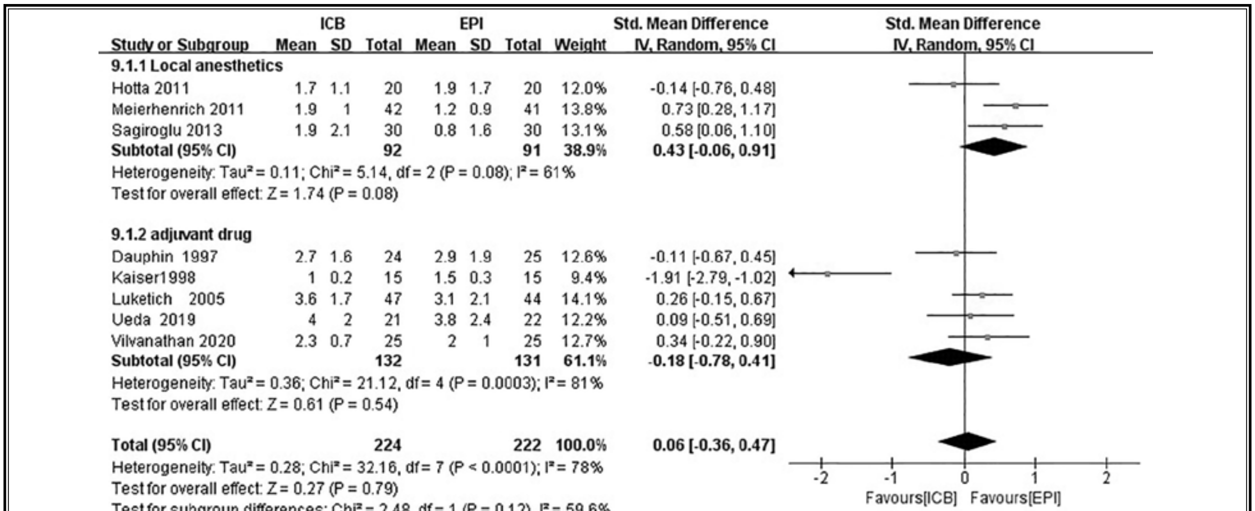

Fig. 9. *Subgroup analysis of the VAS score at 24h~25h between ICB and EPI groups according to different types of epidurals.*

Discussion

This meta-analysis included 9 randomized trials and 498 patients to compare the efficacy of ICB with EPI after thoracotomy. There were no statistically significant differences in the pain scores at rest between the ICB and EPI groups after thoracotomy at 6-8, 12-15, 24-25, and 48-50 hours at rest and at 24 hours during coughing. The most significant finding of this meta-analysis was that ICB might have provided analgesia comparable to EPI in patients who underwent thoracotomy. We also found no significant differences between the 2 groups in the incidences of nausea and vomiting, morphine consumption, and length of hospital stay. To the best of our knowledge, this was the first systematic review to compare the analgesic effects and complications associated with ICB and EPI in adults who underwent thoracotomy. We only compared the analgesic effects of ICB and EPI, and assessed pain scores up to 3 days after thoracotomy.

A multimodal approach to analgesia that combines systemic and regional anesthesia may be the most effective in patients (12,31). One study (11) reported that minimally invasive surgery should require simpler postoperative pain management. With development of minimally invasive techniques in thoracic surgery, EPI is not recommended for VATS, and nerve block tech-

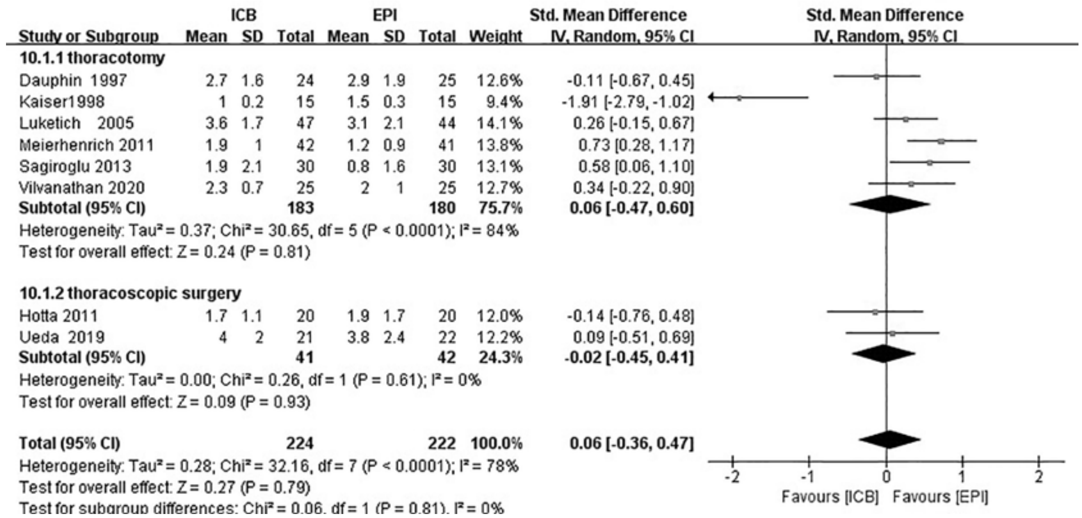

Fig. 10. *Subgroup analysis of the VAS score at 24h~25h between ICB and EPI groups according to different types of surgery.*

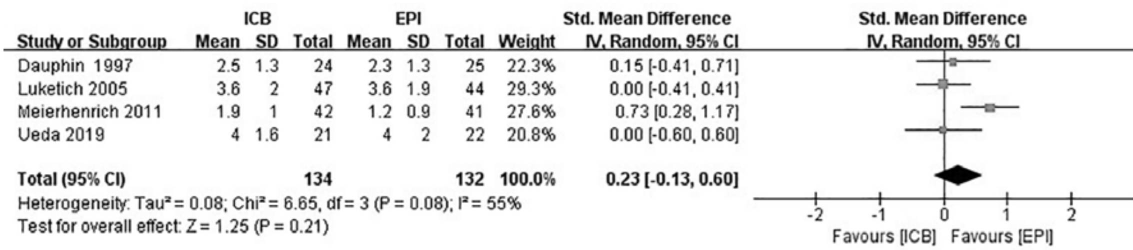

Fig. 11. *The sensitivity analysis of VAS scores after surgery at 48~50h between icb and epi groups.*

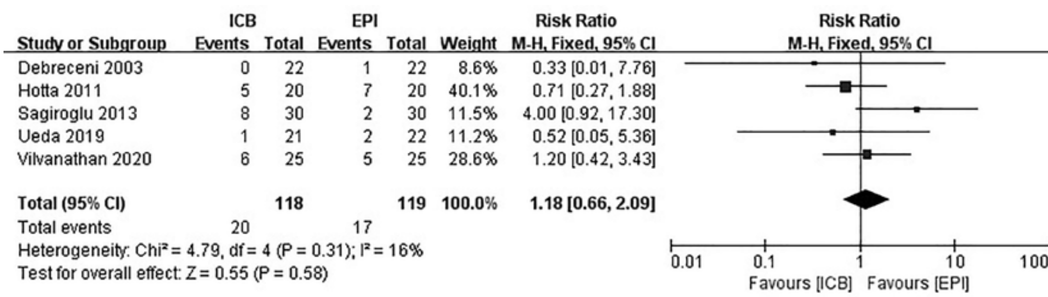

Fig. 12. *Meta-analysis of trails comparing ICB with EPI on nausea and vomiting.*

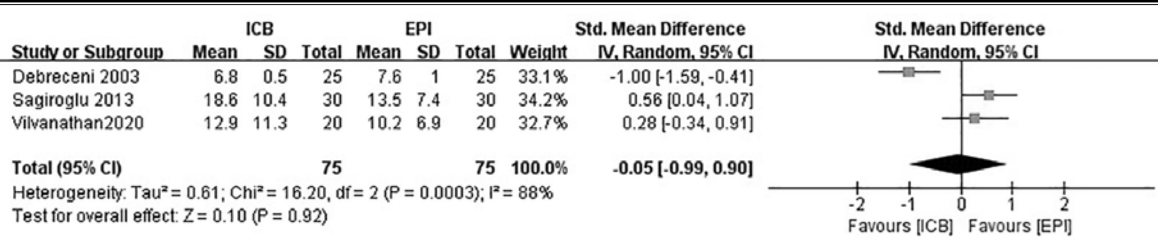

Fig. 13. *Meta-analysis of trails comparing ICB with EPI on morphine consumption.*

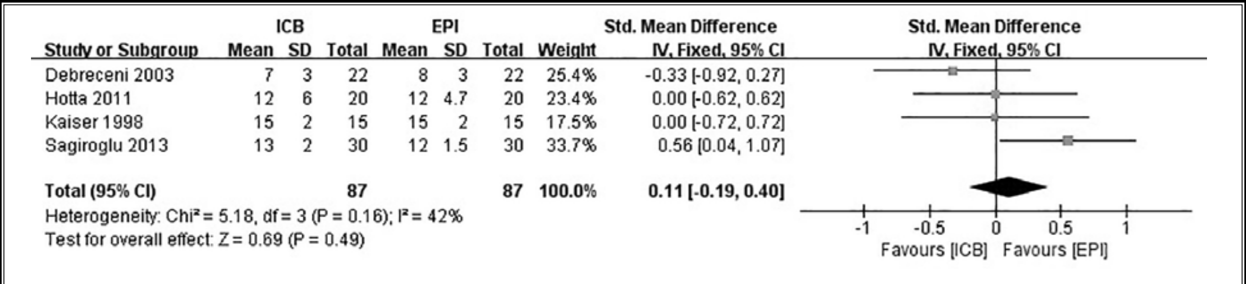

Fig. 14. *Meta-analysis of trails comparing ICB with EPI on hospital stay.*

niques are gradually replacing EPI (32). ICB plays an important role in multimodal analgesia management after thoracotomy. ICB is faster to perform and has been used extensively for postthoracotomy analgesia (33).

The simplest method of ICB administration is by injection of a local anesthetic into multiple intercostal spaces. A single ICB can be maintained for a shorter time. The failure rate of catheters placed in the intercostal space was about 20% by radiological assessment (34). Recent modifications to this technique have been developed; the intercostal catheter can be placed near the intercostal space under direct thoracoscopic vision by the surgeon before closing the chest, which makes the ICB safer and ensures the correct location for drug transfer (35). Ultrasound-guided ICB and placement of catheters can also be performed by skilled anesthetists before an operation with a high success rate. A longer-lasting technique involves inserting a catheter to provide continuous ICB (9), which may be an attractive method because it provides effective analgesia with few adverse effects in patients who undergo thoracotomy (36). Continuous ICB can decrease pain and improve respiratory function after thoracic surgery (37).

Continuous ICB was not only effective in controlling acute pain, but might also reduce the peripheral and central sensitization and the incidence of chronic pain after thoracotomy. Andreae et al (7) prudently demonstrated that EPI and paravertebral block might prevent persistent postoperative chronic pain 6 months after thoracotomy and breast cancer surgery. Ren et al (38) performed a systematic review, which further showed that paravertebral block could reduce the incidence of analgesia-related complications and postoperative chronic pain. Detterbeck (39) indicated that continuous ICB is at least as effective as EPI; it may reduce the rate of chronic pain after thoracotomy. Recently, in the cohort study by Ma et al (40), continuous nerve block was showed to reduce the long-term postoperative pain, but due to the small sample size, no significant difference was observed between continuous nerve block and patient-control analgesia groups. These findings need to be confirmed in further clinical research.

There are several systematic reviews that addressed our research topic and compared ICB and EPI. Joshi et al (9), in 2008, systematically reviewed regional techniques for postthoracotomy analgesia. They concluded that ICB is recommended if EPI and paravertebral block are contraindicated, and EPI was superior to ICB. Steinthorsdottir et al (41) compared the effectiveness of different regional techniques for acute postoperative pain following VATS and found that EPI and paravertebral block may reduce pain score, but other regional analgesia did not show any clear results in terms of pain relief. Guerra-Londono et al (42) found that single-injection ICB was associated with reduced pain during the first 24 hours after thoracic operation and was clinically noninferior to EPI. Their findings on pain scores at 24 hours after surgery are consistent with our results. ICB was inferior to EPI with regard to opioid consumption at 24 hours after the operation. Different trends were observed for nausea and vomiting. In the thoracotomy subgroup, no significant differences were observed between ICB and EPI. In addition, their data did not reveal differences in hospital length of stay between the ICB and EPI groups.

Current guidelines suggest that continuous ICB is similar to EPI in thoracotomy analgesia (43).Yamazaki et al (44) found that ICB was often discontinued early, preemptive ICB can be performed easily by thoracic surgeons, and ICB has similar pain relief, analgesia-related adverse effects, and reduced postoperative complication risk compared to EPI. In their cohort study, they concluded that preemptive ICB might be an alternative for EPI in patients undergoing minimally invasive thoracic surgery. These previous findings support the results of our study. The optimal selection of the postthoracotomy analgesic approach is often based on clinical benefits, disadvantages, and cost of the technique. With the increasing use of VATS, EPI is not recommended for postthoracotomy (33).

Our meta-analysis demonstrated no difference in pain scores and adverse effects between ICB and EPI in patients undergoing thoracotomy. In summary, with the development of minimally invasive techniques in thoracic surgery, ICB, especially continuous ICB, may be a promising technique for postthoracotomy pain management.

Limitations

This meta-analysis has several limitations due to clinical heterogeneity. First, few high-quality, randomized controlled trials have compared ICB with EPI for postthoracotomy pain. Double-blinding and allocation concealment were not clearly reported in the studies included in this meta-analysis. Second, we used digital software for data extraction from a graphic form, which may have been inaccurate for the VAS scores. However, this method is usually adopted when the original data are not available. The pain score depended on the type of thoracic surgery, indicating that thoracotomy may lead to a higher pain score than VATS. Finally, the type of anesthetic and administration of additives might have introduced bias in the pain scores after surgery. Different ICB methods might have influenced the efficacy of analgesia.

Conclusions

ICB may provide pain relief comparable to EPI after thoracotomy. This meta-analysis showed no significant difference in pain management, nausea and vomiting, morphine consumption, and length of hospital stay between patients who were administered either ICB or EPI. The conclusions from this review should be interpreted with caution because of the heterogeneity of the included articles and insufficient evidence. In the future, large, prospective, multicenter, randomized controlled clinical trials that focus on pain effects, as well as major complications, length of stay, and costs, must be conducted.

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