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Regional analgesia techniques for video assisted thoracic surgery: a frequentist network meta-analysis

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Running title: Regional analgesia for VATS
Abstract

Background: Various regional analgesia techniques are used to reduce postoperative pain in patients who received the video-assisted thoracic surgery (VATS). This study aims to determine the relative efficacy of the regional analgesic interventions for VATS using the network meta-analysis (NMA).

Methods: We searched Medline, EMBASE, the Cochrane Controlled Trial Register, Web of Science and Google Scholar databases to identify all randomized controlled trials (RCT) which compare the analgesic effects of the following interventions: control, thoracic paravertebral block (TPVB), erector spinae plane block (ESPB), serratus plane block (SPB), and intercostal nerve block (INB). The primary endpoints were opioid consumption during the postoperative 24 hours. Also collected were the pain scores at three different postoperative periods: early (0-6 h), middle (6-18 h), and late (18-24 h) period.

Results: Twenty-one RCT with a total of 1391 patients were included. TPVB showed a greatest effect on opioid consumption compared with control (mean difference (MD) = -13.2 mg, 95% CI -16.2 to -10.1). In respect of the pain score in the early period, ESPB had the greatest effect compared with control (MD = -1.6, 95% CI -2.3 to -0.9). In the middle and late period, TPVB, ESPB and INB showed superior analgesic effect than control on pain score, but SPB did not.

Conclusions: TPVB showed most superior analgesic efficacy following VATS. ESPB provides a comparable analgesic efficacy with TPVB. However, further studies are needed to determine the optimal regional analgesia technique to improve postoperative pain control for VATS.
Introduction

The video-assisted thoracoscopic surgery (VATS) as a minimally invasive alternative for open thoracotomy has increased over the years. Its clinical application is much accredited for significant reduction in postoperative pain and shorter length of hospital stay. [1,2] However, some patients still complain of moderate to severe pain after VATS and postoperative pain control remains challenging [3,4] Although thoracic epidural analgesia (TEA) have been regarded as the gold standard for postoperative pain management in thoracic surgery [5-8], its complications of epidural hemorrhage, hypotension, and postoperative urinary retention can be fatal to high risk patients. [9-11]. Considering the risks and benefits, it is necessary to use an appropriate regional analgesia technique suitable for minimally invasive thoracic surgery.

Thoracic paravertebral block (TPVB) provides unilateral thoracic analgesia comparable with TEA. TPVB is not only less invasive than is TEA, but it is also known to maintain hemodynamic stability and lower the risk of complications derived from anticoagulation [9,12]. According to the Enhanced Recovery After Surgery (ERAS) guideline and Procedure-specific postoperative pain management (PROSPECT) group, TPVB is recommended as the first line regional analgesia technique in thoracic surgery. [13,14]

Recently, however, various regional analgesia techniques, such as the erector spinae plane block (ESPB) and the serratus plane block (SPB), have superseded the traditional TPVB by offering a lower prevalence of complications while still allowing comparable analgesic effect [15,16]. Although many studies have reported the efficacy of each regional analgesia techniques and compared the effectiveness regarding analgesic techniques in VATS, no previous network meta-analysis (NMA) has yet compared the relative efficacy of various regional analgesic techniques. Therefore, we reviewed all the articles that investigated the effects of various techniques used for postoperative analgesia for VATS, and performed an NMA to retrieve the rank order of effectiveness for regional analgesia block

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in VATS. Our primary outcome was opioid consumptions during postoperative 24 hours, and pain severity at 3 different postoperative periods (early, middle, late) was also evaluated.
Materials and Methods

This study was conducted in accordance with the recommended guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis [17] and was registered with the international prospective register of systematic reviews (PROSPERO, CRD42021252062).

Data source and search strategy

The literature searches were conducted by two authors. To obtain eligible studies for this systematic review and meta-analysis, two researchers independently searched electronic databases, such as Medline, EMBASE, Cochrane Controlled Trial Register, Web of Science and Google Scholar as well as language English. Articles published between September 2005 and December 2020 in peer-reviewed journals were included. The primary search was conducted on January 28, 2020. but additional search was conducted to include more recent studies in the process of revision on February 28, 2021. In addition, the studies referenced in the selected articles were searched manually.

The search strategy was as follows: ("Video assisted thoracoscopic surgery" or VATS) and [("Thoracic paravertebral block" or TPVB) or ("paravertebral block" or PVB) or ("Serratus plane block" or "Serratus anterior plane block" or "Serratus interfascial plane block" or SPB) or ("Erector spinae plane block" or ESPB) or ("Intercostal nerve block" or INB)]

Inclusion and Exclusion Criteria

Studies were considered eligible if they were randomized controlled trials (RCT), published in English, and reported postoperative pain scores in both experimental and control groups or reported outcomes as pain scores and amounts of opioid consumptions. Non-RCTs (quasi-experimental design), abstracts, conference proceedings, unpublished gray literature, and review studies were excluded. Among regional analgesia techniques, continuous block by catheterization were excluded.
**Review procedure**

We performed six steps for selecting the studies. First, two researchers (S.P & B.H) imported titles and abstracts of articles identified in the searches into reference management software and performed a preliminary review. Second, duplicates of papers were identified and eliminated using the reference management software. Third, two researchers (S.P & B.H) independently reviewed the imported studies. If the imported studies could not clearly meet the inclusion criteria, such as study design, participants, type of intervention, and comparisons, we excluded those studies. Fourth, the aforementioned two researchers (S.P & B.H) independently screened the titles, abstracts, and methodology sections of studies appearing to meet inclusion criteria. Fifth, we retrieved the full text of the papers meeting all inclusion criteria for data extraction and linked multiple reports of the same study. Lastly, the studies included in the final selection were confirmed and coded for analysis by two researchers (B.H & Y.J). These coding sheets were independently checked for accuracy by researchers who were not involved in the reviewing process. If there were any differences between the codes provided by the two reviewers, the discrepancies were resolved by consulting a third independent reviewer.

**Data extraction**

The information from the included articles was independently extracted by two reviewers, and each selected article was reviewed twice by both reviewers cooperatively. To determine the outcomes of individual studies, pain scores and opioid consumption were determined for each group and recorded as the mean and standard deviation. Median and interquartile range (IQR) as approximations of mean and standard deviation (SD) were determined by an estimation method proposed by Wan et al [18]. When the outcome data was only set as a plot; virtual ruler was used to extract value by matching the...
interval between the basic unit of the plot and the ruler. Effect size and standard error were calculated.
Additional data, including location, sample size, the characteristics of individual study populations, and the intervention design, were extracted using a predetermined data extraction table.

Outcome definitions
The primary outcome was the cumulative opioid consumption during the first 24 postoperative hours. All opioids were converted to equianalgesic intravenous (iv) morphine doses (iv morphine 1 mg = iv fentanyl 10 µg = iv sufentanil 2 µg = iv tramadol 10 mg). The secondary outcome was the pain score assessed at different time periods during the 24 postoperative hours. The time period was divided into 3 intervals: early (up to 6 hours), middle (6 to 18 hours), and late (18 to 24 hours). When there were several time points of each time period, pain scores close to 1 hour for early, close to 12 hours for middle, and close to 24 hours for late were used. In the study with a timetable expressed as an interval (ex. 6 am to 2 pm), it was designated as the similar period expected to include the interval. Pain scores determined using visual analogue scales (VAS) were converted to a 0–10 analogue scale to permit statistical evaluation.

Data Synthesis and Statistical Analysis
A random-effects NMA within a frequentist framework was performed using R version 4.0.3 software (R Foundation for Statistical Computing, Vienna, Austria) and the “netmeta” package for frequentist NMA [19,20]. The network plot was constructed to evaluate direct and indirect comparisons of network structure including studies. Heterogeneity was evaluated using I² statistics. Q statistic based on the full design-by-treatment interaction random-effects model was calculated to evaluate the global inconsistency [21]. We also evaluated the local inconsistencies between the direct and indirect effect by net splitting technique. If P value of the net splitting was under 0.05, we presumed there was
a significant disagreement (inconsistency) between the direct and indirect estimate. And we visualized the net split results by forest plot and direct evidence plot showing the percentage of direct and indirect evidence used for each estimated comparison. Mean path length > 2 indicates that a comparison estimate should be interpreted with particular caution. Additionally, the net heat plot was constructed to signify importance of each comparison and inconsistency of the design. Network league table and forest plot were produced to demonstrate the results of the comparisons between interventions in detail. Outcomes were presented as mean differences with 95% confidence interval.

To rank the analgesic interventions in order, we reported the P score which measures the extent of certainty that an intervention is better than the competing interventions. [22] In this study, P score ranged from 0 to 1, with 1 indicating that the treatment option was statistically best and 0 the worst.

The potential publication bias was assessed by comparison-adjusted funnel plots and Egger’s test.

The confidence for every outcome was rated according to the grading of recommendations assessment, development and evaluation (GRADE) system with the support of CINeMA (Confidence in Network Meta-Analysis, https://cinema.ispm.unibe.ch/) web application (Institute of Social and Preventative Medicine, University of Bern, Switzerland) [23]. It is based on a methodological framework which considers six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence [24]. The minimal clinically important difference was set at 1 out of 10 for postoperative pain and 10 mg for iv morphine-equivalent consumption.
Results

Baseline Characteristics of Included Studies

The literature screening process and its results are shown in Figure 1. The screening sequence of the PRISMA 2009 flow diagram which compared the analgesic efficacy of TPVB, ESPB, SPB, INB and Control (no block), identified 21 studies [25-45] with a total of 1391 patients. Table 1 shows the characteristics of the included studies. Table 2 shows the numbers of included studies and enrolled patients assorted by outcomes.

Methodological Quality and Risks of Bias

Individual studies were assessed using the Cochrane Collaboration’s Risk of Bias tool [46] and ranked according to a low/high/unclear grading scale (Figure 2). The overall quality of the 21 included studies was moderate. Some of the studies showed possible patient selection bias and bias in methodology, with 70% showing an unclear or a high risk of bias in performance concealment, 25% showing bias in blinding of participants and personnel, and 55% showing bias in blinding of outcome assessment. A comparison-adjusted funnel plot showed evidence of a visually symmetric plot in opioid consumption and pain scores at 3 time periods. A results of Egger’s regression test of outcomes also showed no significant publication bias (P>0.05) (page 14 of each supplementary files). The quality of evidence was rated as very low to low in nature with the GRADE system (Table 2) and confidence rating of each comparison by CINeMA were described in 5th supplement file.

Heterogeneity and Consistency Test

The results of $I^2$ and Q statistics (based on the full design-by-treatment interaction random-effects model) results were suggest that a random-effects model may be advisable to elucidate the inconsistency and heterogeneity in our network model (Table 2). Additionally, according to the
colored background of the net heat plot, random-effects model may be more suitable for our data (page 10 and 11 of each supplementary files). Direct evidence plot (page 5 to 6 of each supplementary files) and forest plot of the net splitting results (page 11 to 12 of each supplementary files) were used to evaluate local inconsistency.

**Efficacy outcomes (Network Meta-analysis)**

17 [25-28,30,31,33,35,37-45] RCTs reported opioid consumption and 18 [25,26,28,30-36,38-45], 16 [25,26,28-35,38-44], 17 [25-27,29,30,33-36,38-45] RCTs reported pain score for each time period during the postoperative 24 hours. The networks for TPVB and Control were greater than the networks for other blocks, followed ESPB and Control. As shown in Figure 3, TPVB showed the most superior analgesic effect on opioid consumption when compared with Control (MD = -13.2 mg, 95% CI -16.2 to -10.1), followed by INB (MD = -9.55 mg, 95% CI -13.2 to -5.9), ESPB (MD = -8.7 mg, 95% CI -11.4 to -6.1), SPB (MD = -5.9 mg, 95% CI -9.4 to -2.5). In terms of pain score in the early period, ESPB had the greatest effect compared with Control (MD = -1.6, 95% CI -2.3 to -0.9), followed by TPVB, INB and SPB consecutively. In the middle and the late period, TPVB, ESPB and INB showed superior analgesic effect over Control in reducing pain score, whereas SPB showed no greater effect. Local inconsistency of ESPB and Control was significant in the early and middle period (Table 2). In the two studies by Ciftci et al. [34,35], effect sizes tended to be higher than those measured in other studies. Table 3 shows the network league table that separately displays direct comparison and full model results.

**Results of the ranking hierarchy**

Table 4 shows the P-scores of the analgesic efficacy and the ranking of the 5 groups. TPVB ranked first in the 24hour opioid consumptions (0.996), middle and late pain score (0.793 and 0.831).
However, ESPB ranked first in the pain score of early period (0.792). INB ranked second in the opioid consumption and third in the pain score of all period. SPB ranked fourth in all outcomes.
Discussion

There are various regional analgesia techniques that are performed in clinical settings in effort to improve postoperative pain control for VATS. This NMA demonstrated the potential benefits of the various regional analgesia techniques for postoperative pain control in patients undergoing VATS and evaluated which of those techniques may exceed others in a manner of rank. When compared with mere systemic analgesia, all four regional analgesic techniques significantly reduced the cumulative opioid consumption during the postoperative 24 hours. Especially, TPVB shows remarkable effectiveness in the reduction of opioid consumption. The effect of ESPB was noteworthy in lowering pain score in the early postoperative period, while the effect size of TPVB was clinically similar to that of ESPB. In the case of SPB, although the statistical significance of the opioid consumption was certain, the effect size was about half that of other methods. Moreover, the pain score measured in the middle and the late periods did not show a significant difference compared to the measurements obtained in the Control.

Statistically significant differences are not always clinically significant. For instance, a difference of 10 mg or more in parenteral morphine was clinically difference [47], and change of 10 mm in the 100 mm visual analogue scale of pain was regarded as clinically important difference [48]. In our opinion, changes about 1-2 points of pain score in patients who had initially addressed moderate to severe pain should be considered to show clinically significant difference. Also, change of pain score from initial values of 4-5 points to values less than 3 were considered to have shown clinically significant differences. As a matter of fact, less than 33 points in 100 scale of VAS is accepted as a state of well–controlled pain in clinical setting [48]. With reference to opioid consumption, TPVB showed reduction of 13.2 mg of opioid consumption and reduction of more than 1 point in pain score, which is viewed as clinically significant. In ESPB, the reduction of opioid consumption was 8.71 mg, which was less than 10 mg, but decrease in pain score was 1.6, showing the best results in the
early postoperative period. However, this result had direct and indirect inconsistencies which demands caution in interpretation. Two studies, performed by Ciftci et al. and included in our NMA, comparing ESPB and control had very large effect size compared to the others, which may have drawn to this inconsistency [34,35].

ESPB as an emerging technique has been applied in a wide variety of field, and above all, even beginners can easily get started [15]. Its analgesic effect has been verified in various studies [49-51]. However, as for the mechanism, no definitive answer is yet to be obtained. The most convincing hypothesis is the physical spread of local anesthetic to the thoracic paravertebral space and the associated neural structures [52]. Penetration via diffusion into the paravertebral space through intertransverse connective tissue complex may continue over a prolonged. Therefore, if anterior spreading to thoracic paravertebral space is sufficient, ESPB should provide an effect similar to that of TPVB. Nonetheless, studies which compare the ESPB and TPVB imply that there is a significant difference in the analgesic effects of the two blocks [38,49]. Improvement in postoperative pain score and reduction of opioid consumption are better in TPVB than ESPB. Unlike the result of single ESPB, according to the study of continuous infusion through the catheter, ESPB was non-inferior to TPVB [53]. In both groups, continuous infusion of 8 mL/hr following 20 mL bolus injection was performed. In the early postoperative period, TPVB presented favorable results with regard to pain score compared to ESPB, but in the long term, the effects of the two blocks were similar, and thus no difference in opioid consumption was observed. If the mechanism is anterior spreading to thoracic paravertebral space by gradual diffusion, continuous infusion can be more effective than a single injection. For reducing heterogeneity, we included RCTs using only single block technique. Continuous block using catheter in TPVB still recommended in thoracotomy by PROSPECT group [14], but it is questionable whether continuous block is necessary in VATS as minimally invasive surgical technique. In most of the RCTs included in this NMA, pain of middle and late
period were mild (NRS <3) in the control group. Multimodal analgesia including regular acetaminophen, NSAIDs and adjuvant for prolongation of block may be sufficient in VATS surgery [54,55].

According to a recent Cochrane review, TPVB was as effective as TEA in controlling acute pain, and TPVB was associated with less complications such as hypotension, urinary retention, nausea and vomiting [56]. Owing to these advantages, TPVB has recently been preferred to TEB in thoracic surgery. In other surgeries, such as breast surgery, the excellent analgesic effect of TPVB is offset by concerns about pneumothorax [57]. However, concerns about pneumothorax are greatly reduced in VATS, which allows for TPVB without burden.

INB is a well-known traditional technique for pain management after thoracic surgery. INB can be performed easily with various techniques using ultrasonography or by blind technique. Also, direct injection inside of the thorax by thoracic surgeon is available [30]. INB would only result in segmental somatic nerve blockade, and thus multiple injections are essential for appropriate pain control. Therefore, it can be expected that the effect size of INB is similar to that of SPB. Although there are only two INB-SPB direct comparisons in this NMA, there are no differences in analgesic effect.

SPB can be easily performed in the lateral decubitus position which is the surgical position in thoracic surgery [58]. Although analgesic effect of SPB was comparable to that of TEB in a previous study [59], our result of NMA showed only limited effect in the early postoperative period. The effect of reduction in opioid consumption is less than half that of TPVB. Among the four block techniques, only SPB was adequate to block the long thoracic nerve which controls pain derived from damage of serratus muscle and strain of surrounding structures [60]. Blockade of long thoracic nerve actually reduced the postoperative pain after VATS [61]. In addition, there is growing evidence that motor nerves are also involved in afferent nociception via sensory innervation and connection
with other nerves [62,63]. However, the clinical effect of long thoracic nerve blockade does not seem to be as great as expected and this is attributable to trivial muscle damage due to VATS, of which its impact on postoperative pain in insignificant.

**Limitation**

This study has several potential limitations. First, the included studies were highly heterogeneous. Despite that the present study includes only RCTs in patients who underwent VATS, the concentrations of drugs and technical details were not consistent. In addition, various drugs were used for multimodal analgesia. Second, the time points at which pain scores were measured were not consistent with each other and were not presented as accurate values. To reduce any bias, we divided the time period into three intervals and used the values corresponding to each interval as representative values. Third, the sample size was insufficient to draw definitive conclusions. Also, ESPB and SPB are currently developing techniques, which may suggest a possibility of publication bias.

**Conclusion**

In conclusion, the NMA performed in this study conducts its strength and significance as an attempt to compare the regional analgesia techniques concerning efficacy of improving postoperative pain control for VATS. TPVB showed outstanding analgesic effect and ESPB ranked the highest in lowering pain score in the early postoperative period. However, in view of the distinguishable reduction of opioid consumption of the four regional analgesic techniques, performing any regional blocks after VATS seems reasonable, regardless of various factors such as the practitioner, patient, and individual working set up. Further and more refined studies are needed to determine the optimal regional analgesia technique to improve postoperative pain control for VATS.
Table 1. Characteristics of the Enrolled Studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Surgery</th>
<th>Port</th>
<th>Group (n)</th>
<th>Block level</th>
<th>Localization</th>
<th>Local anesthetics</th>
<th>Block timing</th>
<th>Opioid data</th>
<th>Pain score data form (early, middle, late period) (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu, 2021 [25]</td>
<td>China</td>
<td>Lobectomy, Wedge resection, Segmentectomy</td>
<td>1</td>
<td>ESPB (40) Control (40)</td>
<td>T5</td>
<td>Ultrasound</td>
<td>25 ml of 0.4% ropivacaine</td>
<td>Before induction</td>
<td>Sufentanil</td>
<td>Table (2, 8, 24)</td>
</tr>
<tr>
<td>Hu, 2021 [26]</td>
<td>China</td>
<td>Wedge resection</td>
<td>1</td>
<td>TPVB (30) Control (30)</td>
<td>T4, intrathoracic approach</td>
<td>Thoracoscopic- assisted</td>
<td>20 ml of 0.375% ropivacaine</td>
<td>End of surgery</td>
<td>Sufentanil</td>
<td>Table (6, 12, 24)</td>
</tr>
<tr>
<td>Zhao, 2020 [27]</td>
<td>China</td>
<td>Lobectomy, Wedge resection, Segmentectomy</td>
<td>NA</td>
<td>ESPB (33) TPVB (33)</td>
<td>T4&amp;6</td>
<td>Ultrasound</td>
<td>30 ml of 0.4% ropivacaine</td>
<td>Before induction</td>
<td>Oxycodone</td>
<td>Table (NA, NA, 24)</td>
</tr>
<tr>
<td>Yao, 2020 [28]</td>
<td>China</td>
<td>Lobectomy, Segmentectomy</td>
<td>NA</td>
<td>ESPB (37) Control (38)</td>
<td>T5</td>
<td>Ultrasound</td>
<td>25 ml of 0.5% ropivacaine</td>
<td>Before induction</td>
<td>Sufentanil</td>
<td>Table (1, 8, 24)</td>
</tr>
<tr>
<td>Viti, 2020 [29]</td>
<td>Italy</td>
<td>Lobectomy, Segmentectomy</td>
<td>3</td>
<td>SPB (46) Control (44)</td>
<td>5th rib</td>
<td>Ultrasound</td>
<td>30 ml of 0.3% ropivacaine</td>
<td>After induction</td>
<td>No data</td>
<td>Plot (NA, 6am to 2pm POD1, 2pm to 10pm POD1)</td>
</tr>
<tr>
<td>Turhan, 2020 [30]</td>
<td>Turkey</td>
<td>Lobectomy, Segmentectomy</td>
<td>2</td>
<td>ESPB (35)</td>
<td>TPVB (35)</td>
<td>INB (36)</td>
<td>20 ml of 0.5% ropivacaine</td>
<td>TPVB, ESPB: Before induction</td>
<td>INB: Thoracoscopic - assisted</td>
<td>Morphine Mg Equivalent</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>Lee, 2020 [31]</td>
<td>Korea</td>
<td>Lobectomy</td>
<td>3</td>
<td>INB (23)</td>
<td>SPB (23)</td>
<td>5th rib</td>
<td>20 ml of 0.375% ropivacaine</td>
<td>INB: end of the surgery</td>
<td>SPB: After induction</td>
<td>fentanyl</td>
</tr>
<tr>
<td>Kim, 2020 [32]</td>
<td>Korea</td>
<td>Wedge resection for primary spontaneous pneumothorax</td>
<td>1</td>
<td>INB (25)</td>
<td>SPB (25)</td>
<td>5th rib</td>
<td>20 mL of 0.375% ropivacaine</td>
<td>INB: end of the surgery</td>
<td>SPB: After induction</td>
<td>Fentanyl, No Standard time (chest tube removal)</td>
</tr>
<tr>
<td>Finnerty, 2020 [33]</td>
<td>Ireland</td>
<td>wedge resection, pleurodesis, pleurectomy, lobectomy, decortication, bullectomy, or pleural biopsy</td>
<td>NA</td>
<td>ESPB (30)</td>
<td>SPB (30)</td>
<td>T5, 5th rib</td>
<td>30 ml of 0.25% levobupivacaine</td>
<td>After induction</td>
<td>oxycodone</td>
<td>Plot (1,12,24)</td>
</tr>
<tr>
<td>Ciftci, 2020 [34]</td>
<td>Turkey</td>
<td>Lobectomy, wedge resection</td>
<td>3</td>
<td>ESPB (30)</td>
<td>TPVB (30) Control (30)</td>
<td>T5</td>
<td>20 ml of 0.25% bupivacaine</td>
<td>Before induction</td>
<td>Fentanyl, 48 hr data only</td>
<td>Plot (1,8,24)</td>
</tr>
<tr>
<td>Ciftci, 2020 [35]</td>
<td>Turkey</td>
<td>Lobectomy</td>
<td>NA</td>
<td>ESPB (30)</td>
<td>T5</td>
<td>Ultrasound</td>
<td>20 ml of 0.25% bupivacaine</td>
<td>Before induction</td>
<td>fentanyl</td>
<td>Table (2,8,24)</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Procedures</td>
<td>N</td>
<td>Anesthesia Technique</td>
<td>Route and Dose</td>
<td>Medications</td>
<td>Control (N)</td>
<td>Outcome</td>
<td>Notes</td>
<td></td>
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<td>------------------</td>
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<tr>
<td>Chu, 2020 [36]</td>
<td>China</td>
<td>Lobectomy, Wedge resection, Segmentectomy</td>
<td>NA</td>
<td>Control (24)</td>
<td>Ultrasound</td>
<td>T4, T7</td>
<td>20 mL of 0.375% ropivacaine</td>
<td>Unknown, Sufentanil, No data</td>
<td>Table (1, NA, 24)</td>
<td></td>
</tr>
<tr>
<td>Cheng, 2020 [37]</td>
<td>China</td>
<td>Lobectomy</td>
<td>1</td>
<td>Control (25)</td>
<td>Ultrasound</td>
<td>4th and 5th rib (modified intercostal nerve block)</td>
<td>10 mL of 0.35% ropivacaine</td>
<td>After induction, sufentanil</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Chen, 2020 [38]</td>
<td>China</td>
<td>Lobectomy, Wedge resection, Segmentectomy</td>
<td>2</td>
<td>TPVB (24), INB (24), ESPB (24)</td>
<td>Ultrasound</td>
<td>TPVB: T5, 6, 7, INB: T4-T9, ESPB: T5</td>
<td>20 mL of 0.375% ropivacaine</td>
<td>After induction, Morphine Mg Equivalent</td>
<td>Plot (2, 8, 24)</td>
<td></td>
</tr>
<tr>
<td>Gaballah, 2019 [39]</td>
<td>Egypt</td>
<td>Wedge resection, Decortication, Bullectomy, Pleural biopsy, Pleurodesis, Repair of bronchopleural fistula, Diaphragmatic plication</td>
<td>NA</td>
<td>ESPB (30), SPB (30)</td>
<td>Ultrasound</td>
<td>ESP: T5, SPB: T7</td>
<td>20 mL of 0.25% bupivacaine</td>
<td>After induction, pethidine</td>
<td>Plot (1, 12, 24)</td>
<td></td>
</tr>
<tr>
<td>Wu, 2018 [40]</td>
<td>China</td>
<td>wedge resection, lobectomy, hilobectomy</td>
<td>NA</td>
<td>TPVB (34), INB (32)</td>
<td>Ultrasound</td>
<td>TPVB: T5, INB: 4th and 7th intercostal space</td>
<td>0.3 mL/kg of 0.5% ropivacaine</td>
<td>Before induction, Sufentanil</td>
<td>Plot (1, 10, 24)</td>
<td></td>
</tr>
<tr>
<td>Authors</td>
<td>Country</td>
<td>Procedures</td>
<td>Group</td>
<td>Level</td>
<td>Method</td>
<td>Anesthesia</td>
<td>Postoperative</td>
<td>Adjuvant</td>
<td>Data Collection</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
<td>------------</td>
<td>--------</td>
<td>-------</td>
<td>----------</td>
<td>-------------</td>
<td>---------------</td>
<td>-----------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td>Okmen, 2018 [41]</td>
<td>Turkey</td>
<td>Wedge resection, Lobectomy</td>
<td>SPB(20) Control(20)</td>
<td>5th rib</td>
<td>Ultrasound</td>
<td>20 ml of 0.25% bupivacaine</td>
<td>End of surgery</td>
<td>Tramadol</td>
<td>Table (2,12,24)</td>
<td></td>
</tr>
<tr>
<td>Kim, 2018 [42]</td>
<td>Korea</td>
<td>Lobectomy, Wedge resection, Segmentectomy</td>
<td>SPB(42) Control(43)</td>
<td>5th rib</td>
<td>Ultrasound</td>
<td>0.4 ml/kg of 0.375% ropivacaine</td>
<td>After induction</td>
<td>Morphine Mg Equivalent</td>
<td>Plot (NA,12,24)</td>
<td></td>
</tr>
<tr>
<td>Ahmed, 2017 [43]</td>
<td>Pakistan</td>
<td>Elective diagnostic VATS</td>
<td>INB (30) Control (30)</td>
<td>5 level</td>
<td>Bone landmark</td>
<td>20 ml of 0.25% bupivacaine</td>
<td>End of surgery</td>
<td>Morphine</td>
<td>Plot (1,12,24)</td>
<td></td>
</tr>
<tr>
<td>Kaya, 2006 [44]</td>
<td>Turkey</td>
<td>Wedge resection, Lung biopsy, Pleural biopsy</td>
<td>TPVB (25) Control (22)</td>
<td>T4–8, 5 level</td>
<td>Bone landmark</td>
<td>20 ml of 0.5% bupivacaine</td>
<td>Before induction</td>
<td>Morphine</td>
<td>Table (1,8,24)</td>
<td></td>
</tr>
<tr>
<td>Vogt, 2005 [45]</td>
<td>Switzerland</td>
<td>Biopsy, Lung resection, Pleurodeses, Resection of intrathoracic tumour</td>
<td>TPVB Control</td>
<td>T6</td>
<td>Bone landmark</td>
<td>0.4 ml/kg of 0.375% bupivacaine</td>
<td>After induction</td>
<td>Morphine</td>
<td>Plot (1,NA,24)</td>
<td></td>
</tr>
</tbody>
</table>

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Table 2. Results of model, heterogeneity, consistency test and GRADE quality of evidence assessment for the primary and secondary outcomes.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>No. of Pairwise comparison</th>
<th>Number of designs</th>
<th>Consistency test</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid consumption</td>
<td>17</td>
<td>1073</td>
<td>21</td>
<td>9</td>
<td>86.9</td>
<td>0.833</td>
<td>All comparisons are insignificant</td>
</tr>
<tr>
<td>Early postoperative period (up to 6 hours) pain score</td>
<td>18</td>
<td>1146</td>
<td>24</td>
<td>9</td>
<td>92.1</td>
<td>0.353</td>
<td>ESPB vs Control significant (p = 0.014), other comparisons are insignificant</td>
</tr>
<tr>
<td>Middle postoperative period (6 to 18 hours) pain score</td>
<td>16</td>
<td>1062</td>
<td>22</td>
<td>9</td>
<td>92.6</td>
<td>0.159</td>
<td>ESPB vs Control significant (p = 0.004), other comparisons are insignificant</td>
</tr>
<tr>
<td>Late postoperative period (18 to 24 hours) pain score</td>
<td>17</td>
<td>1250</td>
<td>23</td>
<td>9</td>
<td>81.8</td>
<td>0.935</td>
<td>All comparisons are insignificant</td>
</tr>
</tbody>
</table>

$I^2$, Higgins' $I^2$; Global inconsistency based on the full design-by-treatment interaction random-effects model [21]; Local inconsistency based on difference between direct and indirect estimates by net splitting technique.
Table 3. Network league table for all the interventions in regard to the opioid consumption, pain score at early (up to 6 hours), middle (6 to 18 hours), and late (18 to 24 hours) during postoperative 24 hours. Estimates are presented as mean differences (95% confidence interval).

Mean differences below 0 favor the column intervention and mean differences above 0 favor the row intervention.

**Opioid consumption**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>8.59 (5.22; 11.96)</th>
<th>7.00 (-2.24; 16.24)</th>
<th>7.09 (2.94; 11.24)</th>
<th>12.64 (8.30; 16.98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.71 (6.06; 11.35)</td>
<td>ESPB</td>
<td>2.75 (-1.78; 7.28)</td>
<td>-6.47 (12.95; 0.02)</td>
<td>5.08 (1.42; 8.74)</td>
<td></td>
</tr>
<tr>
<td>9.55 (5.89; 13.21)</td>
<td>INB</td>
<td>0.85 (-2.63; 4.32)</td>
<td>-1.50 (11.94; 8.94)</td>
<td>3.69 (0.15; 7.23)</td>
<td></td>
</tr>
<tr>
<td>5.92 (2.48; 9.35)</td>
<td>SPB</td>
<td>-2.79 (-6.57; 1.00)</td>
<td>-3.63 (-8.14; 0.88)</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td>13.17 (0.12; 16.21)</td>
<td>TPVB</td>
<td>4.46 (1.53; 7.39)</td>
<td>3.62 (0.43; 6.80)</td>
<td>7.25 (3.03; 11.47)</td>
<td></td>
</tr>
</tbody>
</table>

**Early postoperative period (up to 6 hours) pain score**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>2.25 (1.37; 3.14)</th>
<th>1.10 (-0.63; 2.83)</th>
<th>0.85 (-0.44; 2.14)</th>
<th>1.25 (0.41; 2.09)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.59 (0.88; 2.29)</td>
<td>ESPB</td>
<td>0.43 (-0.98; 1.84)</td>
<td>.</td>
<td>-0.20 (-1.60; 1.20)</td>
<td>0.43 (-0.70; 1.56)</td>
</tr>
<tr>
<td>1.36 (0.50; 2.23)</td>
<td>INB</td>
<td>-0.22 (-1.13; 0.69)</td>
<td>-0.40 (-1.79; 0.98)</td>
<td>0.37 (-0.71; 1.46)</td>
<td></td>
</tr>
<tr>
<td>1.05 (0.17; 1.94)</td>
<td>SPB</td>
<td>-0.53 (-1.45; 0.38)</td>
<td>-0.31 (-1.27; 0.65)</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td>1.47 (0.76; 2.17)</td>
<td>TPVB</td>
<td>-0.12 (-0.94; 0.71)</td>
<td>0.11 (-0.76; 0.97)</td>
<td>0.42 (-0.59; 1.43)</td>
<td></td>
</tr>
</tbody>
</table>

**Middle postoperative period (6 to 18 hours) pain score**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>1.98 (1.15; 2.81)</th>
<th>0.40 (-1.23; 2.03)</th>
<th>0.04 (-1.26; 1.34)</th>
<th>1.25 (0.27; 2.23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.28 (0.59; 1.97)</td>
<td>ESPB</td>
<td>0.62 (-0.86; 2.09)</td>
<td>0.06 (-1.25; 1.37)</td>
<td>0.49 (-0.60; 1.58)</td>
<td></td>
</tr>
<tr>
<td>0.93 (0.09; 1.78)</td>
<td>INB</td>
<td>-0.35 (-1.23; 0.54)</td>
<td>0.04 (-1.22; 1.31)</td>
<td>0.32 (-0.70; 1.34)</td>
<td></td>
</tr>
<tr>
<td>0.78 (-0.07; 1.64)</td>
<td>SPB</td>
<td>-0.50 (-1.37; 0.38)</td>
<td>-0.15 (-1.06; 0.76)</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td>1.30 (0.53; 2.07)</td>
<td>TPVB</td>
<td>0.02 (-0.81; 0.85)</td>
<td>0.37 (-0.47; 1.20)</td>
<td>0.52 (-0.48; 1.52)</td>
<td></td>
</tr>
</tbody>
</table>

**Late postoperative period (18 to 24 hours) pain score**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>1.15 (0.61; 1.69)</th>
<th>0.70 (-0.19; 1.59)</th>
<th>0.21 (-0.47; 0.88)</th>
<th>0.88 (0.42; 1.35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.88 (0.48; 1.28)</td>
<td>ESPB</td>
<td>0.39 (-0.45; 1.22)</td>
<td>-0.73 (-1.49; 0.03)</td>
<td>0.21 (-0.30; 0.72)</td>
<td></td>
</tr>
<tr>
<td>0.86 (0.33; 1.38)</td>
<td>INB</td>
<td>-0.03 (-0.58; 0.52)</td>
<td>.</td>
<td>0.15 (-0.43; 0.73)</td>
<td></td>
</tr>
<tr>
<td>0.18 (-0.35; 0.72)</td>
<td>SPB</td>
<td>-0.70 (-1.25; 0.15)</td>
<td>-0.67 (-1.38; 0.03)</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td>0.97 (0.59; 1.35)</td>
<td>TPVB</td>
<td>0.09 (-0.33; 0.51)</td>
<td>0.11 (-0.38; 0.60)</td>
<td>0.79 (0.17; 1.40)</td>
<td></td>
</tr>
</tbody>
</table>

The upper triangle displays only the pooled effect sizes of the direct comparisons available in our network. No direct comparison is expressed empty field. The lower triangle contains the estimated effect sizes for each comparison even the ones for which only indirect evidence was available.
Table 4. P-scores and ranking

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid</td>
<td>TPVB</td>
<td>INB</td>
<td>ESPB</td>
<td>SPB</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>0.9963</td>
<td>0.6598</td>
<td>0.5610</td>
<td>0.2829</td>
<td>0.0001</td>
</tr>
<tr>
<td>Early</td>
<td>ESPB</td>
<td>TPVB</td>
<td>INB</td>
<td>SPB</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>0.7918</td>
<td>0.6937</td>
<td>0.6148</td>
<td>0.3969</td>
<td>0.0027</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>TPVB</td>
<td>ESPB</td>
<td>INB</td>
<td>SPB</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>0.7927</td>
<td>0.7815</td>
<td>0.5066</td>
<td>0.4060</td>
<td>0.0132</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late</td>
<td>TPVB</td>
<td>ESPB</td>
<td>INB</td>
<td>SPB</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>0.8310</td>
<td>0.7185</td>
<td>0.6895</td>
<td>0.1979</td>
<td>0.0632</td>
</tr>
</tbody>
</table>
Figure 1. Study Flow Diagram

- **Identification:**
  - 308 of records identified through database searching
  - 251 of records after duplicates removed
  - 251 of records screened
  - 208 of records excluded

- **Screening:**
  - 43 of full-text articles assessed for eligibility
  - 22 of full-text articles excluded, with reasons:
    - Study design was not in accordance with inclusion criteria (n=20)
    - No available data for qualitative or quantitative synthesis (n=2)

- **Eligibility:**
  - 21 of studies included in qualitative synthesis

- **Included:**
  - 21 of studies included in quantitative synthesis (meta-analysis)
Figure 2. Assessment of Risk of Bias for Included Studies. The overall quality of the included studies were deemed satisfactory.
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Figure 3. Network plots and forest plots for the network meta-analysis. (A) opioid consumption in the first 24h, (B) Early postoperative period (up to 6 hours) pain score, (C) Middle postoperative period (6 to 18 hours) pain score, and (D) Late postoperative period (18 to 24 hours) pain score. The mean difference (MD) and 95 % confidence interval (95% CI) are shown.
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