

Regional block techniques for pain management after video-assisted thoracoscopic surgery: a covariate-adjusted Bayesian network meta-analysis

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Abstract

Introduction: Nerve block is widely used for pain management after video-assisted thoracoscopic surgery (VATS). Thoracic paravertebral block (TPVB), erector spinae plane block (ESPB), serratus anterior plane block (SAPB), and intercostal nerve block (ICNB) are alternative treatments.

Material and methods: Network meta-analysis based on Bayesian analyses was performed to obtain results for direct comparison, indirect comparison, and network comparison, and to make rankings based on probabilities. Covariates were adjusted to determine the effect of the covariates on results of this study.

Results: The study identified 61 randomized controlled trials (RCTs) (4468 patients). There were results of probability ranking for the first (“best” treatment): 24 h morphine consumption, TPVB > ESPB > ICNB > SAPB. Covariate adjustment allowed the four treatments to change somewhat in the likelihood of the best choice.

Conclusions: TPVB ranks best in our analysis. ESPB is a viable alternative. SAPB and ICNB seem to play a limited role in postoperative pain management.

Key words: network meta-analysis, covariate adjustment, video-assisted thoracoscopic surgery, nerve block.

Introduction

With the further improvement and popularization of lung cancer screening strategies, invasive intervention for pulmonary nodules has become earlier and earlier. The mode of thoracic surgery is also gradually transitioning from thoracotomy to video-assisted thoracoscopic surgery, and 70% of lung cancer operations in the United States are performed using the minimal access approach [1].

However, patients still have moderate to severe pain after video-assisted thoracoscopic surgery. As one of the multimodal analgesic methods, nerve block is widely used for pain management after

thoracoscopic surgery. Both the gold standard “thoracic epidural analgesia” (TEA) and thoracic paravertebral block (TPVB) improve nociceptive somatic pain and sympathetically mediated visceral pain, while attenuating neuropathic pain caused by intercostal nerve injury [2]. Given the numerous risks that epidural block can pose, clinicians often do not choose TEA as the first choice. PROSPECT recommends TPVB as the primary method of regional analgesia in thoracic surgery [3], but considering the risks associated with its operation, such as puncture of the pleura, we are still actively looking for alternatives that are feasible and safe. Erector spinae plane block (ESPB), serratus anterior plane

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block (SAPB), and intercostal nerve block (ICNB) have all become weapons of choice.

Previous attempts to synthesize the available data have been limited to a pairwise meta-analysis of two or three block modalities and have not provided the evidence for comparing all available nerve block options. Network meta-analysis (NMA) using indirect comparison of treatments to replace and supplement direct comparison of block methods can improve the precision of outcome estimates and facilitate ranking of key outcomes. A classical frequentist-based network meta-analysis and a Bayesian-based one were used to compare the differences in opioid use and pain after thoracoscopic surgery with different blocks [4, 5]. Studies were incomplete, and there was a lack of comparison of rescue analgesia, adverse effects, length of hospitalization and other important events. Recently, a net meta-analysis attempted to complement the above-mentioned deficiencies [6]. However, in fact, we have another important issue that should not be overlooked: network meta-analysis tends to be highly heterogeneous. Network meta-regression is one of the main ways to address heterogeneity [7], and covariates should be discussed in the analysis. All the net meta-analyses related to this topic have lacked adjustment for covariates.

Aim

Our research team aimed to summarize many articles in the literature and to rank four nerve block methods based on a Bayesian network approach for different important outcomes. We also aimed to carry out network meta-regression to explore the influence of covariates on the ranking comparison, so as to obtain more realistic and objective results of ranking.

Material and methods

The NMA followed the statement guidelines of PRISMA (Appendix 1, PRISMA NMA Checklist). The protocol was already registered in the Prospective Register of Systematic Reviews (PROSPERO). (CRD42022360509).

Search strategy and selection criteria

As of July 1, 2022, the researchers searched PubMed, Embase, Web of Science, The Cochrane Central Register of Controlled Trials, and clinicaltrials.gov to obtain information about the content of nerve blocks in thoracoscopic surgery. See Appendix 2 for detailed retrieval strategies. To identify more references, we also manually searched for meta-analysis and systematic reviews on this topic. It was emphasized that the literature included in this study was not limited by language.

Two researchers independently reviewed and assessed the full text and identified studies that met the requirements. Any disagreement over the inclusion of a trial was ultimately resolved through discussion or coordination by a third independent author. Inclusion criteria: as long as some results discussed in the reviewed literature exist in the results included in this net meta-analysis, the literature is included. Exclusion criteria: 1) video-assisted thoracoscopic surgery without intubation or preservation of spontaneous breathing; 2) nerve block with catheter insertion or continuous infusion; and 3) the use of opioids as adjuvants when nerve block is performed.

Risk of bias assessment

Risk of bias was determined independently by two authors using the Cochrane Collaborative Assessment Tool. The following areas were assessed as low, unclear, or high risk of bias: random sequence generation; allocation concealment; randomization methods; concealed treatment allocation; blinding in preoperative, perioperative and postoperative care; blinded data collection with analysis; blinded adjudication of study endpoints; and data integrity. Risk of bias was assessed using the Cochrane Risk of Bias tool and a plot of risk of bias was generated.

A funnel plot was constructed to assess publication bias. The Q-Q normal distribution plot was used to identify whether the sample data are approximately normally distributed. As an initial exploration of research heterogeneity, radial plots and Baujat plots were requested.

Data extraction

Data were extracted by one reviewer and checked independently by another reviewer. Disagreements were resolved by re-examination of the manuscript and, if necessary, asking a third investigator to adjudicate. Results recorded in the literature were expressed as mean and standard deviation for continuous variables and the number of occurrences in the

population was recorded for categorical variables. In some RCTs, if the data of interest were expressed in terms of medians and interquartile ranges, we combined the sample size to estimate the mean and standard deviation [8]. If the data were presented graphically, the researchers used Engauge Digitizer software (version 12.1, Mark Mitchell) to create a simulated coordinate system to obtain the required data.

Outcomes

The primary outcome is the 24-hour postoperative morphine dosage. Secondary outcomes are pain scores within 24 h postoperatively, number of remedial analgesia within 24 h postoperatively, length of hospital stay (LOS), and major adverse effects (nausea and vomiting). In view of the different types of postoperative intravenous opioids in different RCTs, the same equivalent intravenous morphine dose is used to represent the opioid use in this study.

The pain scores within 24 h after surgery are all based on the VAS scores (which range from 1 to 10). The pain conditions 24 h after the operation are divided into early (0–6 h), medium (6–12 h) and late (12–24 h), and the researchers select the most severe pain scores in the three stages.

Data analysis

According to the different outcomes discussed in this study, the corresponding network evidence plots were drawn to observe and identify inconsistent nodes. For each outcome variable, we determined which pairs of techniques have appropriate comparative analysis in the studies we included such that a meaningful assessment of their relative effectiveness could be made. These patterns are presented in network evidence plots. In addition to showing whether all nodes (representing the techniques) are connected, these plots also provide an indication of the number of trials in each comparison.

RStudio (version 4.2.1) was required, and the “Gemtc” package of R was invoked to conduct a net meta-analysis based on Bayesian analysis. A random-effect model was used in the Bayesian analysis. On the basis of the prior distribution of the research standard deviation of the uniform distribution, the iterative calculation was carried out using the Markov chain Monte Carlo simulation. This study set up 6000 iterations to provide evidence to confirm the conver-

gence of the model used. Convergence diagnostic plots as well as trace and density plots were used to verify the convergence of the model. The goodness of fit of the model was assessed based on Dbar, pD and deviation information criterion values (DIC).

In fact, this assumption of consistency was rarely fully valid due to inevitable changes in study protocols and population characteristics. In addition to methodological variations that cannot be mathematically neutralized, covariates explain the reported heterogeneity/inconsistency. The study-level covariates included in meta-regression were: (a) number of operating ports; (b) moment of block (pre- or post-operative); (c) types of local anesthetic; (d) number of block segments. Through network meta regression analysis, the regression coefficients and model fitting of different covariates were obtained, and then the influence of covariates on the results of this study was judged.

Under the condition of non-inclusion in covariates, we drew forest plots for different outcome variables. To better represent the differences between interventions, league tables for two-by-two comparisons were needed. For the primary outcome events, we also presented the results of direct and indirect comparisons.

Since the results of network analysis were the sum of direct and indirect comparisons, confidence intervals often overlapped in order to contain inherent imprecision. Therefore, the order results produced by NMA are probabilistic rather than the absolute order. Probability distributions of the five interventions in different orders were generated based on the size of the overlap between confidence intervals, and bar graphs were used to show probability distributions. Additionally, for the primary outcome, we further plotted surface under the cumulative ranking curve (SUCRA).

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence for each outcome [9].

Exploration of inconsistency/heterogeneity

Inconsistency needed to be measured between direct and indirect comparisons in the net meta-analysis. The node splitting method helped us to determine the inconsistency. Through this method, the results of direct comparison, indirect comparison

and network comparison and the p -value between the three were obtained, and the inconsistency test forest plot of node splitting method was drawn.

In a network meta-analysis, heterogeneity was measured between each pair of direct comparisons. A heterogeneity test was performed to obtain the I^2 of comparisons (direct and indirect) and the p -value of heterogeneity test. Finally, the I^2 of the overall direct comparison and indirect comparison is calculated collectively. To directly represent the results, the researchers plotted the heterogeneity test.

Results

Study selection and study characteristics

A total of 732 publications were retrieved for this study, and the inclusion and exclusion process,

shown in Supplementary Figure S1, resulted in the identification of 61 RCT studies with a total of 4468 patients. Details of the included randomized controlled trials are shown in Supplementary Table S1. We explored similarities and differences in pain management and postoperative recovery under five interventions: TPVB, ESPB, SAPB, ICNB, and Placebo (no block or sham block).

Methodological quality and risk of bias

The overall quality of the 61 included studies was high to moderate. Studies were evaluated according to Cochrane recommendations, and the overall study quality scores for each parameter are shown in Supplementary Figure S2. Although we included a large amount of grey literature that can be collect-

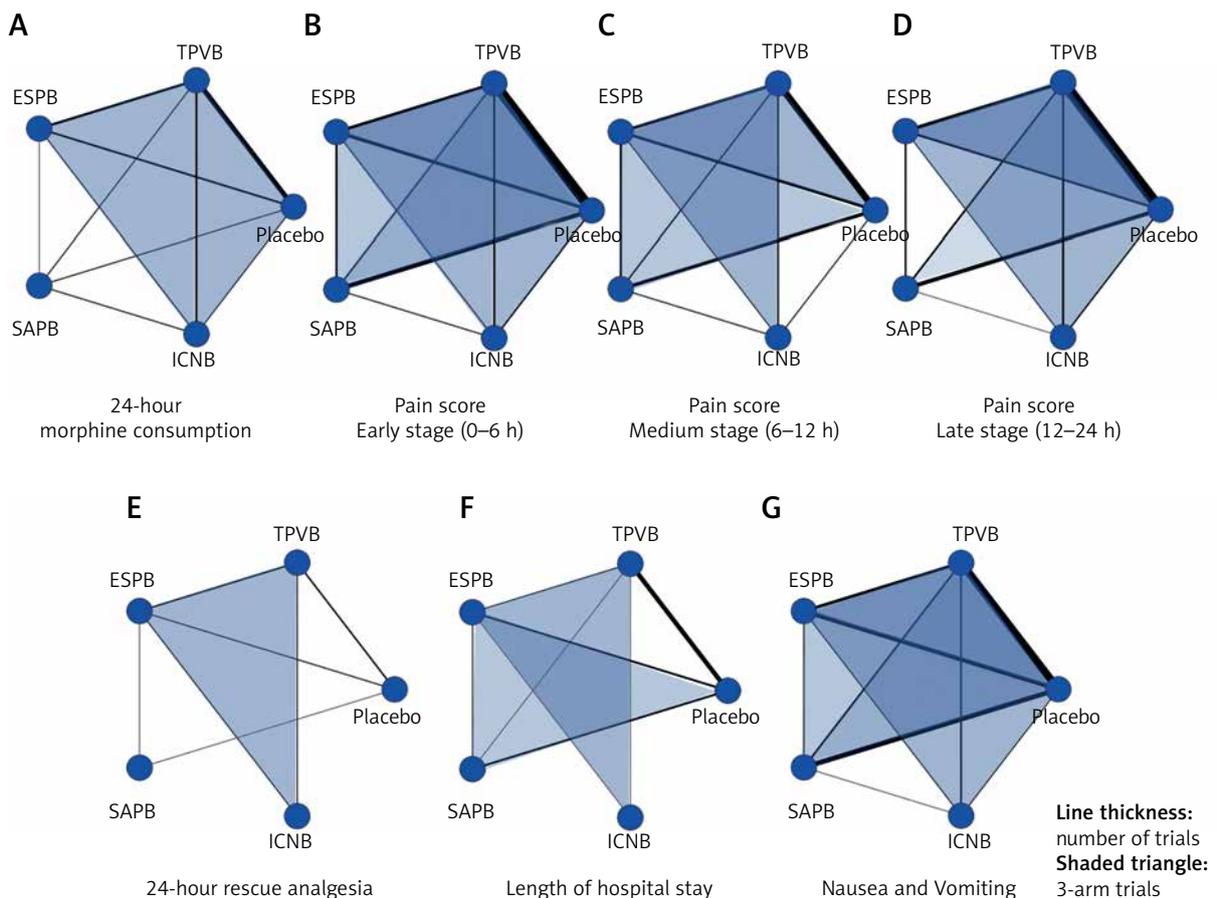


Figure 1. Network geometry. Blue dots indicate the different interventions. Lines between blue dots indicate the presence of RCTs between interventions, where the thickness of the lines indicates the number of trials. The shaded triangles with blue points as vertices represent 3-arm trials

ESPB – Erector Spinae Plane Block, ICNB – Intercostal Nerve Block, SAPB – Serratus Anterior Plane Block, TPVB – Thoracic Paravertebral Block.

ed, this study showed a certain degree of publication bias according to the distribution of funnel plots, as shown in Supplementary Figure S3. The distribution of the sample data showed an approximately normal distribution. The radial plot shows that, except for the large deviation of individual data, the data as a whole are still within the 95% confidence interval, but the data distribution is not around the regression line, considering the existence of large heterogeneity; the maximum source of heterogeneity is indicated in the Baujat plot.

Network geometry, and available outcome data

This study constructs a network of relationships between different interventions (Figure 1). Not all nodes are connected; that is, the network relationship is not complete. There are direct and indirect comparisons between interventions in 24 h morphine consumption, pain scores (early, mid- and late) and postoperative nausea and vomiting (PONV). However, there is no direct comparison in both outcomes of rescue analgesia and length of hospital stay: TPVB vs. SAPB, SAPB vs. ICNB, and Placebo vs. ICNB.

Table I illustrates the included studies, the number of participants and the data nodes involved for seven different outcome events. Of the included studies, 28 RCTs [10–37] reported opioid consumption; from 49 RCTs [10, 12, 14–17, 19, 21–26, 28–30, 32, 34–65], 41 RCTs [10, 12, 15–17, 19, 21–26, 28, 29, 31, 32, 34–37, 39–43, 45–49, 51, 54, 56, 57, 59–65], and 49 RCTs [10, 12, 14–17, 19–26, 28–32, 34–46, 48–53, 55–63, 65, 66], we obtained pain scores for three postoperative time periods (early, midterm, and late); and 10 RCTs [10, 16, 20, 21, 25, 28, 32, 35, 44, 45], 20 RCTs [10, 12, 13, 18, 20, 22, 26, 28, 36, 40, 42, 44, 47, 50, 53, 56, 60, 66–68], and 44 RCTs [10, 12–19, 21, 25, 28–36, 39, 41–43, 45, 47–49, 51–54, 56–60, 63, 64, 66–70] were utilized for rescue analgesia within 24 h, length of hospital stay, and PONV, respectively.

Model goodness-of-fit assessment

A network meta-analysis model was constructed under the Bayesian framework, and the convergence of this model was assessed, as seen in the convergence diagnostic plots as well as the trace and density plots. Supplementary Figures S4 and S5 show diagnostic plots of convergence and trace and

Table I. Available outcome data, model fit, covariate correction and possibility of optimal choice

Covariates	Available outcome data		Model fit (residual deviance)			Regression settings			Possibility of optimal choice				
	Number of RCTs (3-arm)	Number of participants	Data points	Dbar	DIC	Estimates at the centering value	Comments	TPVB	ESPB	ICNB	SAPB	Placebo	
24-hour morphine consumption													
No covariates				59.04	116.42	-	-	0.56	0.42	0.02	0.00	0.00	0.00
Ports of surgical operating				58.95	117.55	0.357	Unrelated coefficients	0.44	0.28	0.23	0.05	0.00	0.00
Moment of block	28 (3)	2002	59	59.21	118.08	1.286	Unrelated coefficients	0.41	0.12	0.39	0.07	0.01	0.01
Types of local anesthetics				59.27	118.42	1.750	Unrelated coefficients	0.43	0.34	0.10	0.12	0.01	0.01

Table I. Cont.

Covariates	Available outcome data		Model fit (residual deviance)				Regression settings				Possibility of optimal choice			
	Number of RCTs (3-arm)	Number of participants	Data points	Dbar	DIC	Estimates at the centering value	Comments	TPVB	ESPB	ICNB	SAPB	Placebo		
Number of block segments				59.01	117.12	1.429	Unrelated coefficients	0.36	0.27	0.06	0.25	0.06		
Pain score	Early stage (0–6 h)													
No covariates				103.66	200.90	–	–	0.36	0.21	0.25	0.18	0.00		
Ports of surgical operating				103.47	200.81	0.327	Unrelated coefficients	0.50	0.15	0.18	0.16	0.00		
Moment of block	49 (6)	3405	104	103.76	201.30	1.184	Unrelated coefficients	0.24	0.48	0.17	0.11	0.00		
Types of local anesthetics				103.99	202.42	1.735	Unrelated coefficients	0.31	0.18	0.30	0.21	0.00		
Number of block segments				104.27	201.45	1.510	Unrelated coefficients	0.31	0.18	0.22	0.29	0.00		
Pain score	Medium stage (6–12 h)													
No covariates				85.18	165.47	–	–	0.47	0.41	0.12	0.01	0.00		
Ports of surgical operating				84.99	166.12	0.293	Unrelated coefficients	0.92	0.06	0.02	0.00	0.00		
Moment of block	41 (4)	2941	86	86.63	168.74	1.220	Unrelated coefficients	0.53	0.32	0.03	0.13	0.00		
Types of local anesthetics				85.84	168.83	1.634	Unrelated coefficients	0.34	0.46	0.17	0.03	0.00		

Table 1. Cont.

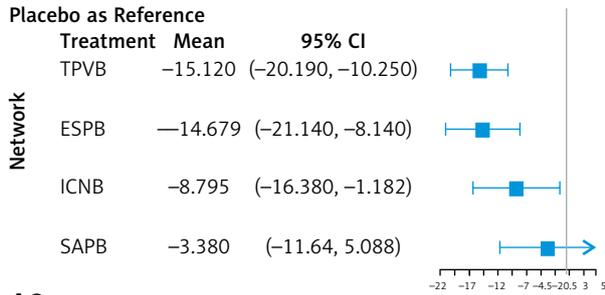
Covariates	Available outcome data	Model fit (residual deviance)				Regression settings				Possibility of optimal choice			
		Number of RCTs (3-arm)	Number of participants	Data points	Dbar	DIC	Estimates at the centering value	Comments	TPVB	ESPB	ICNB	SAPB	Placebo
Number of block segments			84.12	164.63	1.390	Unrelated coefficients	0.48	0.28	0.18	0.06	0.00		
Pain score Late stage (12–24 h)													
No covariates			102.34	198.73	–	–	0.09	0.10	0.47	0.34	0.00		
Ports of surgical operating			102.91	203.71	0.367	Unrelated coefficients	0.26	0.02	0.30	0.42	0.00		
Moment of block	49 (5)	3404	104.07	205.59	1.143	Unrelated coefficients	0.37	0.00	0.37	0.27	0.00		
Types of local anesthetics			104.59	208.96	1.755	Unrelated coefficients	0.05	0.14	0.39	0.42	0.00		
Number of block segments			103.58	204.09	1.571	Unrelated coefficients	0.17	0.00	0.58	0.25	0.00		
24-hour rescue analgesia													
No covariates			21.91	41.13	–	–	0.37	0.07	0.26	0.30	0.01		
Ports of surgical operating			21.59	41.11	0.200	Unrelated coefficients	0.31	0.09	0.30	0.29	0.01		
Moment of block	10 (2)	635	–	–	–	–	–	–	–	–	–		
Types of local anesthetics			21.90	41.12	1.600	Unrelated coefficients	0.54	0.03	0.14	0.29	0.00		
Number of block segments			21.63	40.88	1.500	Unrelated coefficients	0.60	0.11	0.23	0.06	0.00		

Table 1. Cont.

Covariates	Available outcome data		Model fit (residual deviance)				Regression settings				Possibility of optimal choice			
	Number of RCTs (3-arm)	Number of participants	Data points	Dbar	DIC	Estimates at the centering value	Comments	TPVB	ESPB	ICNB	SAPB	Placebo		
Length of hospital stay														
No covariates				42.78	83.16	–	–	0.36	0.22	0.13	0.30	0.00		
Ports of surgical operating				42.70	83.20	0.350	Unrelated coefficients	0.48	0.23	0.18	0.11	0.00		
Moment of block	20 (2)	1485	42	42.19	82.38	1.050	Unrelated coefficients	0.25	0.33	0.30	0.12	0.00		
Types of local anesthetics				42.00	82.60	1.700	Unrelated coefficients	0.39	0.19	0.29	0.14	0.00		
Number of block segments				42.79	83.36	1.700	Unrelated coefficients	0.47	0.23	0.16	0.15	0.00		
Nausea and Vomiting														
No covariates				92.05	151.93	–	–	0.55	0.36	0.04	0.06	0.00		
Ports of surgical operating				87.91	145.81	0.295	Unrelated coefficients	0.32	0.64	0.01	0.02	0.00		
Moment of block	44 (6)	3149	94	92.08	155.76	1.136	Unrelated coefficients	0.56	0.29	0.04	0.11	0.00		
Types of local anesthetics				92.48	154.87	1.841	Unrelated coefficients	0.42	0.35	0.05	0.19	0.00		
Number of block segments				93.12	155.05	1.409	Unrelated coefficients	0.42	0.31	0.09	0.17	0.00		

DIC – Deviation Information Criterion Values, ESPB – Erector Spinae Plane Block, ICNB – Intercostal Nerve Block, LOS – Length of Hospital Stay, RCT – Randomized Controlled Trial, SAPB – Serratus Anterior Plane Block, TPVB – Thoracic Paravertebral Block.

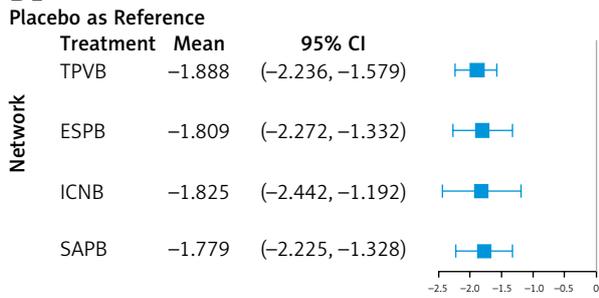
A1 24-hour morphine consumption [mg]



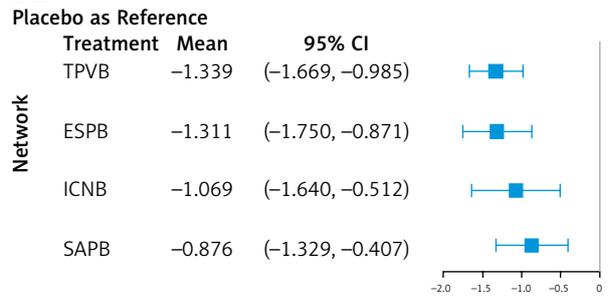
A2

	Placebo	TPVB	ESPB	ICNB	SAPB
Direct		-14.0 (-24.0, -3.8)	-16.0 (-25.0, -6.5)	-7.8 (-18.0, 2.0)	-3.6 (-15.0, 7.8)
Indirect			2.5 -8.2, 13.0)	14.0 (1.5, 28.0)	7.1 (-2.9, 17.0)
					10.0 (0.3, 21.0)
					-12.0 (-24.0, -0.7)
		21.0 (6.7, 35.0)	17.0 (-15.0, 48.0)	3.6 (-9.5, 17.0)	

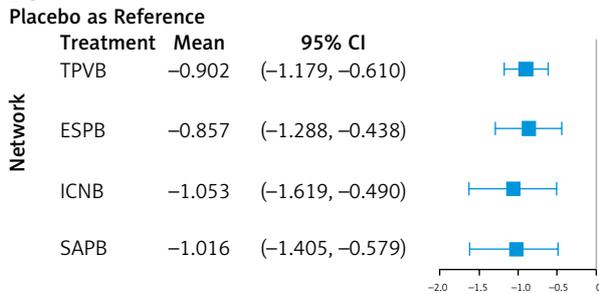
B1 Pain score Early stage (0-6 h)



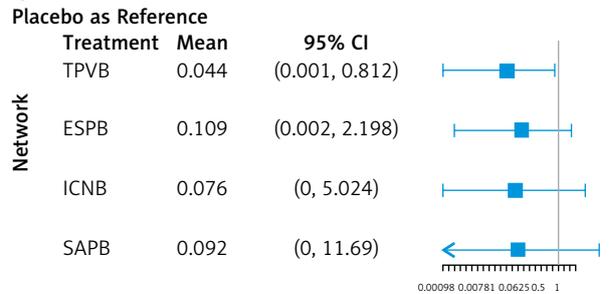
B2 Pain score Medium stage (6-12 h)



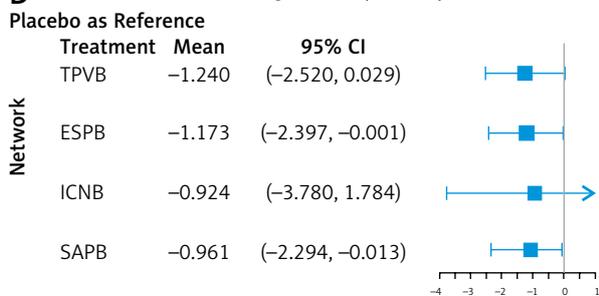
B3 Pain score Late stage (12-24 h)



C 24-hour rescue analgesia



D Length of hospital stay



E Nausea and vomiting

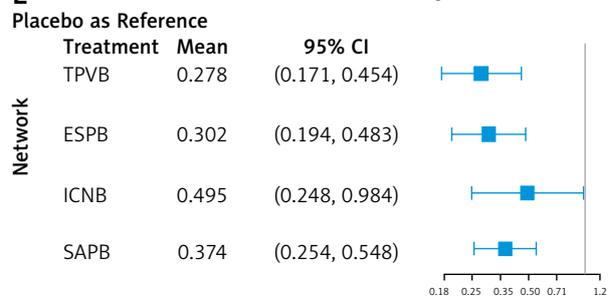


Figure 2. Forest plots of network comparison. Using placebo as a reference, synthetic effect value (mean or OR) for the four interventions in outcome events are engaged in a net comparison. For the primary outcome event, direct and indirect comparisons are also presented in Figure 1 A.1

CI – confidence interval, ESPB – Erector Spinae Plane Block, ICNB – Intercostal Nerve Block, OR – odd ratio, SAPB – Serratus Anterior Plane Block, TPVB – Thoracic Paravertebral Block.

density plots of the primary outcome (24 h morphine use), respectively.

In terms of model goodness of fit evaluation, without considering the influence of covariates on the model, ratio of dbar to data points is close to 1, and the value of deviation information criterion (DIC) is shown in Table I.

Efficacy outcomes (network meta-analysis)

As shown in Figure 2, all interventions show positive effects on seven outcomes, concerning improvement of pain and postoperative recovery, compared with the control group. Supplementary Table SII is a network league table, which shows the pairwise network comparison relationship of all interventions.

In the network comparison, TPVB, ESPB and ICNB are significantly different from the Placebo group in terms of 24 h morphine consumption, except for SAPB. The mean reductions compared to Placebo (with 95% CI) for the three successful modalities were 15.120 (10.250, 20.190) mg, 14.679 (8.140, 21.140) mg and 8.795 (1.182, 16.380) mg, respectively, as shown in Figure 2 A.1. As shown in Figure 2 A.2, there are significant differences in direct comparisons: Placebo vs. TPVB, Placebo vs. ESPB, and TPVB vs. SAPB. Indirect comparisons show differences except Placebo vs. ICNB, Placebo vs. SAPB, TPVB vs. ESPB, and TPVB vs. SAPB.

In the network comparison, TPVB, ESPB and ICNB are significantly different from the Placebo group in terms of 24 h morphine consumption, except for SAPB, which can be reduced by 15.120 (10.250, 20.190) mg, 14.679 (8.140, 21.140) mg and 8.795 (1.182, 16.380) mg, respectively, as shown in Figure 2 A.1. As shown in Figure 2 A.2, there are significant differences in direct comparisons: Placebo vs. TPVB, Placebo vs. ESPB, and TPVB vs. SAPB. Indirect comparisons show differences except Placebo vs. ICNB, Placebo vs. SAPB, TPVB vs. ESPB, and TPVB vs. SAPB.

As shown in Figure 2 B, in the early and mid-term pain scores, TPVB and SAPB are two extremes; however, the late VAS scores are reversed, and ICNB and SAPB showed lower pain scores. Notably, there are significant differences between TPVB and ESPB in direct, indirect, and network comparisons in late VAS scores; see Supplementary Table SII.

As shown in Figure 2 C, the incidence of rescue analgesia is low and its confidence interval is wide. TPVB and ICNB are less likely to require rescue analgesia.

There are significant differences between Placebo vs. SAPB and ESPB vs. SAPB in direct, indirect and network comparisons; see Supplementary Table SII.

As shown in Figures 2 D and 2 E, the performance of intervention measures in the two events of the length of hospital stay and PONV are similar: TPVB < ESPB < SAPB < ICNB.

Results of ranking probabilities

Prioritization is shown in Figure 3. For a particular outcome, the first-ranked one (“best” treatment) represented the intervention that is considered to have the highest likelihood of having the lowest incidence of outcome events or the most positive performance, i.e., the least morphine consumption, the most satisfactory pain scores, the least rescue analgesia, the shortest length of hospital stay, and the least PONV.

Figure 3 A.1 is a bar graph of the probability distribution of morphine consumption within 24 h after surgery for five interventions. The combined probability of TPVB (ranked first) and ESPB (ranked first) as the “best” treatment exceeds 90%. Figure 3 A.2 is a SUCRA of morphine consumption in the five interventions at 24 h after surgery, and the cumulative probability of TPVB or ESPB in the top 2 is close to 85%. The order of this variable is TPVB > ESPB > ICNB > SAPB > Placebo.

For early pain scores, ranking probabilities are similar between the four treatments (Figure 3 B.1); for mid-term pain scores, TPVB and ESPB have higher probability distributions for first or second than ICNB and SAPB (Figure 3 B.2); for late pain scores, there is an inversion phenomenon: ICNB and SAPB performed better than TPVB and ESPB (Figure 3 B.3).

Figures 3 C–E show the ranking probability distribution of rescue analgesia, length of hospital stay, and PONV. Probability rankings for the first (“best” treatment) are TPVB > SAPB > ICNB > ESPB > Placebo, TPVB > ICNB > ESPB > SAPB > Placebo, TPVB < ESPB < SAPB < ICNB < Placebo. TPVB performs the best; ESPB, except for the poor performance of rescue analgesia, also shows certain advantages.

Certainty of evidence

The population included in the NMA is large, and the precision of the study is so sufficient that the effect of this factor on the quality of the evidence can be ignored. This study focuses on other factors that

may reduce the quality of evidence: limitations of the study, inconsistency of results, indirect evidence, and publication bias. There is a degree of publication bias in this NMA. As shown in Supplementary Table SIV, there is inconsistency of results for both late pain scores and rescue analgesia, and indirect

evidence for both rescue analgesia and length of hospital stay. In summary, there are the results of evidence quality: 24-hour postoperative morphine dosage, moderate quality ($\oplus\oplus\oplus$); early and mid-term analgesia scores, moderate quality ($\oplus\oplus\oplus$); late pain scores, low quality ($\oplus\oplus$); rescue analgesia, very

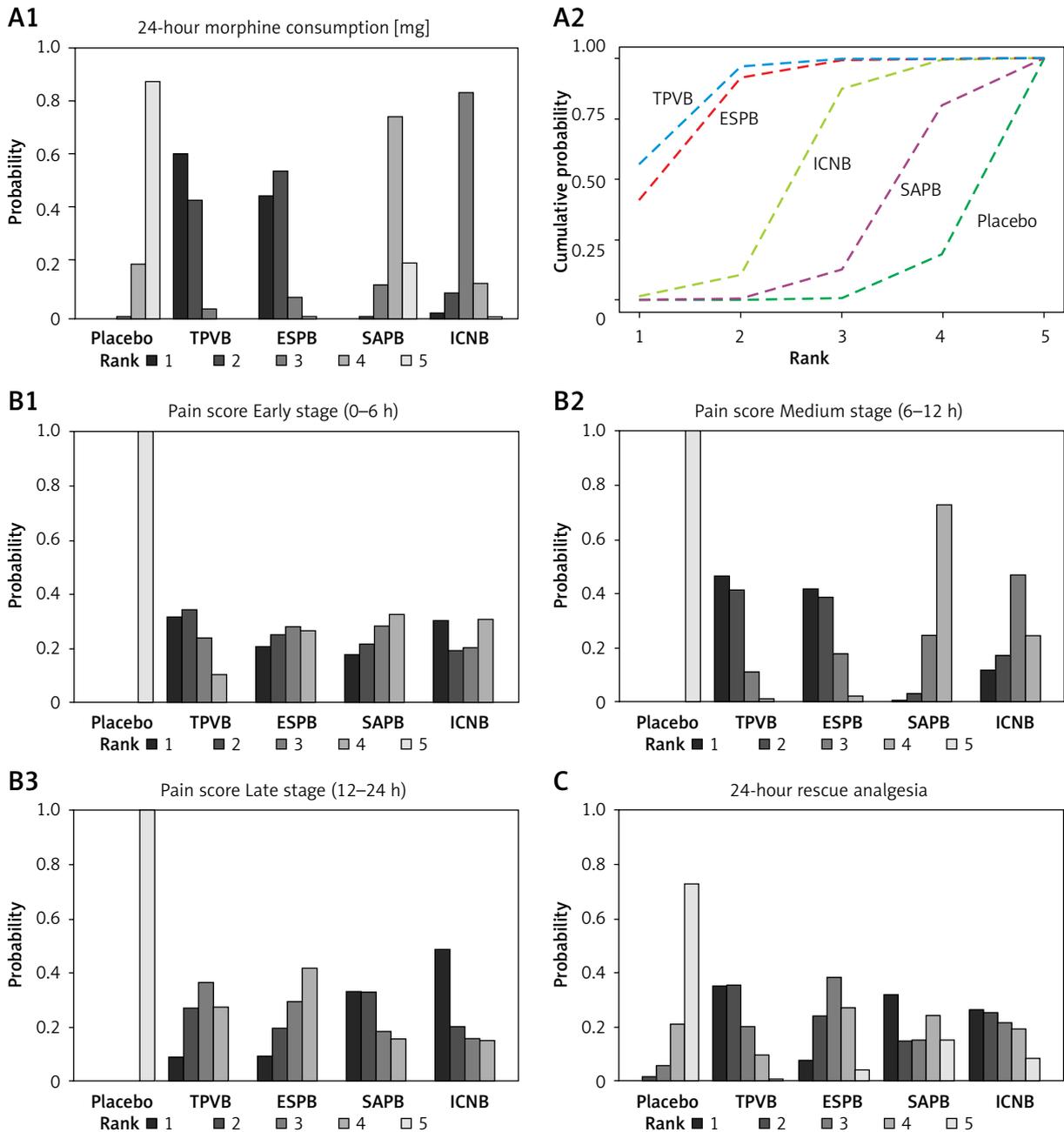


Figure 3. Probability of rank. Probability distributions of the five interventions in different orders are generated based on the size of the overlap between confidence intervals, and bar graphs are used to show probability distributions

ESPB – Erector Spinae Plane Block, ICNB – Intercostal Nerve Block, SAPB – Serratus Anterior Plane Block, TPVB – Thoracic Paravertebral Block.

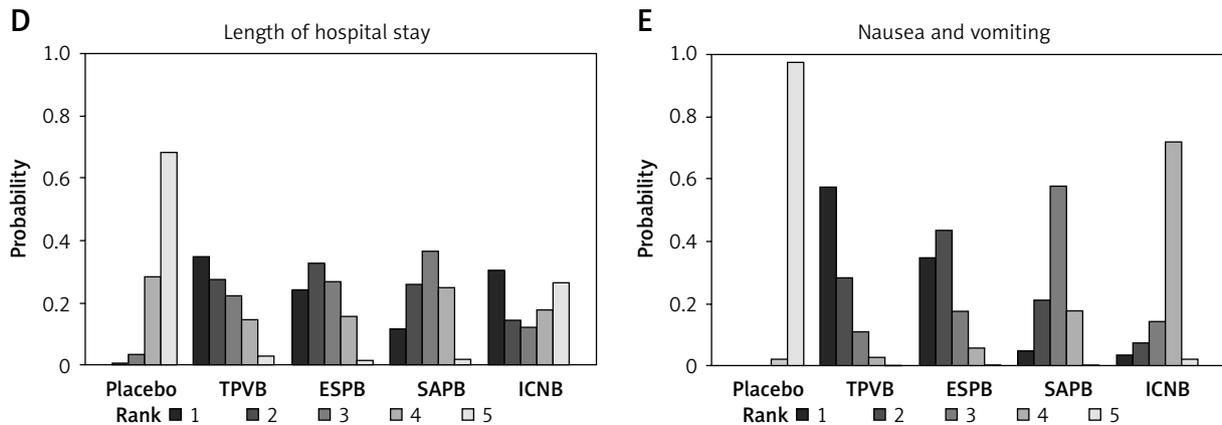


Figure 3. Cont.

ESPB – Erector Spinae Plane Block, ICNB – Intercostal Nerve Block, SAPB – Serratus Anterior Plane Block, TPVB – Thoracic Paravertebral Block.

low quality (⊕); length of hospital stay, low quality (⊕⊕); and PONV, moderate quality (⊕⊕⊕).

Exploration of Inconsistency/heterogeneity

Supplementary Table SIII shows the results of the heterogeneity test. Regardless of whether it is a direct comparison or an indirect comparison, I^2 is relatively unsatisfactory, and there is a certain degree of heterogeneity; the p -values of the consistency test are all greater than 0.05, and there is no difference between the direct comparison and the indirect comparison. Supplementary Figure S6 is a heterogeneity test plot for the primary outcome.

The nodal splitting method was used to measure inconsistency and Supplementary Table SIV shows the results of direct comparison, indirect comparison and network comparison for different treatments. Of note, there are significant differences in Placebo vs. ICNB for late VAS scores and Placebo vs. SAPB and ESPB vs. SAPB for rescue analgesia. Supplementary Figure S7 shows the inconsistency test forest plot for the primary outcome.

Exploration of net-meta regression

Table I documents the changes of DIC values in the random-effect model. Compared with the unadjusted model, the covariate-adjusted models do not significantly improve DIC. In each adjusted model, the 95% confidence intervals for the interaction coefficients intersect with 0. For the primary outcome of 24 h morphine consumption, the curves with 95% confidence intervals in the regression plots contain null values, as shown in Supplementary Figure S8.

The adjustment of the covariates changes the likelihood of optimal selection of the four treatments to some extent, as shown in Table I. It is worth noting that after adjustment for the covariate “port of surgical operation”, two changes occur: ICNB is replaced by SAPB in the late pain scores; TPVB is also replaced by ESPB in postoperative nausea and vomiting. Adjustment for the covariate “moment of block” results in a better length of stay for ESPB than for TPVB, and the adjustment for the covariate “type of local anesthetic” causes a change in the optimal solution for the mid- and late pain scores.

Discussion

Where traditional meta-analysis was limited to pairwise comparisons, we are now able to compare multiple nerve block techniques associated with thoracoscopic surgery within the same scope and rank pros and cons based on probability. Besides late pain scores, TPVB performed overwhelmingly better than the other three measures. ESPB is an alternative, secondary to TPVB. ICNB and SAPB play a considerable role in pain management and postoperative recovery after VATS, but they should not be taken as the primary measures.

Opioid-free or low-opioid analgesia after surgery has become an important perioperative issue [71, 72]. Through the comparison of opioid and non-opioid analgesia after discharge from the hospital, we can find that opioid-free analgesia leads to numerous favorable prognostic events for patients [73, 74]. We chose 24 h morphine consumption as the primary outcome of this study to explore which treatment

can reduce morphine consumption to the greatest extent. In our analysis, all four agents reduced morphine use to varying degrees, with a maximum of 15.12 mg and a minimum of 3.38 mg. TPVB and ESPB were similar in their effects on opioid reduction. ESPB has unique advantages: the needle tip is far away from the paravertebral space and away from the pleura; it is technically easier to perform [75]; and it is recommended for the same rating as TPVB in the PROSPECT guidelines [3]. ICNB is injected in multiple segments, which can counteract postoperative pain caused by the drainage tube, but this contradicts the result: in this study, network meta-regression was performed, and no effect of block segment on morphine dosage was found. SAPB covers the lateral cortical branch of the intercostal nerve and does not block pleural/internal sensation transmitted through sympathetic fibers [76], which could explain this phenomenon: the dose of postoperative opioids was slightly and insignificantly lower in the SAPB group compared to the control group.

There is one prerequisite of opioid-free or low-opioid analgesia after surgery: satisfactory pain scores. The PROSPECT panel used a 1.0-point reduction on a 0-10 NRS to indicate “clinically relevant” differences between techniques [3]. The greatest pain reduction occurred in the early phase (0–6 h postoperatively), with all four treatments showing clinically significant differences compared to the control group. In the mid-term (6–12 h) pain scores, the clinical difference disappeared first for SAPB. It was unlikely to affect the pleura, which was richly innervated and may be significantly painful during the coughing period [77]. When we take into account the anatomical basis of cough-related pain, it may explain that SAPB may not be clinically effective for active pain. In addition, ICNB can still maintain minor pain scores in the mid-term. The intercostal nerve travels anatomically between the most medial intercostal and intercostal spaces, which is functionally critical for respiratory and cough efficacy through innervation of the corresponding intercostal muscles. Also, after ICNB implementation, a local anesthetic can gradually infiltrate the pleura, thus attenuating the effect of stimulation on the pleura. The pain scores reversed in the later period: compared with the control group, both SAPB and ICNB showed clinically significant differences, but TPVB and ESPB did not. Both SAPB and ICNB can involve the long thoracic nerve [78–80], which relieves chest tube re-

lated secondary ipsilateral shoulder pain (ISP) [81] and incision induced body surface pain late in the procedure.

Although low opioid use and satisfactory pain intensity are considered as important patient comfort outcomes, the occurrence of rescue analgesia, length of hospital stay, and PONV should also be emphasized.

The incidence of rescue analgesia reflects postoperative interventions for pain management. The fewer remedial actions occur and the less medical and nursing involvement, the more effective pain management is. A systematic review suggests that TPVB reduces postoperative analgesia requirements [82]. This NMA study compared TPVB with a blank control, and there was a significant difference in the incidence of remedial analgesia. However, the performance of ESPB in this area was unsatisfactory for reasons not yet supported by the relevant literature.

Length of hospital stay reflects overall postoperative recovery. Pain is one of the most important factors impeding early postoperative bedside activity. TPVB and ESPB can suppress postoperative pain, improve postoperative mortality, and are associated with shorter hospital stay and higher patient satisfaction [83]. Some studies have shown that the duration of LOS is apparently not influenced by SAPB, which may be biased by various confounding factors, such as the number of ports [78]. However, in this study, after introducing covariates, the net-meta result showed that SAPB shortened LOS and the result was significant. In addition, compared with other treatment methods, the stay time of patients with ICNB is slightly longer [84], which may be due to the following reasons: 1) edema in some tissues of the incision that may be caused after the specific operation, which in turn prolongs the wound healing; 2) inadequate analgesia can cause inhibitory respiration, which is not conducive to the recovery of pulmonary function; and 3) intercostal nerves innervate intercostal muscles, which may weaken the strength of cough after blocking. Although ICNB is second only to TPVB in the probability ranking of the first (“best” treatment), we attribute this result more to the effect of covariates. After adjusting for covariates, it is clear that the probability of the “best” treatment for ICNB varies significantly.

PONV is the most common and unpleasant opioid-related side effect. PONV may increase length of hospital stay [85]. A study of patient preferences

for postoperative anesthesia outcomes showed that avoiding PONV was preferable to postoperative pain [86]. For postoperative nausea and vomiting, the following two factors should be considered: 1) the dose of opioids used; and 2) visceral traction, pain and other discomfort. On the one hand, TPVB and ESPB are significantly better than ICNB and SAPB in reducing postoperative morphine consumption, with a lower incidence of drug-induced nausea and vomiting; on the other hand, TPVB and ESPB both showed blocking effects on visceral and sympathetic nerves [87], that is, visceral related nausea and vomiting decreased, but there is no relevant evidence for ICNB and SAPB. There is solid evidence that TPVB and ESPB lead to a reduction in the incidence of clinically relevant nausea and vomiting [88–90]. Additionally, it has been shown that SAPB also reduced postoperative findings of nausea and vomiting compared to controls, possibly due to reduced opioid use [78].

A unique advantage of this NMA is that we were able to perform meta-regressions on multiple covariates (ports, moment of block, type of local anesthetic, and segment of block). This tool has not been tried in any previous meta-analysis on this topic. This helps us mitigate biases that may arise from changes in covariates. Adjustment for covariates also helps resolve the controversy of high heterogeneity. Meta-regression had little effect on the choice of treatment rank for the outcome, although the adjusted probabilities of optimal ranking changed to some extent.

Several limitations must be borne in mind when interpreting the results of this review. First, the study heterogeneity is high (Supplementary Figure S3, Supplementary Figure S6 and Supplementary Table SIII), which obviously limits and weakens the strength of our conclusions. High heterogeneity is unavoidable because both SAPB and ESPB are emerging and still in development. Furthermore, differences in the method used for the same nerve block, local anesthetic concentration and volume, and surgical approach may contribute to high heterogeneity. Therefore, in an effort to counteract heterogeneity, we made an effort to collect a large amount of grey literature while performing a network meta-regression, but considerable heterogeneity still exists. Second, as a control group, no block and sham block were considered identical, although opening of the fascial plane by saline diffusion (sham block) [12, 13, 15, 19, 61] was not the

same as without injection (no block). Opioids used for postoperative analgesia varied, but ultimately morphine was used as the equivalent dose. Despite these limitations, the findings from the network meta-analysis represent the most comprehensive evidence base available to guide the choice of nerve block modalities in thoracic surgery.

Conclusions

Taken together, SAPB and ICNB appear to play a limited role in postoperative pain management compared with other clinically used nerve blocks in thoracic surgery. TPVB, currently recommended as a consensus choice, ranked best in our analysis. Our analysis suggests that ESPB is a viable alternative. After adjustment of covariates, both TPVB and ESPB are superior to SAPB and ICNB except for late pain scores. More research on these treatments, preferably trials of multiple treatments, is needed to improve the strength of the evidence and to inform clinical practice.

Supplementary data

Supplementary data available at *Videosurgery and Other Miniinvasive Techniques* online.

Conflict of interest

The authors declare no conflict of interest.

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