Systematic Review

Regional Analgesia Techniques Following Thoracic Surgery: A Systematic Review and Network Meta-analysis

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Background: Regional analgesia techniques have become the basis of multimodal analgesia for acute and chronic pain. They are widely used in thoracic surgery, but the best treatment is still uncertain.

Objectives: We aimed to compare and rank the effectiveness of regional analgesia techniques for thoracic surgery.

Study Design: A systematic review and network meta-analysis.

Methods: PubMed, MEDLINE, Embase, Cochrane Library, Science-Direct, and Web of Science were searched for articles published from inception through the end of January 2023. The network meta-analysis was conducted using Stata 15.1 software (StataCorp, LLC). The certainty of evidence was assessed by using Confidence in Network Meta-analysis (CINeMA https://cinema.ispm.unibe.ch/ A (unibe.ch). The primary outcome was cumulative opioid consumption within postoperative 24 hours. The secondary outcomes included pain scores at postoperative 6 hours, 12 hours, and 24 hours.

Results: A total of 32 trials with 1,996 patients and 11 techniques were included. No major network inconsistency or heterogeneity were found. Postoperative opioid consumption within postoperative 24 hours was decreased most by continuous extrapleural block (cEPB) (standardized mean difference [SMD] = 0.00; 95% CI,: 0.00-0.00), followed by continuous thoracic epidural analgesia (cTEA) and continuous serratus plane block (cSAPB). In the postoperative 6 hour analysis, pain scores were decreased most by cTEA (SMD = 0.16; 95% CI,: 0.05-0.49), followed by thoracic paravertebral block (TPVB) and ESPB (erector spinae plane block). In the postoperative 12 hour analysis, pain scores were decreased most by cSAPB (SMD = 0.12; 95% CI, 0.011.84), followed by TPVB and cTEA. In the postoperative 24 hour analysis, pain scores were decreased most by ESPB (SMD = 0.09; 95% CI, 0.030.32), followed by cSAPB and continuous thoracic paravertebral block (cTPVB).

Limitations: Our study has several limitations. First, 4 enrolled studies had a sample size of less than 40 patients. Second, the different regimens were potential factors contributing to heterogeneity, such as local anesthetic dose and volume, infusion time, infusion mode, adding adjuncts, and rescue analgesic regimens. Third, the number of primary and secondary outcomes is limited. Fourth, the number of randomized controlled trials for cEPB is limited.

Conclusions: The cTEA and cSAPB techniques are more likely to reduce the cumulative opioid consumption within 24 hours. The cTEA, cSAPB, ESPB techniques were more likely to improve pain at postoperative 6, 12, and 24 hours. Therefore, cTEA, cSAPB, and ESPB are the first choices for pain relief post thoracic surgery, whereas wound infiltration, intercostal block, continuous wound infiltration, and continuous intercostal block were less likely to be effective. We need more high-quality randomized controlled trials with larger sample sizes to validate our results and to determine the ideal regional analgesia technique and the optimal drug formula.

Key words: Thoracic, pain, epidural, analgesia, network meta-analysis, randomized controlled trial

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Severe postoperative pain is frequently observed in patients who have undergone thoracic surgery., This pain leads to harmful cough and expectoration, disrupted sleep, stress, and interferes with recovery (1). Sufficient analgesia management should not only be defined as relieving pain, but also should consider the effect of analgesic interventions related to Enhanced Recovery after Surgery (ERAS) protocols, which include faster gastrointestinal recovery, earlier mobilization, earlier discharge, and other outcomes (2).

Numerous studies have documented regional analgesia techniques as the basis of multimodal analgesia mainly due to their improving patient comfort, reducing opioid consumption, and benefiting ERAS (3-5). Continuous thoracic epidural analgesia (cTEA) is a classic treatment for pain relief post thoracic surgery (6). In addition, the following techniques are also widely used: thoracic paravertebral block (TPVB) (7), intercostal block (ICB) (8), serratus plane block (SAPB) (9), erector spinae plane block (ESPB) (10), wound infiltration (WI) (11), continuous intercostal block of local anesthetics via a catheter (cICB) (12), continuous serratus plane block (cSAPB) (13), continuous thoracic paravertebral block (cTPVB) (14), continuous wound infiltration (cWI) (15), continuous extrapleural block (cEPB) (16), or a combination of these techniques.

Given the variety of regional analgesia techniques, the best choice to reduce postoperative pain and opioid consumption has been controversial. Previous traditional meta-analyses have been limited to pairwise analyses of 2 or 3 analgesia techniques,; none of them provided an evidence evaluation comparing all available treatment options together (17-24). The selection of regional analgesia techniques for thoracic surgery, therefore, is still influenced by clinical dogma, convenience, or institutional availability. To address this shortcoming, we performed a network meta-analysis (NMA) to combine direct and indirect evidence from trials to help better understand the merits of different interventions and provide objective rankings of various interventions based on the corresponding surface under the cumulative ranking curve (SUCRA).

Our NMA provides a more comprehensive evidence synthesis for the relative efficiency of different regional analgesia techniques after thoracic surgery. We will compare all commonly used regional analgesia techniques together on the same scale, unlike previous meta-analyses that were limited to pairwise comparisons.

Methods

Literature Retrieval

Our study protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO) and assigned the identification number CRD42020211357. We followed the Preferred Reporting Items for Systematic Reviews (PRISMA) Extension Statement for Network Meta-analyses (25). We searched PubMed, MEDLINE, Embase, Cochrane Library, Science-Direct, and Web of Science without language restriction for articles published from inception through the end of January 2023.

The search strategy was made up of key words and related synonyms: "thoracotomy," "thoracic surgery," "Video-Assisted Thoracic Surgery," "thoracic epidural analgesia," and "thoracic paravertebral block,""serratus plane block," "erector spinae plane block," "wound infiltration,""intercostal block,""extrapleural block." The full PubMed search strategy is shown in Supplementary Material One.

Eligibility Criteria

Inclusion Criteria

The inclusion criteria were designed according to patient, intervention, comparison, outcome, study (PICOS) criteria: P) patients undergoing thoracic surgery receiving regional analgesia techniques; I) regional analgesia techniques including cTEA, TPVB, SAPB, ESPB, WI, ICB, cSAPB, cEPB, cWI, cTPVB, cICB, or a combination of these techniques; C) one of these regional analgesic techniques, plus a placebo or no intervention; O) postoperative opioid consumption or pain score within the first postoperative 24 hours; S) randomized controlled trials (RCTs).

Exclusion Criteria

Study exclusion criteria were: 1) incomplete data which could not be used for statistical analysis; 2) unpublished studies, parallel and crossover randomized design studies; 3) duplicate data used for several studies and studies with incomplete data.

Outcome Measures

Primary Outcome Measures

The primary measured outcome was cumulative opioid consumption within the first postoperative 24 hours. Opioid consumption was converted to intravenous morphine milligram equivalent doses to allow comparison of different regimens.

Secondary Outcome Measures

The secondary outcomes included pain scores at postoperative 6 hours, 12 hours, and 24 hours. Pain scores were converted to the corresponding number on the 0-10 Visual Analog Scale (VAS), where 0 equates to no pain at all and 10 to the worst pain. We selected the maximum pain scale value from 0 h to 6 h after surgery as the VAS at 6 h, the maximum pain scale value from 7 h to 12 h as the VAS at 12 h, and the maximum pain scale value from 13 h to 24 h as the VAS at 24 h.

Literature Screening and Data Extraction

Assessment of Methodological Quality

We assessed the quality of eligible articles independently using either the Cochrane Collaboration's tool or Confidence in Network Meta-analysis (CINeMA 2.0.0, https://cinema.ispm.unibe.ch/ A (unibe.ch). Both are considered to be reliable tools and are used widely. The Cochrane Collaboration's tool measures random sequence generation, allocation concealment, performance bias, detection bias, attribution bias, reporting bias, and other biases (26). The CINeMA is used to evaluate confidence in NMA findings based on 6 domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence (27,28). Additionally, a comparison-adjusted funnel plot analysis was performed in order to detect any publication bias as well as the presence of any small study bias.

Data Collection

Two investigators sequentially reviewed all titles, abstracts, and then full texts. Any disagreements on eligibility between the 2 reviewers were resolved by a third reviewer. We extracted the relevant data from eligible literature; the accuracy was confirmed by 2 investigators. The relevant data were collected as follows: study name, authorship, country, and publication date; blinding (single blinding, double blinding, triple blinding, not reported); sample size; intervention description; control description; type of surgery (thoracotomy or video-assisted thoracic surgery [VATS]); pain assessment methods; the outcomes of pain scores and cumulative opioid consumption; and any rescue analgesic regimens.

Statistical Analysis

The variables were extracted as means ± SDs for continuous variables. The data expressed as median and interquartile range were converted to mean and SDs using the validated Luo's and Wan's formula (https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html) (29,30). Statistical analysis was carried out in STATA 15.1 software (StataCorp, LLC), network package was used to conduct an NMA. The data were synthesized by network meta-analysis of random-effects model. The results were evaluated by standardized mean differences with CIs.

Network geometry maps provided visual and concise descriptions between pairs of interventions; nodes corresponded to analgesic interventions, the node size was the proportion of sample size; width of the lines was the number of trials comparing pairwise intervention. Consistency was evaluated by node-splitting inconsistency model and loop inconsistency model. CIs and their corresponding prediction intervals for all comparisons were used to judge the inherent imprecision and the results were summarized and presented in interval plots. Forest plots display study outputs and the results of global heterogeneity. We assessed statistical heterogeneity in each pairwise comparison with the I^2 statistic, τ^2, and *P* value; $I^2 > 50\%$ was considered as statistical heterogeneity. Netleague tables were plotted in order to visualize the relative effectiveness of each intervention for a particular outcome. The SUCRA was used to estimate the ranking probabilities for all interventions. A funnel plot was used to assess publication bias of every particular outcome. Additionally, a contribution matrix showed how much information each study contributed to the results from the network meta-analysis.

Results

Search Results and Characteristics of Selected Studies

We identified a total of 1,083 potentially relevant records. The full-text manuscripts of the remaining 71 studies were assessed. After including studies from hand searches and a search revision, 32 trials with 11 analgesic techniques were included in this NMA (31-62). The process of literature selection is shown in Fig. 1. Table 1 shows the trial characteristics. A total of 1,609 patients were randomly assigned to an active analgesia technique and 387 to placebo.

The primary outcome was reported in 17 RCTs (31,32,35,37,38,40,42,43,44,46,47,50,51,53,54,59,60). Use of cTEA (32,33,36,47,49,52,54-56,60,62) and cTPVB (32,36,45,46,49,52,55,56,62) were the most

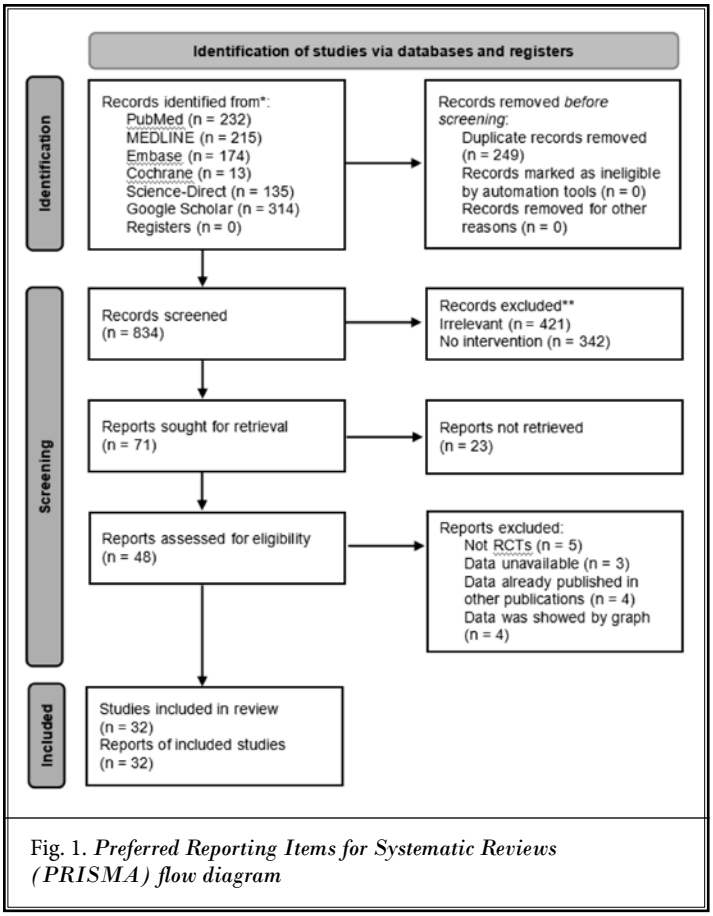

Fig. 1. *Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram*

frequent interventions followed closely by TPVB (31,43,44,48,50,51,58,59). The technique of analgesia with single-shot or using a continuous catheter, were found in 32 and 26 treatment arms, respectively. The majority of RCTs were in patients undergoing VATS (31,32,34-43,45,46,48-51,54,58,59,61) followed by thoracotomy (33,44,47,52,53,55-57,60,62). The contribution matrix showed the proportion of direct evidences (Supplementary Material 2).

Risk of Bias Assessment

The risk of bias of every outcome was shown in Supplementary Material 3. Small study bias or any publication bias was not observed in the funnel plot (Supplementary material 4).

Results of Heterogeneity and Consistency

Forest plots of all directly compared treatments were carried out as shown in Supplementary Material 5, which showed that no global heterogeneity existed between trials and that the results support the consistency model.

For testing inconsistency between direct and indirect comparisons, excepting the result of node-splitting, showed that TPVB vs SAPB had a high risk of inconsistency on opioid consumption within postoperative 24 hours (Table 2); the other results did not show any significant inconsistency (Supplementary Material 6). Excepting the result of loop inconsistency showed that cTPVB and cSAPB VAS scores at postoperative 12 hours (Supplementary Material 6), as well as cTPVB and cSAPB and TPVB, ICB, and SAPB on opioid consumption within postoperative 24 hours (Fig. 2) had a high risk of inconsistency; the other results did not show any significant inconsistency (Supplementary Material 6). The interval plots estimated effect sizes and uncertainties for all pairwise comparisons (Supplementary Material 7).

Results of Pairwise and Network Meta-analysis

The absolute value difference of eligible comparisons for all outcomes are shown in the league table (Supplementary Material 8).

Primary Outcome

Cumulative Opioid Consumption Within Postoperative 24 Hours

This NMA included patients from 17 studies (31,32,35,37,38,40,42-44,46,47,50,51,53,54,59,60). The network geometry of eligible comparisons displayed complete, as all nodes could be connected (Fig. 3). The cEPB technique provides the best analgesia based on estimated probabilities (cEPB: 7.5%; cTEA: 10.8%; cSAPB: 14.5%; TPVB: 33.2%; cTPVB: 35.3%; SAPB: 54%; ICB: 60.8%; ESPB: 71.2%; cWI: 75.5%, control: 90.2%; and WI: 96.9%) (Fig. 4).

Secondary outcomes

Visual Analog Scale at Postoperative 6 Hours

This NMA included 1,134 patients from 20 studies (31,33, 38-42.44,45,47,48,50,52,55-58,60-62). The network geometry of eligible comparisons displayed complete, as all nodes could be connected (Supplementary Material 9). The cTEA technique seemed to be the best for analgesia among all the treatments. The SUCRA values established a hierarchy for the 9 treatments: cTEA: 23.1%; TPVB: 23.3%; ESPB: 28.8%; SAPB:

Table 1. *Characteristics of included studies.*

References	Year	Country	Blinding	ASA	Surgery	Comparison (n)	Analgesic Technique	Rescue Analgesic Regimen	Pain Assessment Scale
Baytar, et al (31)	2021	Republic of Turkey	2	I-II	VATS	SAPB (31): 0.25% bupivacaine 0.4 mL/kg (max 20 mL)	USG	Tramadol PCIA	VAS
						TPVB (31): 0.25% bupivacaine 0.4 mL/kg (max 20 mL)			
Huang, et al (32)	2020	People's Republic of China	2	II–III	VATS	cTEA (39): 0.1% ropivacaine 300ml (loading dose of 5 ml, background dose of 5 ml/h, locking time of 20 min)	Landmark-guided	(IV) flurbiprofen and opioids	NRS-11
						cTPVB (32): 0.2% ropivacaine 300 mL (loading dose of 0.5 mg/kg, background dose of 0.25 mg/kg/h, PCA of 0.25 mg/kg, lockout time of 60 min)	USG		
Vilvanathan, et al (33)	2020	Republic of India	NR	I-III	thoracotomy	cTEA (25): loading dose of 0.25% bupivacaine 5-10 mL, background dose of 0.1% bupivacaine + 2 μg/ml fentanyl, 5 - 8 mL/h over a period of 20 min toward the end of the surgery	Landmark-guided	(IV) morphine 2 mg if patient reported pain and NRS-11 > 5	NRS-11
						ICB (25): T3-T8 intercostal spaces; 0.25% bupivacaine 20 mL	thoracoscopic assistance		
Viti, et al (34)	2020	Italian Republic	2	I-III	VATS	SAPB (46): 0.3% ropivacaine 30 mL	USG	(IV) ketorolac 30 mg or tramadol 100 mg	NRS-11
						Control (44): no block without placebo or sham procedure			
Finnerty, et al (35)	2020	Republic of Ireland	2	I-III	VATS	ESPB (30): 0.25% levobupivacaine* 30 mL	USG	(IV）oxycodone 1- 2 mg if VRS > 2	VRS
						SAPB (30): 0.25% levobupivacaine 30 mL			
Wei, et al (36)	2020	People's Republic of China	NR	I-III	VATS	cTEA (30): 0.25% ropivacaine 100 mL, loading dose of 0.5 mL, background dose of 2 mL/min, lockout time of 15 min.	Landmark-guided	NR	VAS
						cTPVB (30): 0.25% ropivacaine 100 mL, loading dose of 0.5 mL, background dose of 2 mL/min, lockout time of 15 min	USG		
Chen, et al (37)	2020	People's Republic of China	2	I-II	VATS	ICB (24): T4-T9 intercostal spaces, 0.375% ropivacaine 20 mL	USG	(IV）oxycodone if VAS > 3	VAS
						TPVB (24): T5-T7, 0.375% ropivacaine 20 mL			
						ESPB (24): T5; 0.375% ropivacaine 20 mL			

Table 1 cont. *Characteristics of included studies.*

References	Year	Country	Blinding	ASA	Surgery	Comparison (n)	Analgesic Technique	Rescue Analgesic Regimen	Pain Assessment Scale
Lee, et al (38)	2020	Republic of Korea	2	I-III	VATS	ICB (23): 0.375% ropivacaine 20mL	thoracoscopic assistance	ketorolac 30mg, if NRS-11 = 4 or 5; (IV) fentanyl 50 μg, if NRS-11 ≥ 6	NRS-11
						SAPB (23): 0.375% ropivacaine 20mL	USG		
Gaballah, et al (39)	2019	Arab Republic of Egypt	1	I-II	VATS	ESPB (30): 0.25% levobupivacaine* 20 mL	USG	(IV) ketorolac 30 mg, if VAS ≥ 4; if no improvement within 15 minutes, pethidine 0.5 mg/kg	VAS
						SAPB (30): 0.25% levobupivacaine 20 mL			
Kim, et al (40)	2018	Republic of Korea	3	I-II	VATS	Control (43): normal saline	USG	tramadol 75 mg or oxycodone 10 mg every 12 h, if NRS-11 ≥ 4; (IV) pethidine 25 mg, tramadol 50 mg, or oxycodone 5 mg, if persistent NRS-11 ≥ 4.	NRS-11
						SAPB (42): 0.375% ropivacaine 0.4 mL/kg			
Park, et al (41)	2018	Republic of Korea	3	I-II	VATS	Control (42): no block without placebo or sham procedure	USG	(IV) ketorolac 15 mg every 6 h for the next 24 h, (ORAL) hydromorphone 8 mg the following morning	NRS-11
						SAPB (42): 0.375% ropivacaine 30 mL			
Ökmen, et al (42)	2018	Republic of Turkey	1	I-III	VATS	SAPB (20): 0.25% bupivacaine 20 mL	USG	acetaminophen 1 g, if VAS > 5	VAS
						Control (20): no block without placebo or sham procedure			
Wu, et al (43)	2018	People's Republic of China	2	I-III	VATS	ICB (32): 0.5% ropivacaine + 1/200 000 epinephrine, 0.3mL/kg	USG	sufentanil PCIA	VAS
						TPVB (34): 0.5% ropivacaine + 1/200 000 epinephrine, 0.3mL/kg			
Saad, et al (44)	2018	Arab Republic of Egypt	2	I-II	thoracotomy	SAPB (30): 0.5% bupivacaine 30 mL	USG	ketorolac 30 mg, if VAS > 4; morphine 3mg, if VAS > 5	VAS
						TPVB (30): T5; 0.5% bupivacaine 20ml			
						Control (30): no block without placebo or sham procedure			

Table 1 cont. *Characteristics of included studies.*

References	Year	Country	Blinding	ASA	Surgery	Comparison (n)	Analgesic Technique	Rescue Analgesic Regimen	Pain Assessment Scale
Kadomatsu, et al (45)	2018	Japan	NR	NR	VATS	cTPVB (26): loading dose of 0.375% ropivacaine 20 mL, background dose of 0.2% ropivacaine 5 mL/h for 48 h	thoracoscopic assistance	flurbiprofen axetil and pentazocine or loxoprofen {Savannah—loxoprofen not approved in the US} sodium hydrate and diclofenac sodium suppository	VAS
						cICB (24): 2 intercostal spaces; loading dose of 0.375% ropivacaine 10 mL to each space, background dose of 0.2% ropivacaine 5 mL/h for 48 h			
Hutchins, et al (46)	2017	United States of America	NR	I-III	VATS	cTPVB (23): 0.2% ropivacaine 0.4 mg/kg/h, a rate between 10 mL/h and 14 mL/h	USG	hydromorphone PCIA	NRS-11
						ICB (25): 0.25% or 0.5% bupivacaine	thoracoscopic assistance		
Khalil, et al 47 (47)	2017	United States of America	2	II-III	thoracotomy	cSAPB (20): loading dose of 0.25% levobupivacaine{Savannah—withdrawn from US market} 30 mL, background dose of 0.125% levobupivacaine 5 mL/h	USG	(IV) morphine 0.1 mg/kg then titration of one mg/15min as required to keep VAS < 3	VAS
						cTEA (20): loading dose of 0.25% levobupivacaine 15 mL, background dose of 0.125% levobupivacaine 5 mL/h	Landmark-guided		
Zhang, et al (48)	2016	People's Republic of China	2	I-III	VATS	TPVB (20): T5-T7; 0.50% ropivacaine 20ml	USG	(IM) tramadol hydrochoride 100 mg, if NRS > 4	NRS-11
						TPVB (20): T5-T7; 0.50% ropivacaine+ sufentanil 5μg, 20 mL			
						Control (20): no block without placebo or sham procedure			
Okajima, et al (49)	2015	Japan	NR	I-III	VATS	cTEA (33): 150 mL (0.1 % ropivacaine + 0.6 mg fentanyl), 4 mL/h for 36 h, when weight > 65 kg; 75 mL (0.1 % ropivacaine + 0.6 mg fentanyl), 2 mL/h for 36 h, when weight ≤ 65 kg	Landmark-guided	(IV) fentanyl	NRS-11
						cTPVB (36): T4, 220 mL (0.1 % ropivacaine + 0.6 mg fentanyl), 6 mL/h for 36 h	USG		
Chen, et al (50)	2015	People's Republic of China	NR	I-II	VATS	TPVB (20): T4-T7; 0.375% ropivacaine 20 mL	Landmark-guided	dezocine* PCIA	VAS
						Control (20): no block without placebo or sham procedure			
Zhang, et al (51)	2015	People's Republic of China	3	I-II	VATS	TPVB (31): T4,T7; 0.5% ropivacaine 8 mL	thoracoscopic assistance	morphine PCIA	VAS
						WI (30): 0.5% ropivacaine (max 40 mL)			

Table 1 cont. *Characteristics of included studies.*

References	Year	Country	Blinding	ASA	Surgery	Comparison (n)	Analgesic Technique	Rescue Analgesic Regimen	Pain Assessment Scale
Kobayashi, et al (52)	2013	Japan	NR	I-II	thoracotomy	cTEA (35): loading dose of 0.2 % ropivacaine 5 mL, then 84 mL (0.2 % ropivacaine+ fentanyl 800 μg), 5 mL/h	Landmark-guided	NR	VAS
						cTPVB (35): loading dose 0.375% ropivacaine 10 mL, then 84 mL (0.2 % ropivacaine+ fentanyl 800 μg), 5 mL/h	thoracoscopic assistance		
Fortier, et al (53)	2012	French Republic	OL	II-III	thoracotomy	cTPVB (44): 0.2% ropivacaine 0.3 mg/kg/h for 48 h	thoracoscopic assistance	morphine PCIA	VAS
						cWI (46): 0.2% ropivacaine 4 mL/h for 48 h			
						Control (50): no block without placebo or sham procedure			
Hotta, et al (54)	2011	Japan	OL	I-II	VATS	cTEA (20): loading dose of 0.75% ropivacaine 5mL, then 0.2% ropivacaine 4mL/h, for a period of 60 h	Landmark-guided	morphine PCIA	VAS
						cEPB (20): loading dose of 0.75% ropivacaine 5mL, then 0.2% ropivacaine 4mL/h, for a period of 60 h	thoracoscopic assistance		
Pintaric, et al (55)	2011	Republic of Slovenia	NR	II-III	thoracotomy	cTEA (16): 200 mL (0.25% levobupivacaine* + 20 μg/mL morphine), background dose of 0.1 mL/kg/h for 48 h, PCA of 0.1mL/kg, lockout time of one h	Landmark-guided	(IV） piritramide** 3 mg,if VAS > 4	VAS
						cTPVB (16): 200 mL （0.25% levobupivacaine + 20 μg/mL morphine), background dose of 0.1 mL/kg/h for 48 h, PCA of 0.1 mL/kg, lockout time of one h			
Messina, et al (56)	2009	Italian Republic	NR	II-III	thoracotomy	cTEA (12): 0.125% levobupivacaine* + 2 μg/mL fentanyl, 0.08 mL/kg/h	Landmark-guided	morphine PCIA	VAS
						cTPVB (12): 0.25% levobupivacaine + 1.6 μg/mL fentanyl, 0.1 mL/kg/h			
D'Andrilli et al. (57)	2006	Italian Republic	NR	NR	thoraacotomy	ICB (60): T4-T8; 0.75% ropivacaine 4 mL to each intercostal space	Landmark-guided	(IV) propacetamol (acetaminophen) chlorhydrate one g	VAS
						Control (60): no block without placebo or sham procedure			
Kaya, et al (58)	2006	Republic of Turkey	2	I-III	VATS	TPVB (25): T4-T8; 4 mL (0.5% bupivacaine + 1:200,000 epinephrine) to each space	Landmark-guided	morphine PCIA	VAS
						Control (22): no block without placebo or sham procedure			

Table 1 cont. *Characteristics of included studies.*

References	Year	Country	Blinding	ASA	Surgery	Comparison (n)	Analgesic Technique	Rescue Analgesic Regimen	Pain Assessment Scale
Vogt, et al (59)	2005	Swiss Confederation	NR	I-III	VATS	TPVB (20): 0.375% bupivacaine + 1:200 000 adrenaline, 0.4 mL/kg	Landmark-guided	morphine PCIA	VAS
						Control (20): no block without placebo or sham procedure			
Debreceni, et al (60)	2003	Hungary	2	NR	thoracotomy	cTEA (25): loading dose of 0.25% bupivacaine 0.2 mL/kg, background dose of 0.25% bupivacaine 5 mL/h	Landmark-guided	the infusion rate was increased to 10 mL/h, if VAS > 4; (IV) fentanyl 100 ug, if the perfusion dose of bupivacaine exceeded the maximum allowable value	VAS
						ICB (22): loading dose of 0.25% bupivacaine 0.2 mL/kg, background dose of 0.25% bupivacaine 5 mL/h	thoracoscopic assistance		
Bolotin, et al (61)	2000	State of Israel	NR	NR	VATS	ICB (16): T2-T4 intercostal space; 0.5% bupivacaine 3mL to each space	thoracoscopic assistance	NR	VAS
						Control (16): normal saline			
Perttunen, et al (62)	1995	Republic of Finland	NR	I-III	thoracotomy	ICB (15): T3-T7 intercostal space; 0.5% bupivacaine 16 mL	surgeon	morphine PCIA	VAS
						cTEA (15): loading dose of 0.25% bupivacaine 8-12 mL according to height, background dose of 4 -8 mL/h according to height	Landmark-guided		
						cTPVB (25): loading dose of 0.25% bupivacaine 8-12 mL according to height, background dose of 4 -8 mL/h according to height	surgeon		

Abbreviations: NR, not reported. OL, open label. VATS, video-assisted thoracic surgery. cTEA, continuous thoracic epidural analgesia. TPVB, thoracic paravertebral block. SAPB, serratus plane block. ESPB, erector spinae plane block. WI, wound infiltration. ICB, intercostal block. cSAPB, continuous serratus plane block. cEPB, continuous extrapleural block. cWI, continuous wound infiltration. cTPVB, continuous thoracic paravertebral block. cICB, continuous intercostal block. USG, Ultrasonography. PCIA, patient-controlled intravenous analgesia. IV, intravenous. VAS, visual analog scale. NRS, numeric rating scale. VRS, verbal rating scale.

* This medication was withdrawn from US market.

** This medication is not approved for use in the US.

Table 2. *Inconsistency of cumulative opioid consumption within postoperative 24 hours*

Side	Direct		Indirect		Difference		P > z
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	
A C	-12.8	3.103104	-13.18901	3.676871	0.3890139	4.811303	0.936
A F	-3.399997	3.142043	-3.408554	4.18526	0.0085569	5.233434	0.999
A G	-16.55378	2.560013	-9.462812	2.719406	-7.090968	3.769552	0.06
A I	-5.929276	2.636932	-11.66357	3.121999	5.734291	3.995488	0.151
B C	6.62377	2.228015	9.118068	9.199425	-2.494298	9.465487	0.792
B D *	-1.4	3.553614	39.46077	442.7658	-40.86077	442.7838	0.926
B E *	0.6999998	2.993411	39.47863	230.967	-38.77863	230.9884	0.867
B H	15.19996	8.599666	12.47653	4.029925	2.723425	9.497081	0.774
C F	9.400005	3.149398	9.848806	4.268324	-0.4488007	5.30446	0.933
C H	8.59987	9.373808	5.885726	3.321805	2.714144	9.94498	0.785
G H	7.124097	2.479116	5.051839	2.788644	2.072258	3.727514	0.578
G I	1.307441	0.4983268	7.867401	1.175762	-6.55996	1.277006	0 $
G J	8.999801	3.575253	7.132666	4.10327	1.867134	5.44233	0.732
G K *	19.6	6.062134	26.30099	1326.752	-6.700988	1326.762	0.996
H I	0.0999999	2.858731	-2.552014	2.889236	2.652014	4.064485	0.514
H J	2.699961	3.737639	1.093994	4.123063	1.605967	5.565027	0.773
I J	-16.49998	12.88638	4.350332	2.8686	-20.85031	13.20181	0.114

* Warning: all the evidence about these contrasts come from the trials which directly compare them.
$ - Nodes highlighted in red had evidence of inconsistency.
Treatment groups are: A - Control. B - cTEA, continuous thoracic epidural analgesia. C - cTPVB, continuous thoracic paravertebral block. D - cEPB, continuous extrapleural block. E - cSAPB, continuous serratus plane block. F - cWI, continuous wound infiltration. G - TPVB, thoracic paravertebral block. H - ICB, intercostal block. I - SAPB, serratus plane block. J - ESPB, erector spinae plane block. K - WI, wound infiltration.

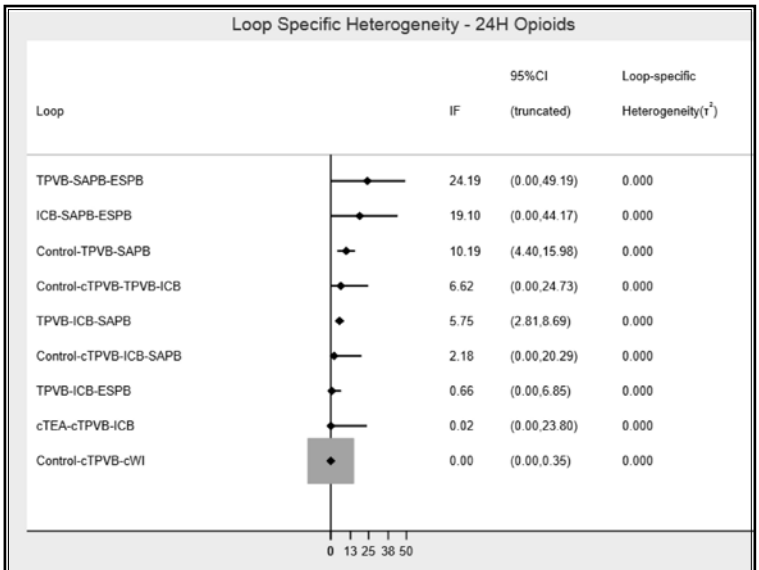

Fig. 2. *Loop-specific approach of cumulative opioids consumption within 24 hours*
cTEA, continuous thoracic epidural analgesia. TPVB, thoracic paravertebral block. SAPB, serratus plane block. ESPB, erector spinae plane block. ICB, intercostal block. cWI, continuous wound infiltration. cTPVB, continuous thoracic paravertebral block.

34.3%; cTPVB: 50.9%; ICB: 58.7%; cSAPB: 17.8%; cICB: 66.5%; and control: 71.9% (Supplementary Material 10).

Visual Analog Scale at Postoperative 12 Hours

This NMA included 776 patients from 12 studies (31,33,34,38,39,41,42,44,47,57, 58,60). The network geometry of eligible comparisons displayed complete, as all nodes could be connected (Supplementary Material 9). The cSAPB technique seemed to be the best for analgesia among all the treatments. The SUCRA values established a hierarchy for the seven treatments: cSAPB: 25.5%; TPVB: 29.1%; cTEA: 33.5%; ESPB: 45.6%; ICB: 58.4%; SAPB: 62.3%; and control: 95.7% (Supplementary Material 10).

VAS at 24 hour

This NMA included 1,155 patients from 20 studies (31,33-35,38,41,42,44-

48,50,52,55-58,60,62). The network geometry of eligible comparisons displayed complete, as all nodes could be connected (Supplementary Material 9). The ESPB technique seemed to be the best for analgesia among all the treatments. The SUCRA values established a hierarchy for the 9 treatments: ESPB: 5.2%; cSAPB: 27.9%; cTPVB: 31.7%; cTEA: 40.9%; SAPB: 56.6%; TPVB: 57.4%; ICB: 58.1%; cICB: 75.6%; and control: 96.6% for (Supplementary Material 10).

Discussion

Our systematic review and NMA demonstrates that all treatments (cTEA, TPVB, SAPB, ESPB, WI, ICB, cSAPB, cEPB, cWI, cTPVB, cICB) reduced pain post thoracic surgery compared with either placebo or no intervention. Our results suggest that the cTEA, cSAPB, and ESPB techniques were more effective in reducing pain scores at 6, 12, and 24 hours, respectively. The cEPB technique was ranked first out of all the treatments for the smallest cumulative opioid consumption within

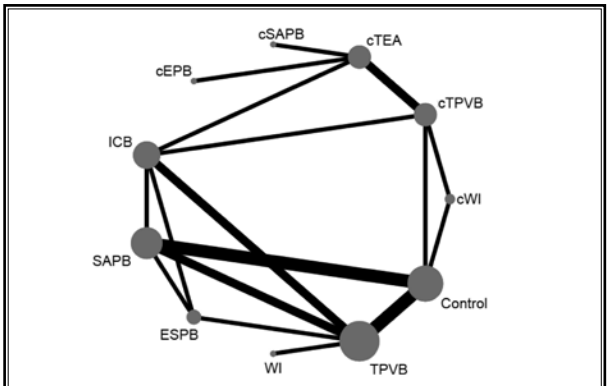

Fig. 3. *Network geometry of cumulative opioids consumption within 24 hours postoperative*
cTEA, continuous thoracic epidural analgesia. TPVB, thoracic paravertebral block. SAPB, serratus plane block. ESPB, erector spinae plane block. WI, wound infiltration. ICB, intercostal block. cSAPB, continuous serratus plane block. cEPB, continuous extrapleural block. cWI, continuous wound infiltration. cTPVB, continuous thoracic paravertebral block. cICB, continuous intercostal block.

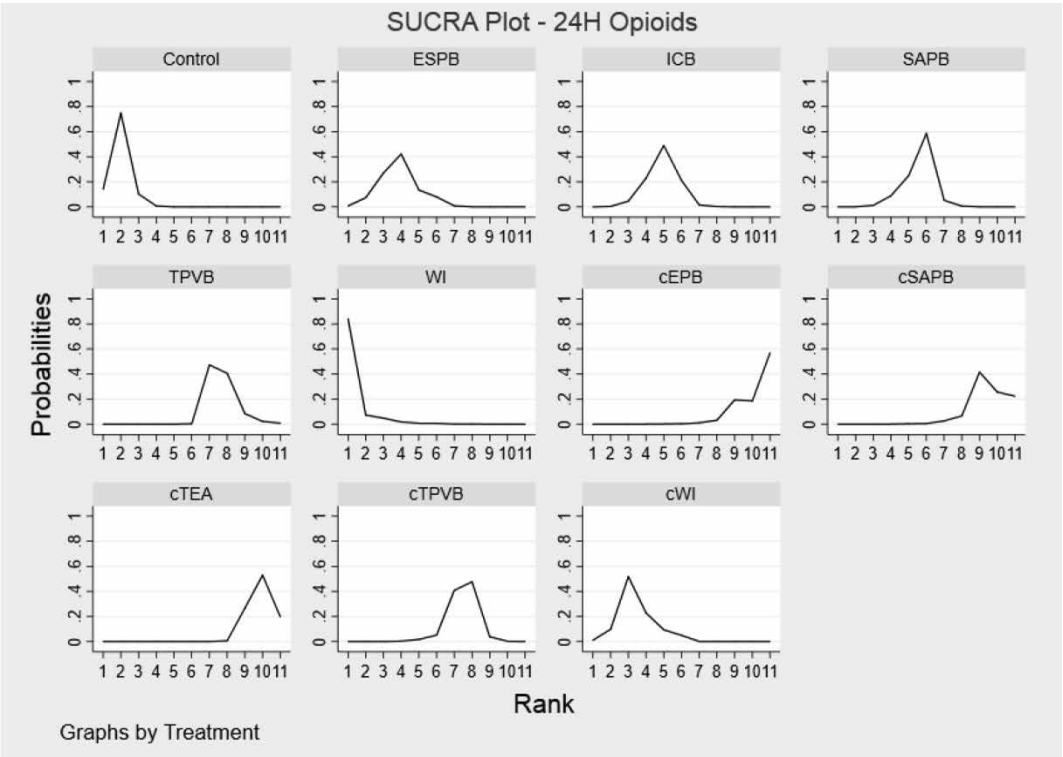

Fig 4. *Surface under the cumulative ranking curve (SUCRA) rankings of cumulative opioid consumption within postoperative 24 hours.*
Control (90.2%). wound infiltration (96.9%). cWI, continuous wound infiltration (75.5%). ESPB, erector spinae plane block (71.2%). ICB, intercostal block (60.8%). SAPB, serratus plane block (54%). cTPVB, continuous thoracic paravertebral block (35.3%). TPVB, thoracic paravertebral block (33.2%). cSAPB, continuous serratus plane block (14.5%). cTEA, continuous thoracic epidural analgesia (10.8%). cEPB, continuous extrapleural block (7.5%).

postoperative 24 hours, but only one of the included studies compared the effectiveness of cEPB and cTEA (40 patients) (54). Further research is needed in order to determine whether the effectiveness of cEPB is superior to cTEA and cSAPB.

A recent network meta-analysis (63) determined that TPVB generated the best analgesic effectiveness post-VATS; ESPB provided a comparable analgesic effectiveness with TPVB, but SAPB and ICB were not superior. These results were similar to ours. We speculate that TPVB and ESPB provide both visceral and somatosensory blockade. We also found ICB, cICB, WI and cWI had the highest probability of being the worst techniques; this can be explained by these treatments only affecting wound pain.

Postoperative pain continues to be a concern in clinical practices, as it seriously affects quality of life and a patient's prognosis. The TEA technique was once considered as the gold standard for pain management. However, it was gradually replaced by other regional and local analgesia techniques because they had similar analgesic effects without the potential risks of TEA, such as hypotension, bradycardia, pruritis, dural perforation, and epidural hematoma or epidural abscess in rare cases or urinary retention in rare cases (6,64).

The TPVB technique produces unilateral, somatic, and sympathetic nerve blockade in multiple contiguous thoracic dermatomes; it provides inferior analgesia compared with TEA but has a lower number of potential risks (17).

The ESPB technique provides superior analgesia to SAPB, ICB and WI because it blocks both dorsal and ventral rami of the thoracic spinal nerves and provides some degree of sympathetic blockade (65). The SAPB technique provides analgesia in the chest wall by blocking the lateral branches of the thoracic intercostal nerves, usually between the T2-T9 levels (66). The ICB technique is reported to be effective in improving pain; performing it is safe and simple, but it requires multiple injections (12). The cEPB technique results in unilateral and multiple blockade of intercostal nerves with a minimal risk of spinal injury, which could be considered a good alternative to cTEA post VATS (16). WI is a safe and effective fast-track approach for patients undergoing thoracotomy surgery (67).

A previous meta-analysis found that TPVB (18), SAPB (19-21), and ESPB (22-24) significantly reduced postoperative pain when compared with control groups in patients undergoing thoracic surgery. Xu and colleagues' (17) meta-analysis determined that TPVB did not provide superior analgesia compared with TEA, but TPVB reduced side effects.. Balzani and colleagues' (68) meta-analysis showed that almost all peripheral regional anesthesia techniques were effective on reducing postoperative 24-hour opioid consumption. Huan and colleagues' (69) meta-analysis determined that TPVB provides better analgesia and causes lower consumption of morphine when compared with ICB (69). The above conclusions were similar to our results, but they are limited in scope regarding treatments and pairwise comparisons.

Given that neither pairwise comparisons nor network comparisons demonstrated a common treatment to be the best choice for reducing postoperative pain within 24 hours, other considerations should be taken into account when selecting an analgesic technique, such as adding adjuncts to local anesthetics and improving the infusion mode. Administering adjuncts is an attractive and simple strategy to increase the mean duration of analgesia beyond the conventional maximum of 8-14 hours (70). Zhang and colleagues' (71) trial determined that adding perineural dexmedetomidine and dexamethasone to ropivacaine for ICB prolonged analgesia with almost no adverse effects (71). Gao and colleagues' (72) trial determined that using dexmedetomidine (one μg/kg) as an adjuvant of ESPB with ropivacaine prolonged sensory block duration, provided effective acute pain control, and required less rescue analgesia and shorter hospital stays when compared with dexamethasone (10 mg). However, dexmedetomidine and dexamethasone cannot fulfill all the criteria of the ideal local anesthetic adjunct. Dexmedetomidine can cause bradycardia, hypotension, and sedation, while dexamethasone slightly increases glycemia (70). In addition, the safety of perineural adjuncts continues to be a concern, as the findings of a neurotoxic effect associated with perineural dexmedetomidine during in vitro studies are conflicting (70). Interestingly, existing evidence shows that a local anesthetic administered as a programmed intermittent bolus infusion provides a wider sensory blockade and superior analgesia to a continuous infusion post cTPVB in patients undergoing VATS (73,74). However, the effect of programmed intermittent bolus infusion in cTEA, cEPB, cSAPB, cICB, cWI were not analyzed, but if the analgesia were more efficient, then programmed intermittent bolus infusion would be a recommended choice.

Our systematic review and NMA includes as many regional analgesia techniques as possible and synthesized data from both direct comparison trials and indi-

rect evidence. This method increased the precision of effect estimates and also helped rank the treatments. Other strengths include the comprehensive literature search and using CINeMA to assess risk of bias for every comparison.

Limitations

There are several potential limitations in our NMA, many of which are inherent to NMAs. First, 4 enrolled studies had a sample size less than 40 patients, which are categorized as smaller studies with a high risk of sampling errors. Therefore, we performed a comparison-adjusted funnel plot to detect any small study effect bias.

Second, these different regimens are potential factors contributing to heterogeneity for the same treatment between 2 studies, such as drugs doses and injection volumes, infusion time (preoperative, intraoperative, and postoperative), infusion mode (single-shot or continuous injection), adding adjuncts (clonidine, dexmedetomidine, dexamethasone), and rescue analgesic regimens. We attempted to minimize this effect by conducting subgroup analyses, but it was not implemented because of the sparsity of data. We speculate that those differences contributed to inconsistency on the results of loops of control-TPVB-SAPB on VAS at postoperative 12 hours, and control-TPVB-SAPB and TPVB-ICB-SAPB on opioid consumption within 24 hours postoperative.

Third, we only focused on short-term outcomes (resting VAS and opioid consumption within 24 hours postoperative), but in fact, these outcomes were also important in effectiveness evaluation such as specific adverse effects, pain scores on movement, patient comfort, recovery of lung function, postoperative nausea and vomiting, hospital length of stay, and health-related quality of life.

Finally, owing to the limited number of RCTs for cEPB, we need high-level evidence to determine the effectiveness of this technique.

Conclusions

In conclusion, our systematic review and NMA demonstrates that there is no common treatment determined to be the best choice for reducing acute pain after thoracic surgery, but cTEA and cSAPB are more likely to reduce the cumulative opioid consumption within 24 hours postoperative, while cTEA, cSAPB, ESPB were more likely to improve pain at postoperative 6, 12, 24 hours, respectively. Therefore, cTEA, cSAPB, and ESPB are the first choices for pain relief post thoracic surgery, whereas ICB, cICB, WI and cWI were less likely to be effective. More high-quality RCTs with larger sample sizes are needed to validate our results and to get the ideal regional analgesia technique and the optimal drug formula in the future.

Author Contributions

The concept and study was designed by YMJ and ZD. Statistical analysis was performed by ZXM, LG and ZXW. Manuscript preparation was performed by YMJ and ZD. Manuscript revision was performed by YWJ and ZD. All authors contributed to preparation of the manuscript, and they reviewed and approved the final version's content.

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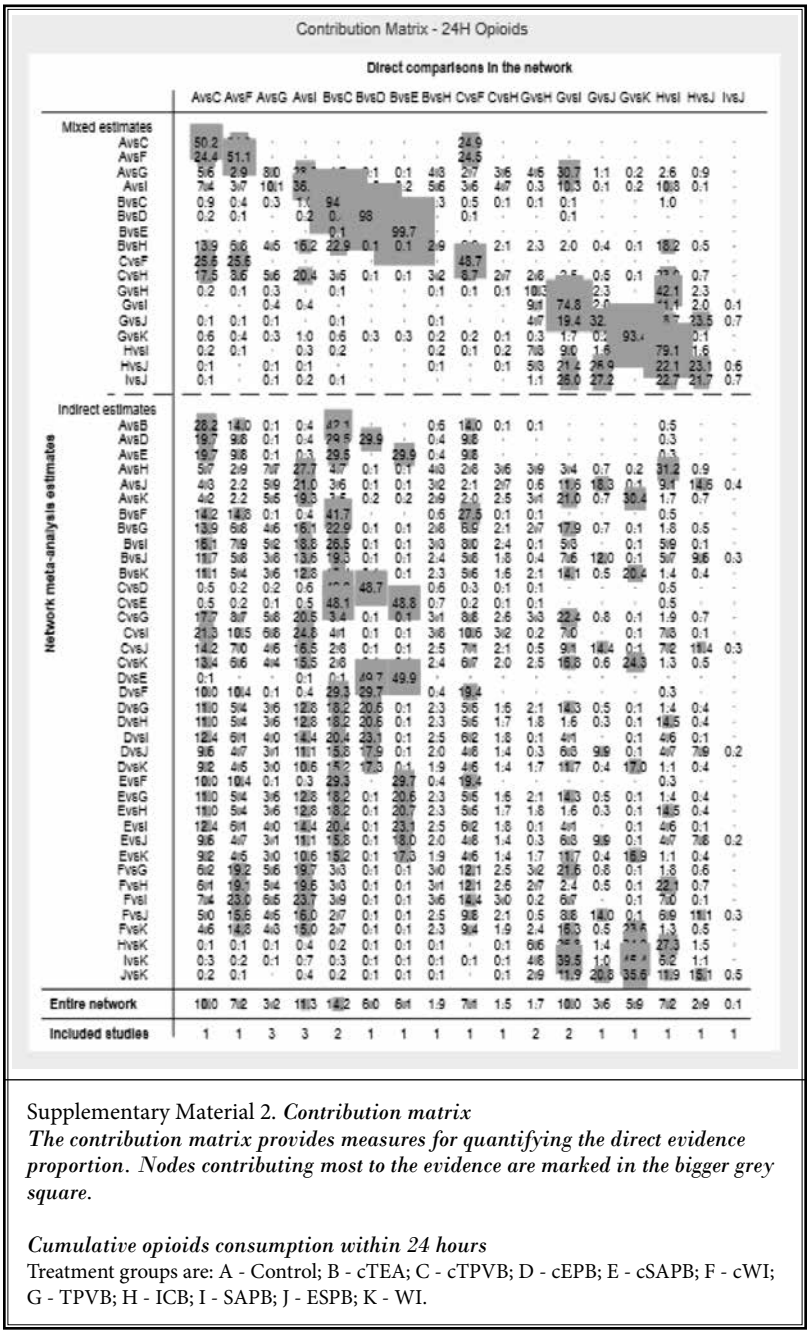
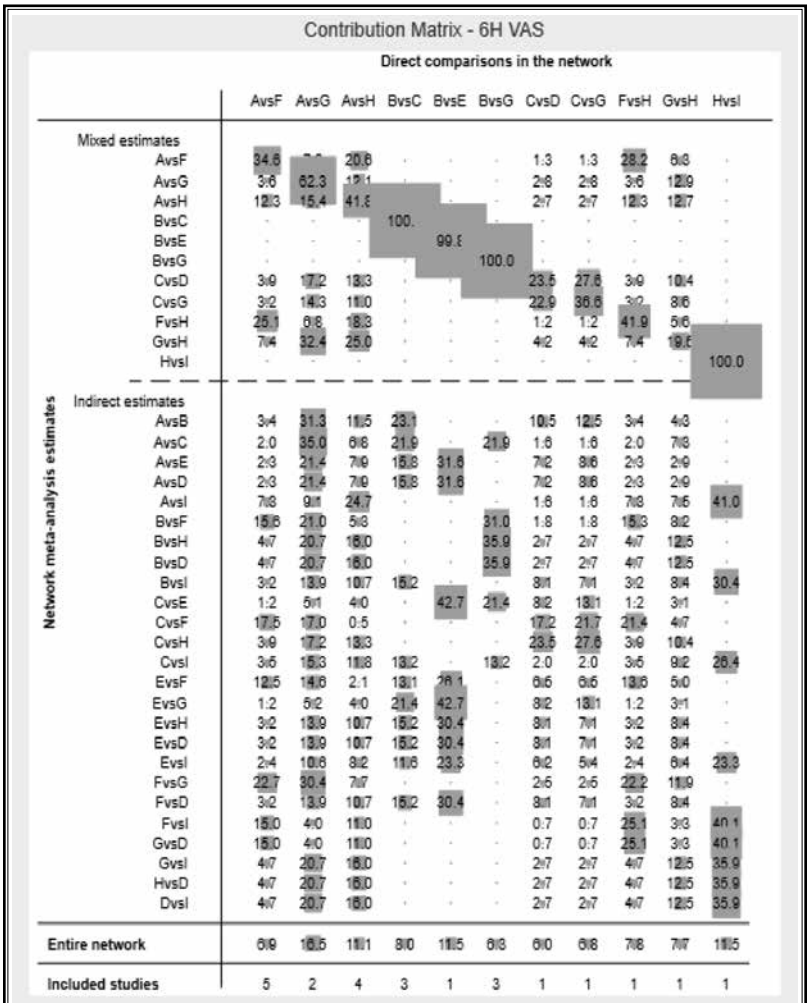
Supplementary Material 1. *Search Strategy*

#	Searches	Results
1	((thoracotomy) OR (thoracic surgery)) OR (Video-Assisted Thoracic Surgery)	543723
2	(((((((thoracic epidural analgesia) OR (thoracic paravertebral block)) OR (serratus plane block)) OR (erector spinae plane block)) OR (wound infiltration)) OR (intercostal block)) OR (extrapleural block)	19765
3	1 and 2	3615
4	3 Filters: Clinical Trial	1083

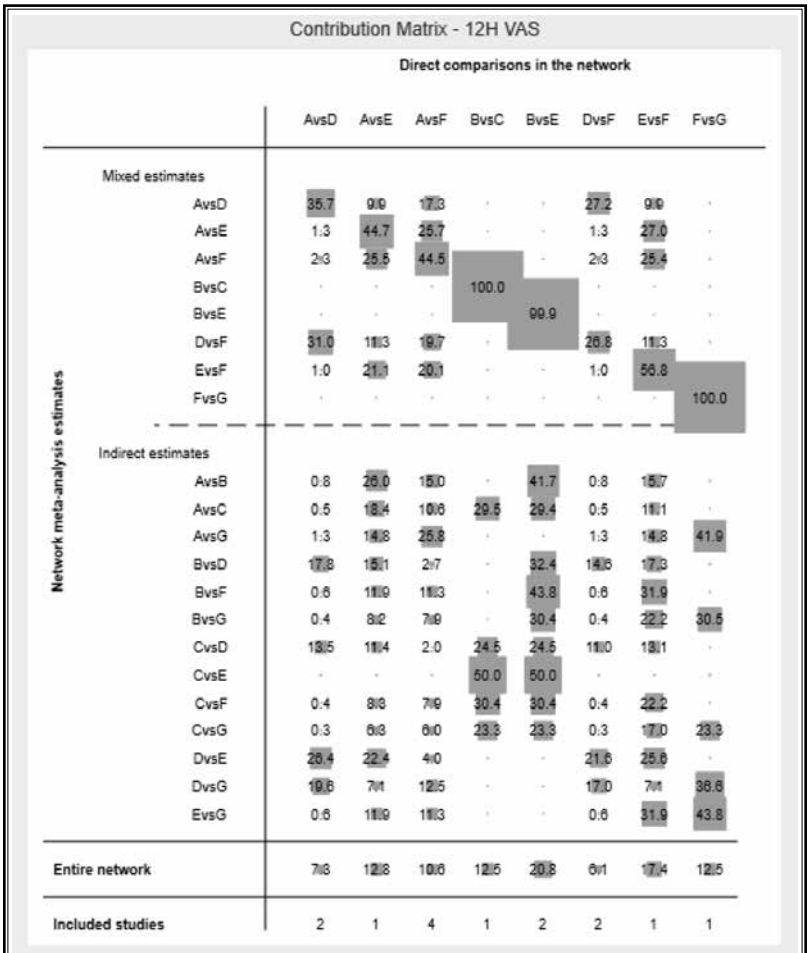


Supplementary Material 2. *Contribution matrix*
The contribution matrix provides measures for quantifying the direct evidence proportion. Nodes contributing most to the evidence are marked in the bigger grey square.

Cumulative opioids consumption within 24 hours
Treatment groups are: A - Control; B - cTEA; C - cTPVB; D - cEPB; E - cSAPB; F - cWI; G - TPVB; H - ICB; I - SAPB; J - ESPB; K - WI.



Supplementary Material 2 cont. ***Contribution matrix***
Postoperative VAS at 6 hour
Treatment groups are:A - Control; B - cTEA; C - cTPVB; D - cICB; E - cSAPB; F - TPVB; G - ICB; H - SAPB; I - ESPB.



Supplementary Material 2 cont. ***Contribution matrix***
Postoperative VAS at 12 hour
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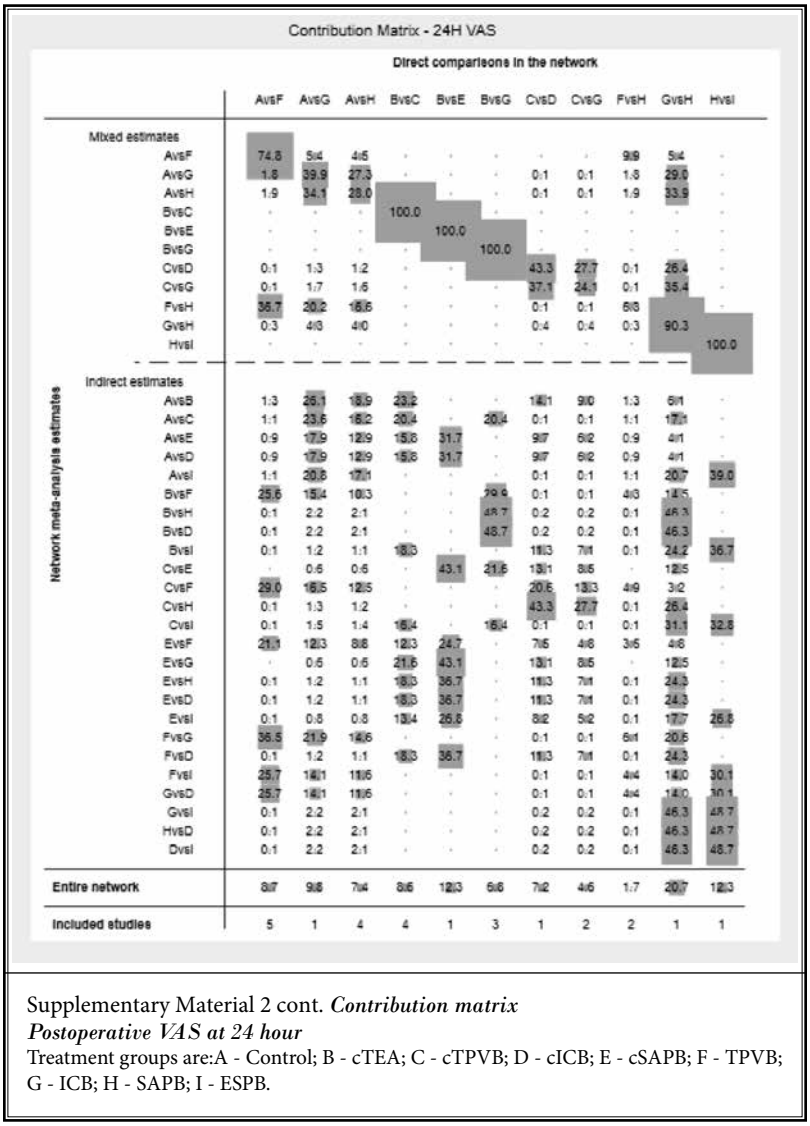
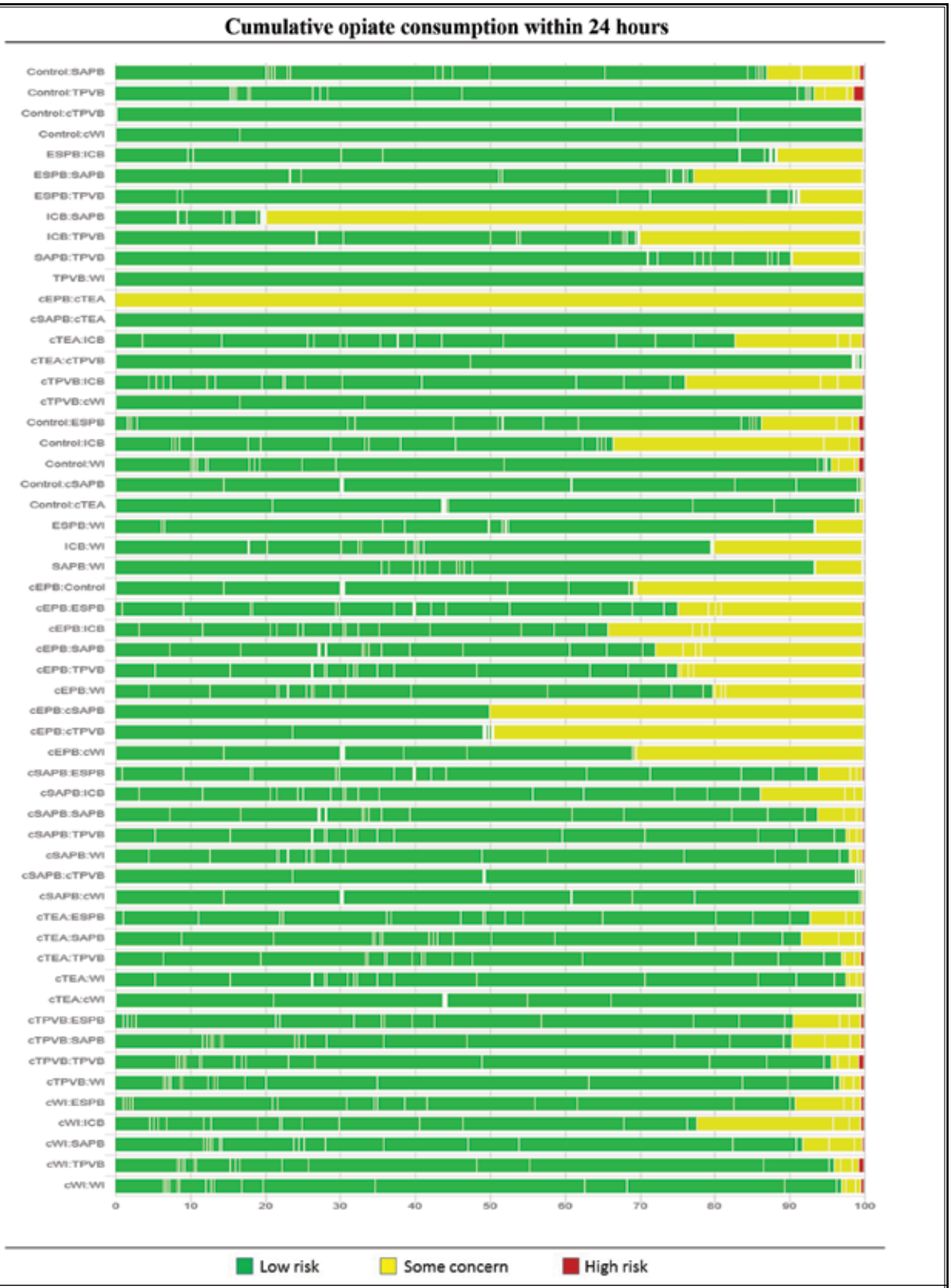
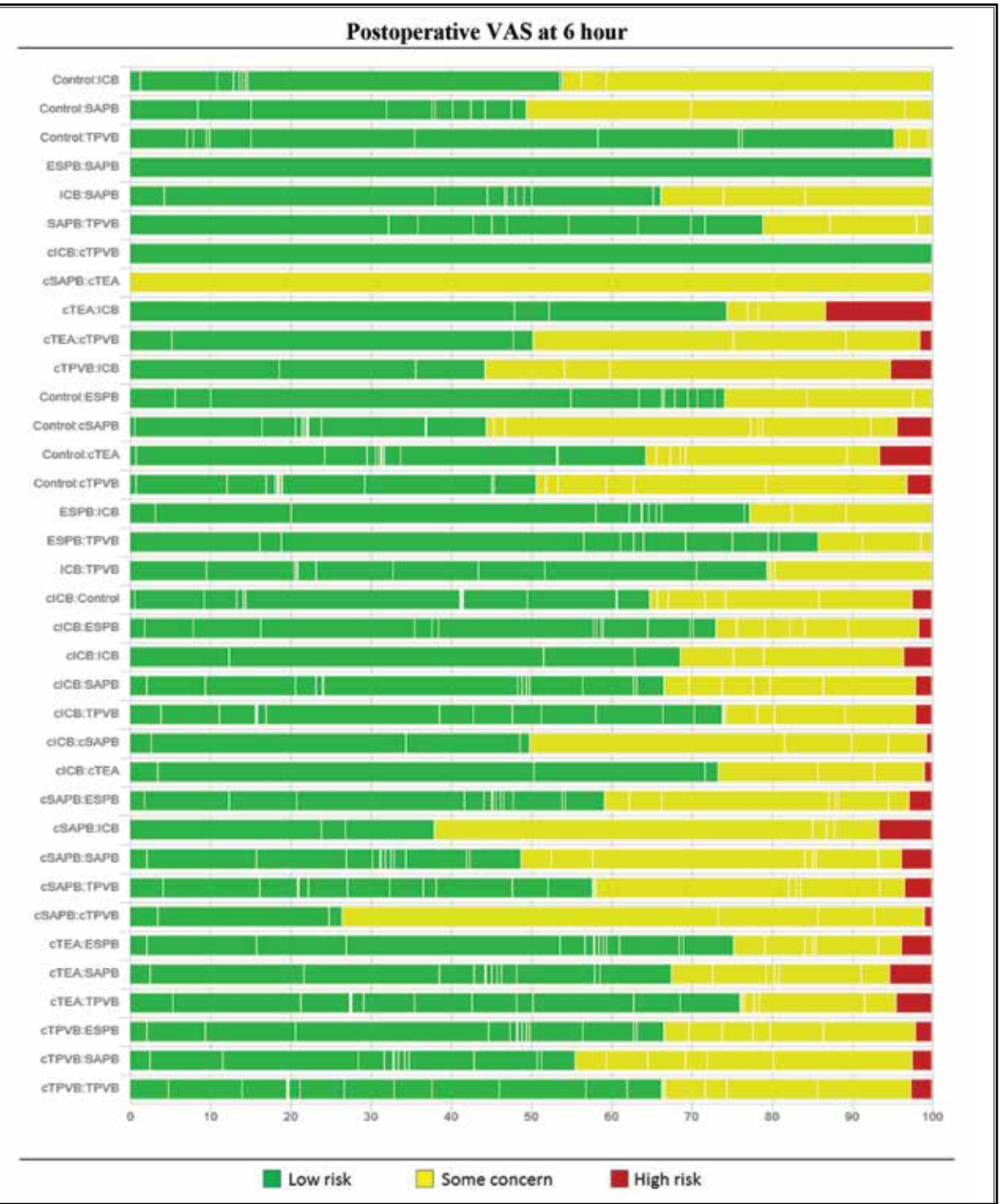


Supplementary Material 2 cont. ***Contribution matrix***
Postoperative VAS at 24 hour
Treatment groups are:A - Control; B - cTEA; C - cTPVB; D - cICB; E - cSAPB; F - TPVB; G - ICB; H - SAPB; I - ESPB.



Supplementary Material 3. ***Comparison specific risk of bias***
This was done in CINeMA. Available from https://cinema.ispm.unibe.ch/



Supplementary Material 3 cont. ***Comparison specific risk of bias***
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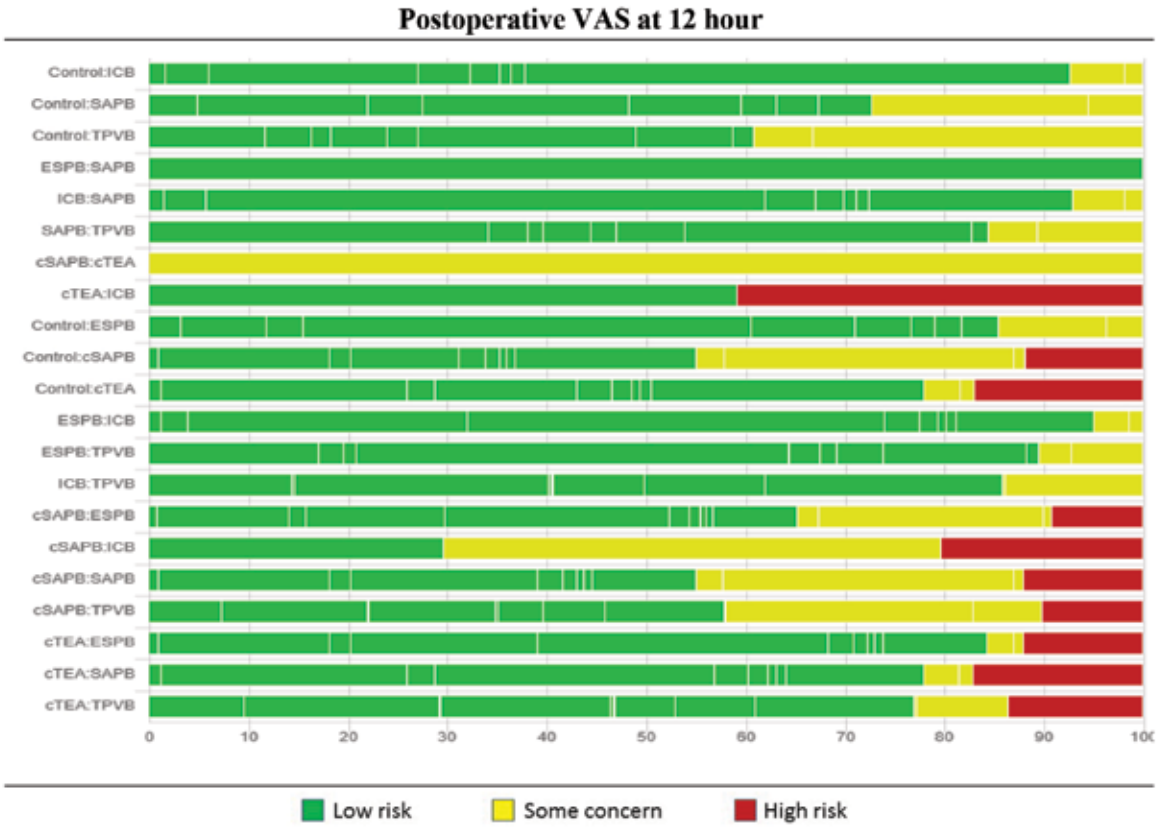
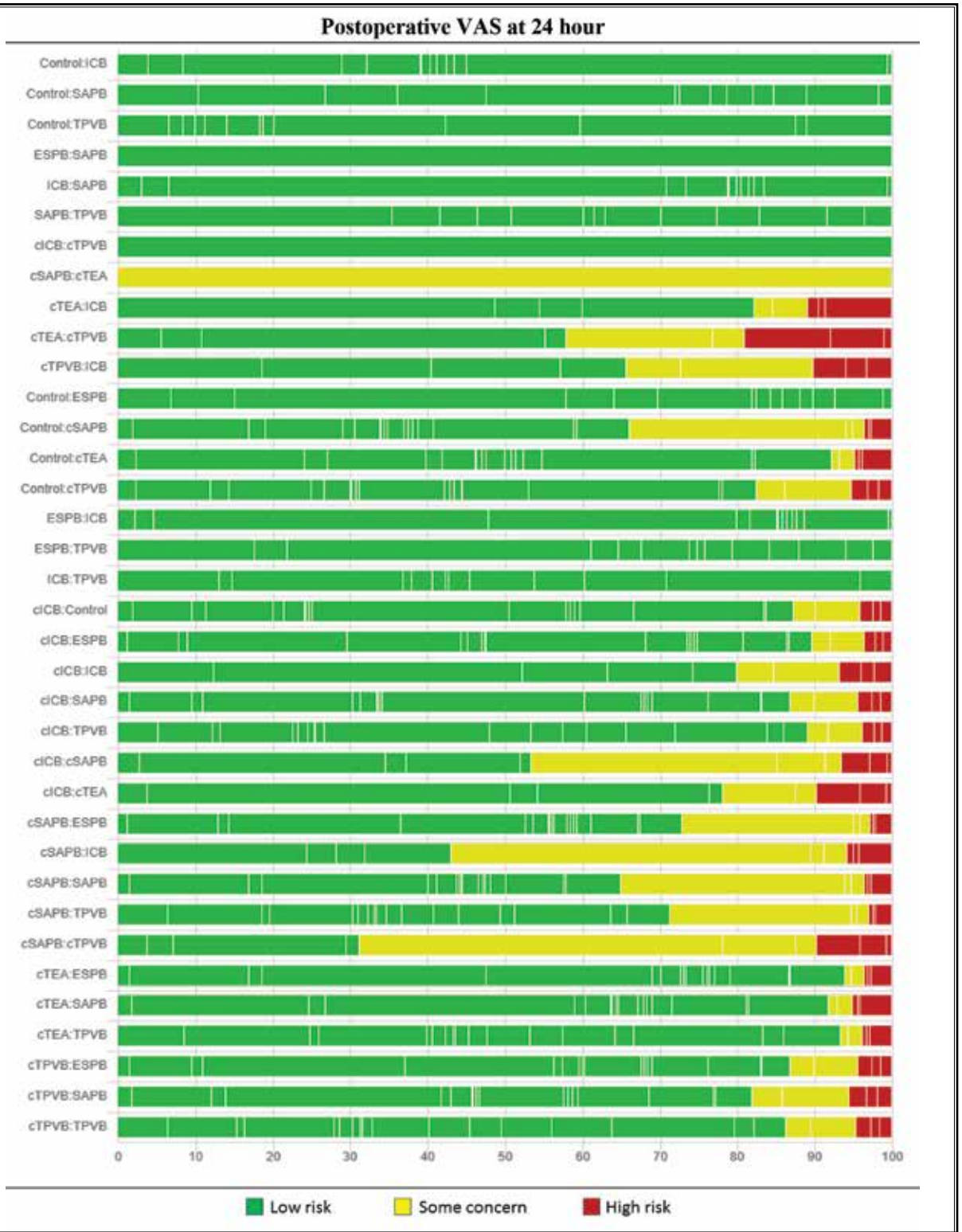
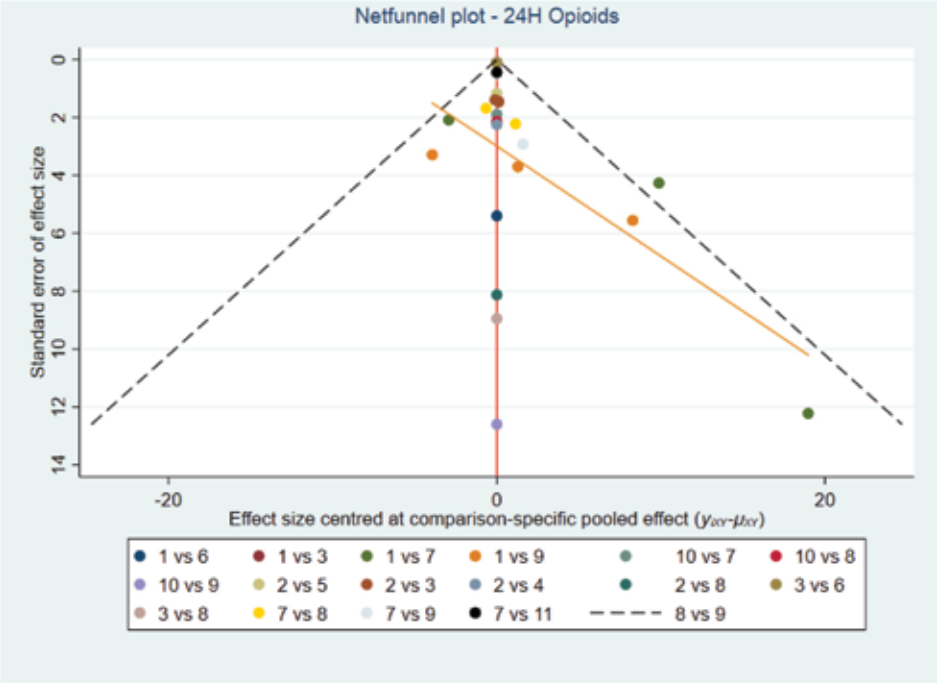


Supplementary Material 3 cont. ***Comparison specific risk of bias***
This was done in CINeMA. Available from https://cinema.ispm.unibe.ch/

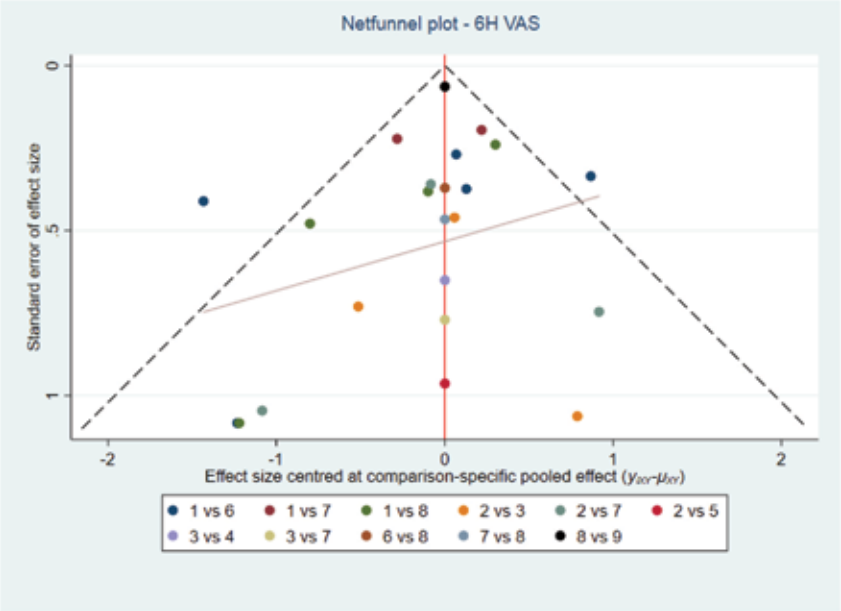


Supplementary Material 3 cont. ***Comparison specific risk of bias***
This was done in CINeMA. Available from https://cinema.ispm.unibe.ch/

Cumulative opioids consumption within 24 hours

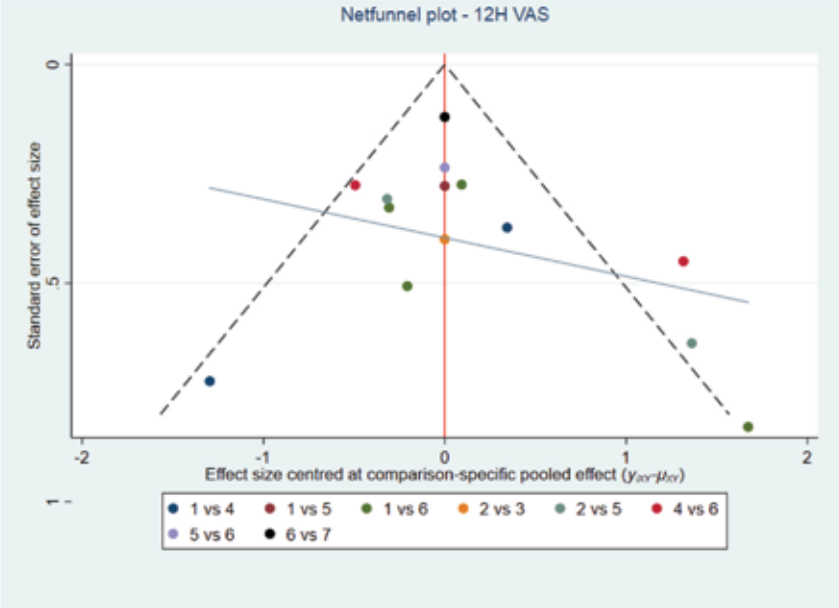


Postoperative VAS at 6 hour

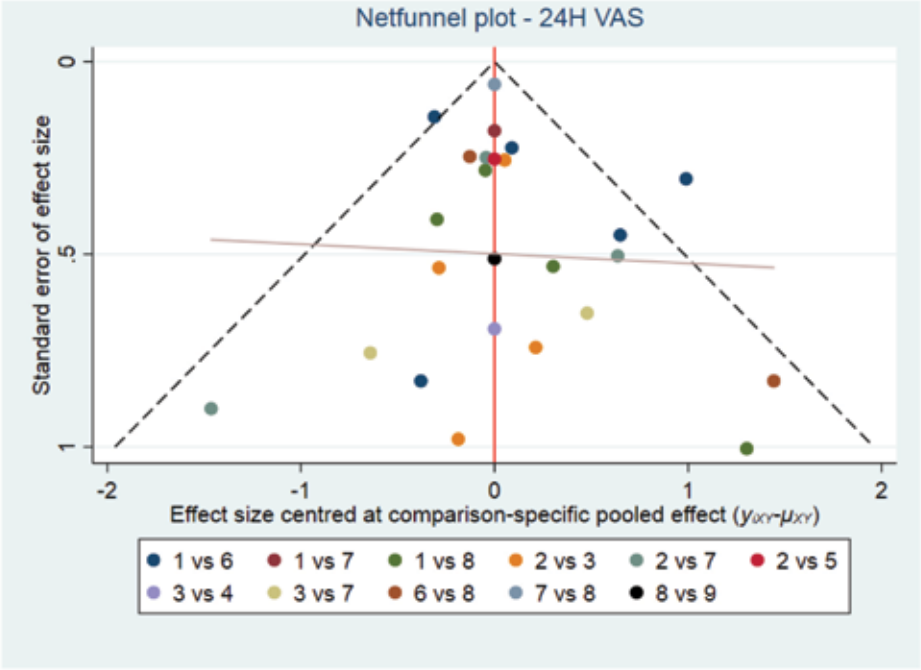


Supplementary Material 4. ***Publication bias (Netfunnel)***
A comparison-adjusted funnel plot is used to assess publication bias. In the funnel plot, the horizontal axis represents the direct summary effect, the vertical axis represents a measure of dispersion, different color represents every comparison. If small-study affect the symmetry around the zero line of the funnel plot, the result suggests publication bias. None of the netfunnel plots below suggested any publication bias.

Postoperative VAS at 12 hour

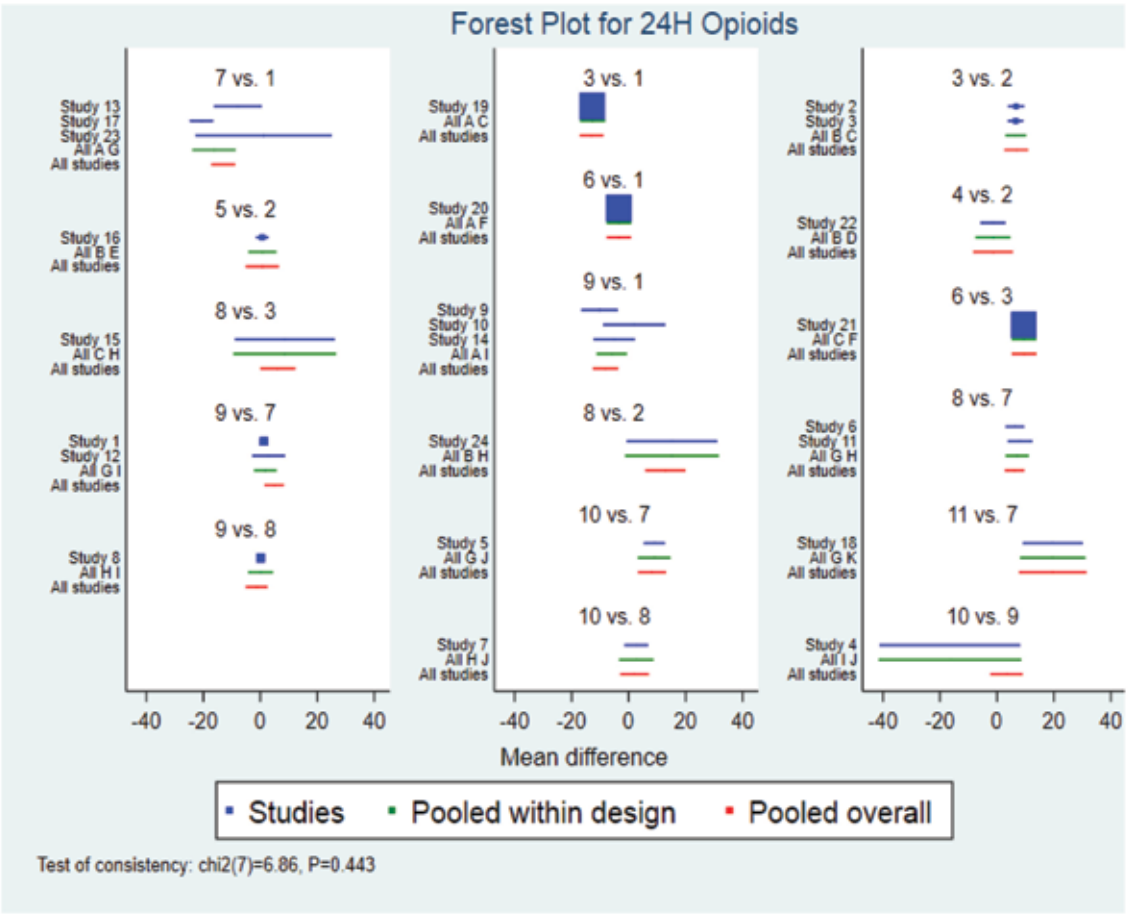


Postoperative VAS at 24 hour



Supplementary Material 4 cont. ***Publication bias (Netfunnel)***
A comparison-adjusted funnel plot is used to assess publication bias. In the funnel plot, the horizontal axis represents the direct summary effect, the vertical axis represents a measure of dispersion, different color represents every comparison. If small-study affect the symmetry around the zero line of the funnel plot, the result suggests publication bias. None of the netfunnel plots below suggested any publication bias.

Cumulative opioids consumption within 24 hours



Supplementary Material 5. ***Network forest plots***

A network forest plot displays the following results:

1.'Studies': each study which reported one outcome (the direct evidence);

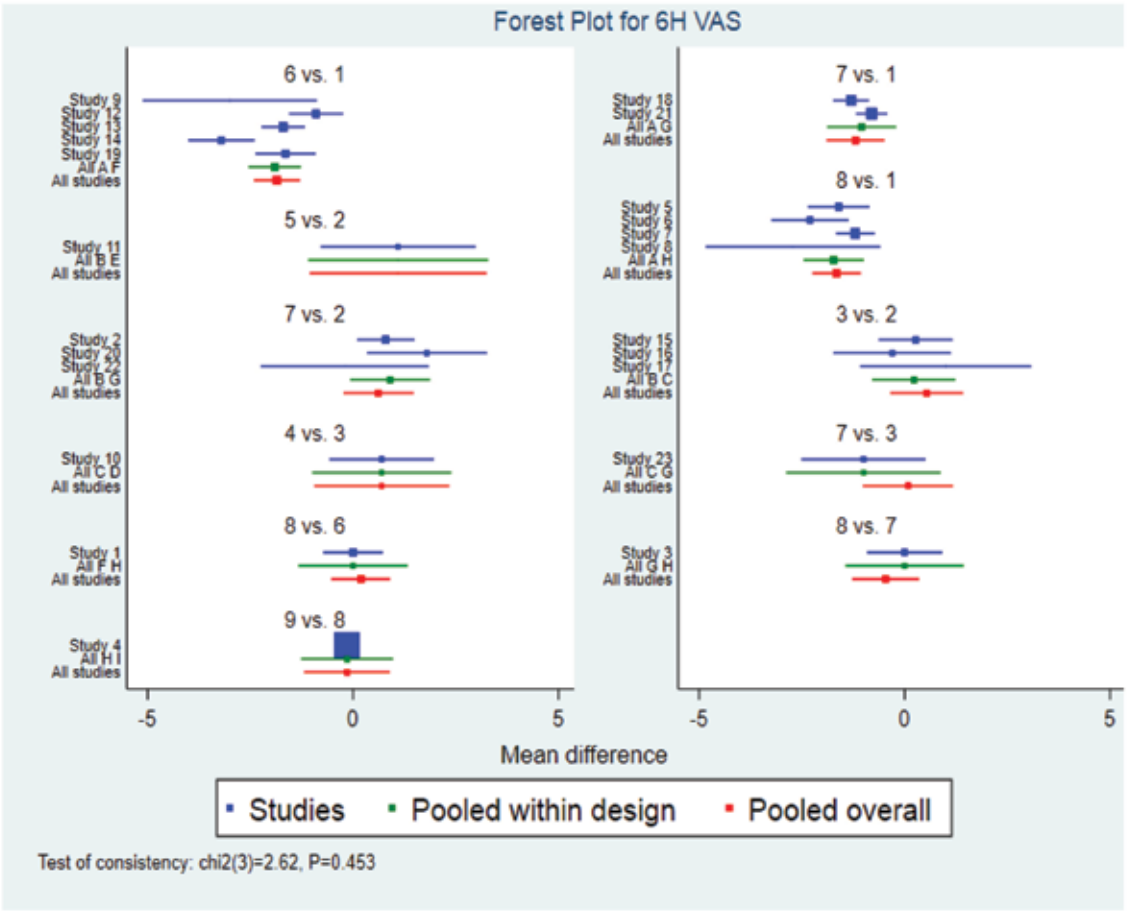
2.'Pooled within design': using the inconsistency model to estimate the pooled treatment effect in each design

3.'Pooled overall': using the consistency model to estimate the overall treatment effect.

If the 'pooled within design' and 'pooled overall' are similar, the results support the consistency model, while the dissimilarity supports the inconsistency model.

Similarity between the 'pooled within design' and 'pooled overall' results support the consistency model.

Postoperative VAS at 6 hour



Supplementary Material 5 cont. ***Network forest plots***

A network forest plot displays the following results:

1.'Studies': each study which reported one outcome (the direct evidence);

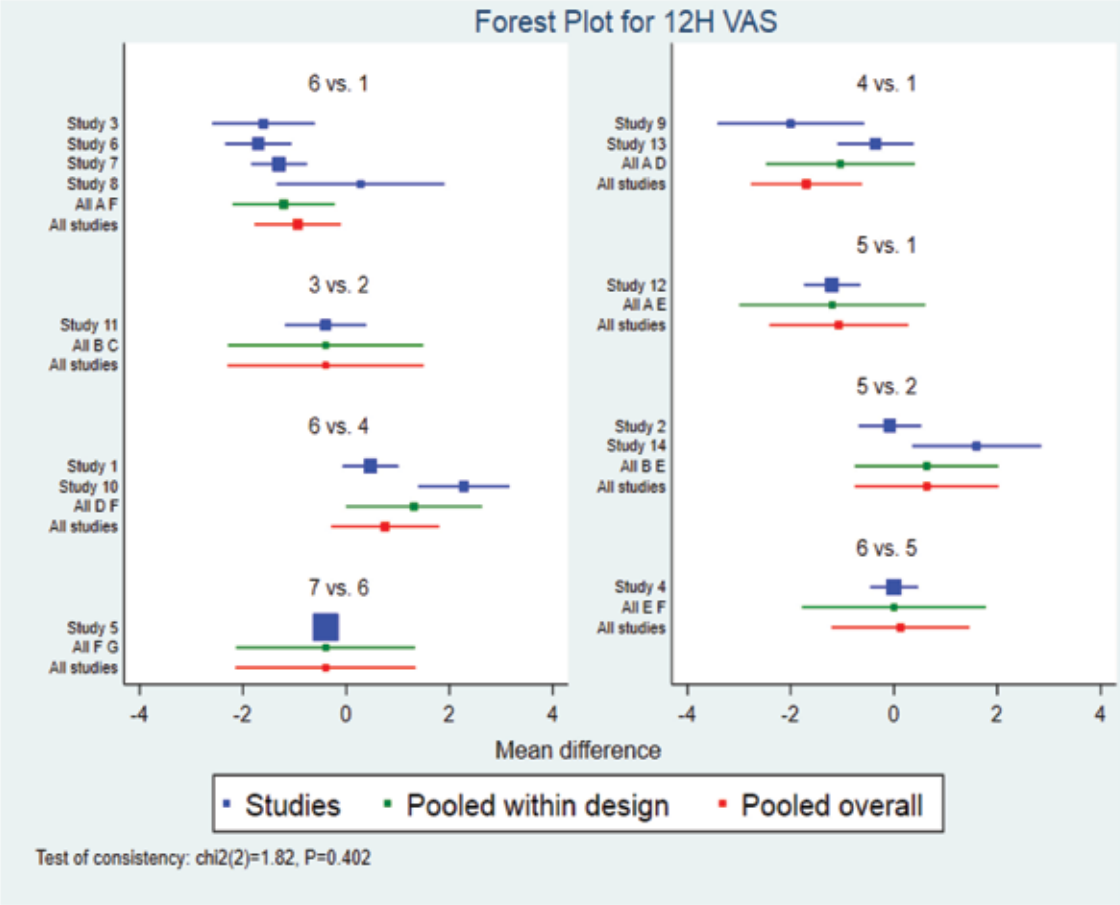
2.'Pooled within design': using the inconsistency model to estimate the pooled treatment effect in each design

3.'Pooled overall': using the consistency model to estimate the overall treatment effect.

If the 'pooled within design' and 'pooled overall' are similar, the results support the consistency model, while the dissimilarity supports the inconsistency model.

Similarity between the 'pooled within design' and 'pooled overall' results support the consistency model.

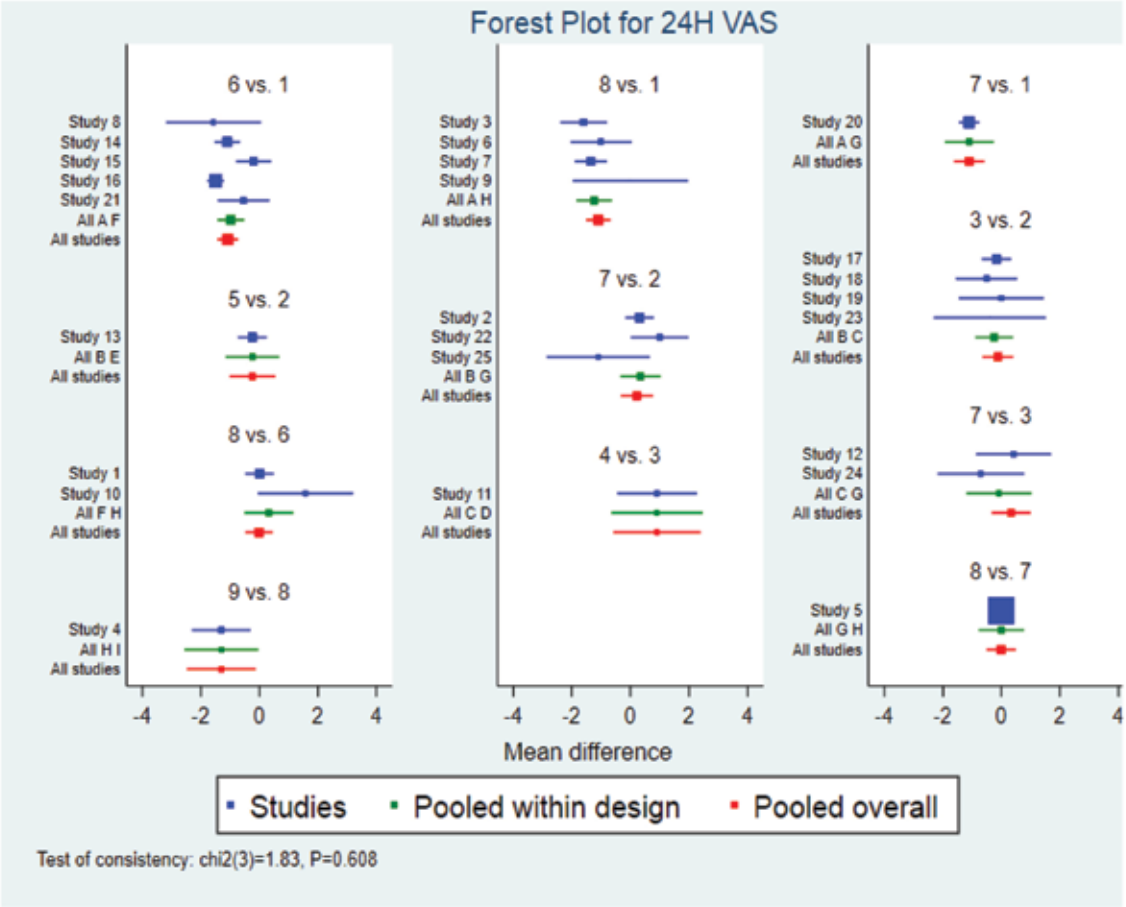
Postoperative VAS at 12 hour



Supplementary Material 5 cont. *Network forest plots*
A network forest plot displays the following results:
1.'Studies': each study which reported one outcome (the direct evidence);
2.'Pooled within design': using the inconsistency model to estimate the pooled treatment effect in each design
3.'Pooled overall': using the consistency model to estimate the overall treatment effect.
If the 'pooled within design' and 'pooled overall' are similar, the results support the consistency model, while the dissimilarity supports the inconsistency model.

Similarity between the 'pooled within design' and 'pooled overall' results support the consistency model.

Postoperative VAS at 24 hour



Supplementary Material 5 cont. *Network forest plots*
A network forest plot displays the following results:
1.'Studies': each study which reported one outcome (the direct evidence);
2.'Pooled within design': using the inconsistency model to estimate the pooled treatment effect in each design
3.'Pooled overall': using the consistency model to estimate the overall treatment effect.
If the 'pooled within design' and 'pooled overall' are similar, the results support the consistency model, while the dissimilarity supports the inconsistency model.

Similarity between the 'pooled within design' and 'pooled overall' results support the consistency model.

Supplementary Material 5 cont. *Summary of global test of consistency*

Outcome	**Chi square value**	***P*-value of Consistency model**	**Interpretation**
Cumulative opiate consumption within 24 Hours	Chi2(7) = 6.86	*P* = 0.4431	Global consistency satisfied
Postoperative VAS at 6 Hour	Chi2(3) = 2.62	*P* = 0.4533	Global consistency satisfied
Postoperative VAS at 12 Hour	Chi2(2) = 1.82	*P* = 0.4018	Global consistency satisfied
Postoperative VAS at 24 Hour	Chi2(3) = 1.83	*P* = 0.6077	Global consistency satisfied

The global test of consistency judges whether heterogeneity is independent of the comparison being made. If statistically significant (p–value < 0.1), this implies global consistency not satisfied, and reasons for this were sought further (using node-splitting and loop-specific inconsistency).

Supplementary Material 6. ***Exploration of inconsistency***

Node-splitting reports the estimated direct and indirect effects of two treatments in studies (the direct estimate) and in other studies (the indirect estimate) and their difference; the p-value for the difference is a test of consistency.

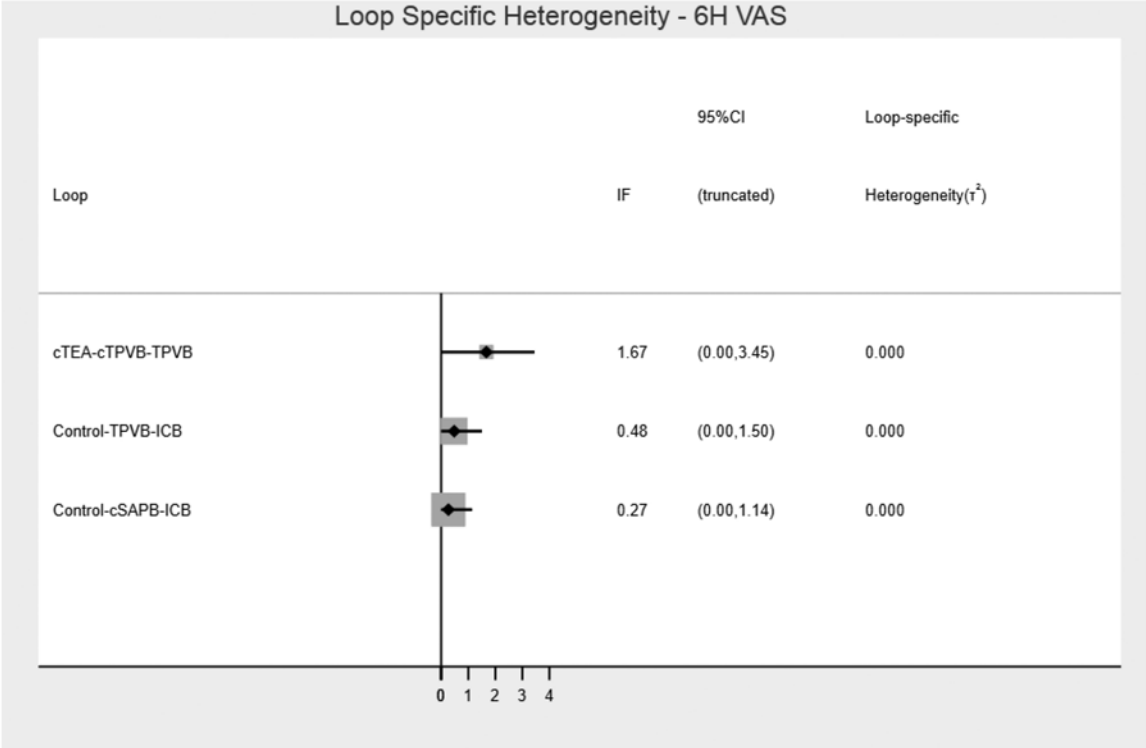
The loop-specific approach can evaluate inconsistency separately in every closed loop of every outcome, but the power is low. If the lower limit of 95% CI does not reach the zero line, the loop are probably considered to present statistically significant inconsistency.

Postoperative VAS at 6 hour

Treatment groups are:A - Control; B - cTEA; C - cTPVB; D - cICB; E - cSAPB; F - TPVB; G - ICB; H - SAPB; I - ESPB.

Node-splitting							
Side	**Direct**		**Indirect**		**Difference**		**P>z**
	Coef.	**Std. Err.**	**Coef.**	**Std. Err.**	**Coef.**	**Std. Err.**	
A F	-1.901781	0.3248217	-1.617013	0.7617379	-0.2847684	0.8255951	0.73
A G	-1.046024	0.4197194	-1.75356	0.7967801	0.7075361	0.9004291	0.432
A H	-1.73489	0.378743	-1.511407	0.5640067	-0.2234824	0.6781954	0.742
B C	0.2226528	0.4916482	1.907308	1.032066	-1.684655	1.143195	0.141
B E *	1.1	1.100507	3.634586	177.0866	-2.534586	177.0862	0.989
B G	0.9072518	0.4670674	-0.7779307	1.042956	1.685182	1.142761	0.14
C D *	0.7	0.8404275	2.587862	145.7318	-1.887862	145.7344	0.99
C G	-1.000006	0.9204607	0.6837792	0.6780467	-1.683785	1.14324	0.141
F H	-3.33E-09	0.6798	0.2845102	0.4685534	-0.2845102	0.8256333	0.73
G H	-6.63E-10	0.7251437	-0.7109006	0.5348347	0.7109006	0.9010447	0.43
H I *	-0.15	0.5369518	3.322522	11.43759	-3.472522	11.44983	0.762

* Warning: all the evidence about these contrasts comes from the trials which directly compare them.



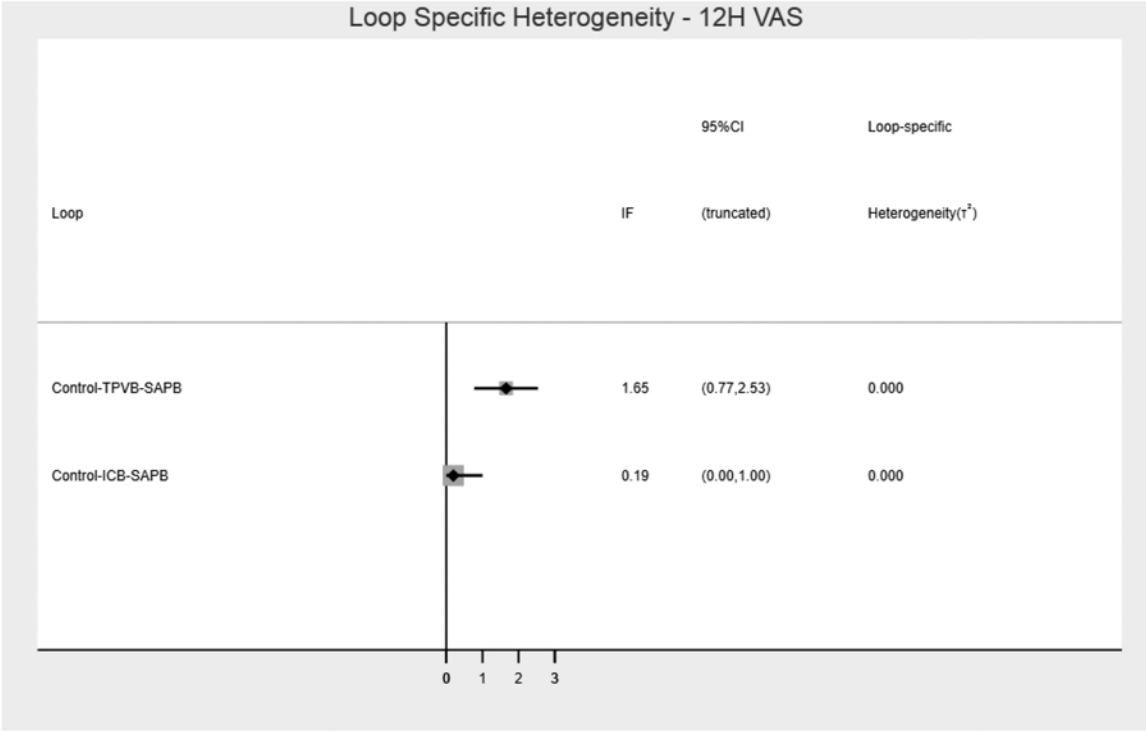
Supplementary Material 6 cont. ***IFPLOT***

None of the loops has significant inconsistency.

Supplementary Material 6 cont. ***Postoperative VAS at 12 hour***
Treatment groups are:A - Control; B - cTEA; C - cSAPB; D - TPVB; E - ICB; F - SAPB; G - ESPB.

Node-splitting							
Side	**Direct**		**Indirect**		**Difference**		**P>z**
	Coef.	**Std. Err.**	**Coef.**	**Std. Err.**	**Coef.**	**Std. Err.**	
AD	-1.007661	0.6676278	-2.525701	0.731133	1.518039	0.9906085	0.125
AE	-1.2	1.009139	-0.8969719	1.10887	-0.3030283	1.499318	0.84
AF	-1.217672	0.4989476	-0.2694483	0.777475	-0.9482234	0.9230622	0.304
BC*	-0.4	0.9690586	3.40143	75.93821	-3.80143	75.94565	0.96
BE*	0.6329096	0.7119298	-1.507846	32.23463	2.140755	32.24246	0.947
DF	1.295886	0.6016602	-0.2233818	0.7960041	1.519268	0.9906239	0.125
EF	-1.29E-12	0.9983576	0.295148	1.11912	-0.295148	1.499715	0.844
FG*	-0.4000001	0.8910055	1.884822	29.46141	-2.284822	29.47485	0.938

* Warning: all the evidence about these contrasts comes from the trials which directly compare them.

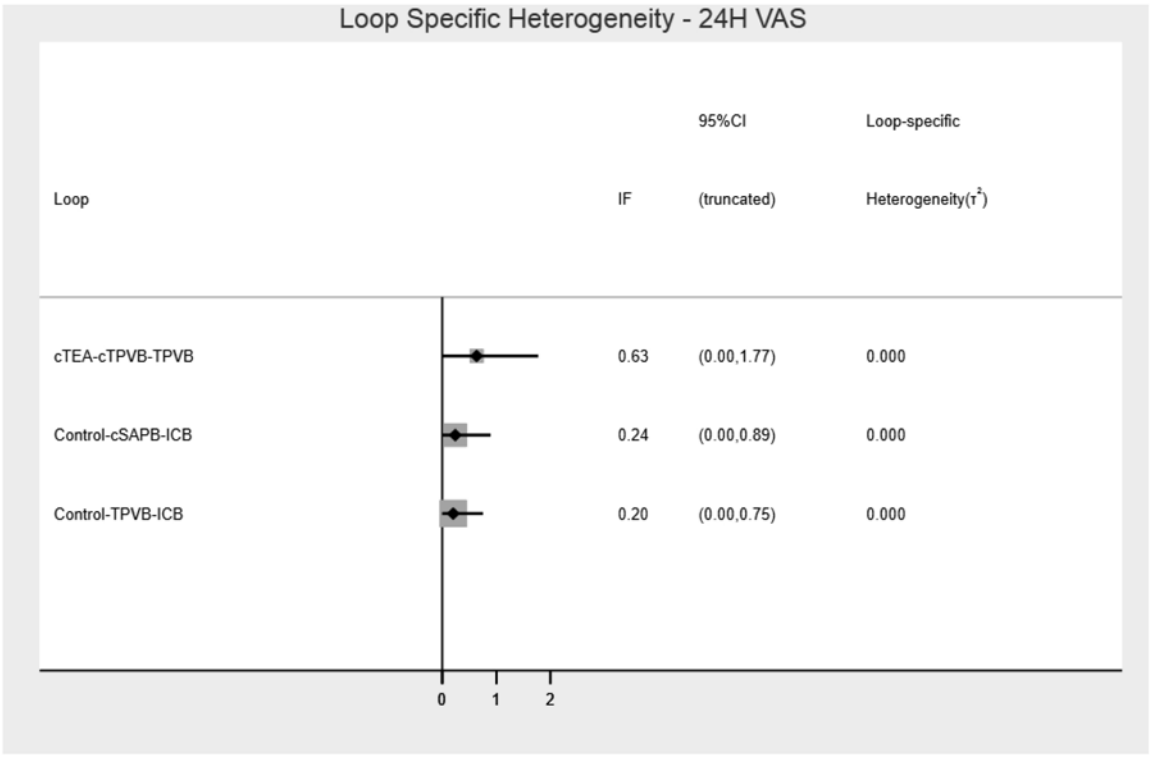


Supplementary Material 6 cont. ***IFPLOT***
Loop Control-TPVB-SAPB has significant inconsistency

Supplementary Material 6 cont. ***Postoperative VAS at 24 hour***
Treatment groups are: A - Control; B - cTEA; C - cTPVB; D - cICB; E - cSAPB; F - TPVB; G - ICB; H - SAPB; I - ESPB.

Node-splitting							
Side	**Direct**		**Indirect**		**Difference**		**P>z**
	Coef.	**Std. Err.**	**Coef.**	**Std. Err.**	**Coef.**	**Std. Err.**	
A F	-0.9845771	0.2170626	-1.499671	0.4676597	0.5150936	0.5218949	0.324
A G	-1.1	0.4037	-1.070743	0.4455244	-0.029257	0.6012202	0.961
A H	-1.250503	0.2904816	-0.8648466	0.3503139	-0.3856561	0.4463964	0.388
B C	-0.2371399	0.299026	0.4280224	0.6262882	-0.6651623	0.6938852	0.338
B E *	-0.24	0.4010471	2.633896	50.60463	-2.873896	50.60622	0.955
B G	0.3562116	0.3138668	-0.310491	0.6190864	0.6667025	0.6935454	0.336
C D *	0.9099998	0.7602428	2.897436	152.2892	-1.987436	152.2902	0.99
C G	-0.0718642	0.5423286	0.5925159	0.4329603	-0.6643801	0.6938713	0.338
F H	0.28753	0.3968004	-0.2277805	0.3324292	0.5153105	0.5219519	0.324
G H	-3.66E-09	0.366321	0.0217989	0.4763752	-0.0217989	0.6009363	0.971
H I *	-1.3	0.5987543	2.189586	123.2751	-3.489586	123.2773	0.977

* Warning: all the evidence about these contrasts comes from the trials which directly compare them.



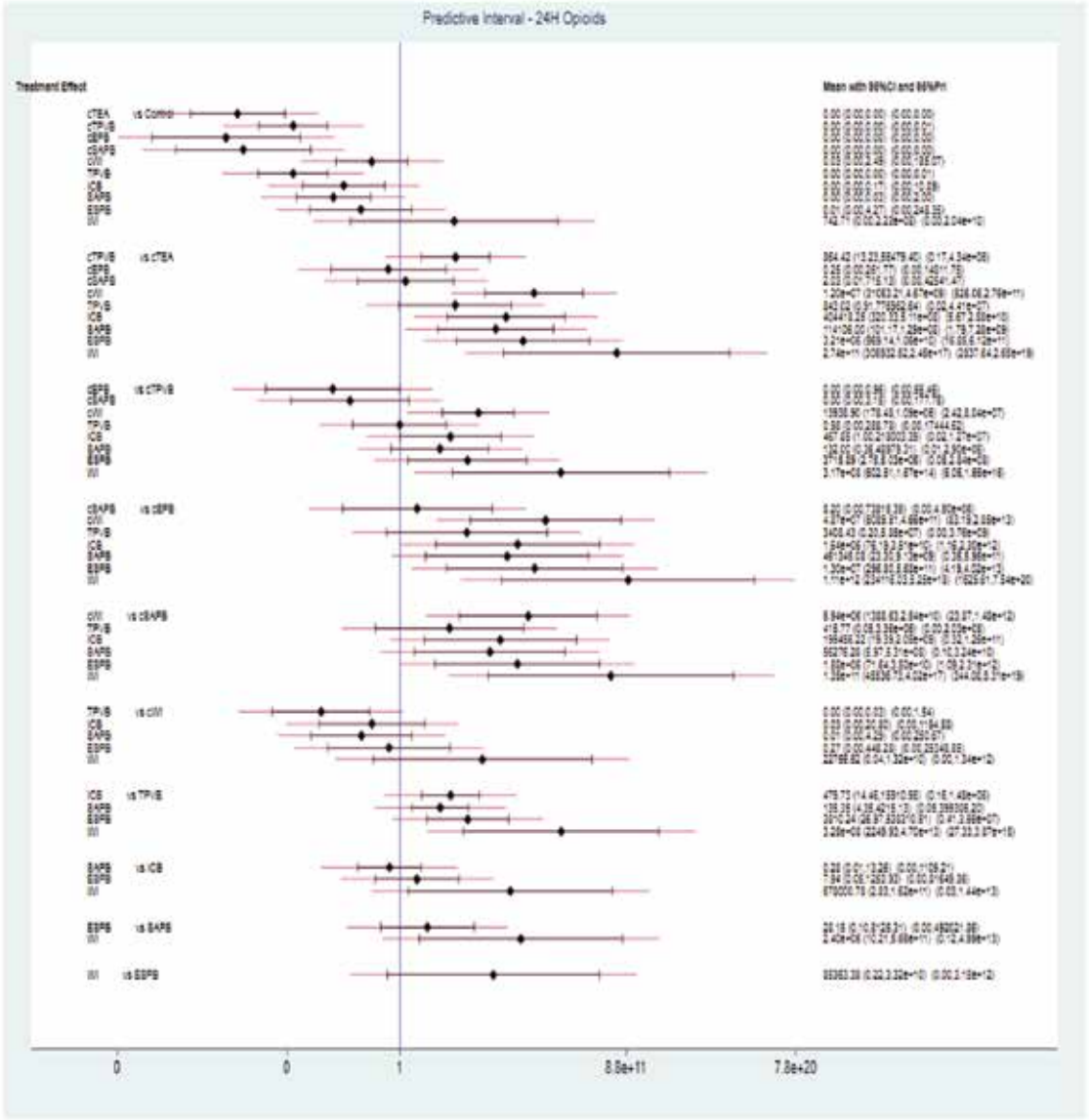
Supplementary Material 6 cont. ***IFPLOT***
None of the loops has significant inconsistency.

Supplementary Material 6 cont. *Summary of inconsistency testing*

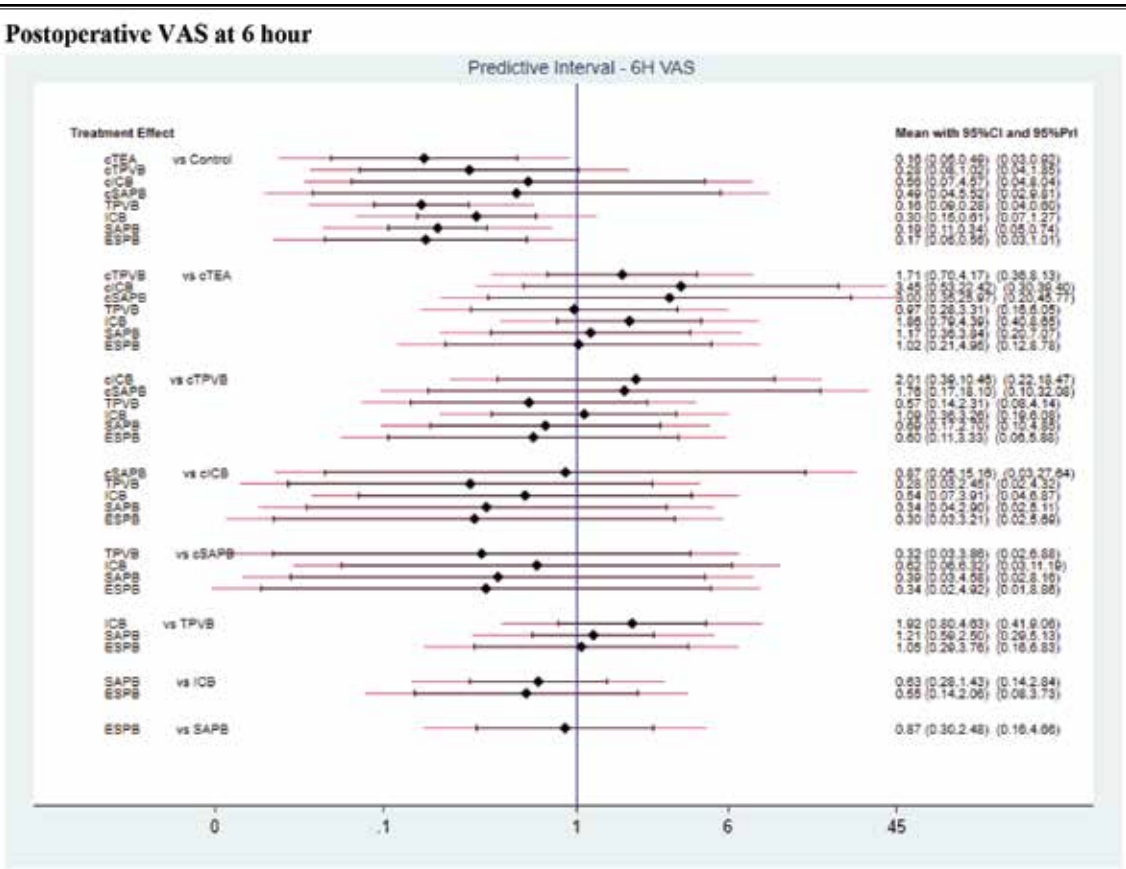
	Global consistency	**Node-splitting**	**Loop-specific**	**Network forest plots**
Cumulative opioids consumption within 24 hours	Consistent	1 out of 17 nodes inconsistent (TPVB vs SAPB)	3 out of 9 loops inconsistent (Control-TPVB-SAPB, TPVB-ICB-SAPB)	Support consistency model
Postoperative VAS at 6 hour	Consistent	No nodal inconsistency	No loop inconsistent	Support consistency model
Postoperative VAS at 12 hour	Consistent	No nodal inconsistency	1 out of 2 loops inconsistent (Control-TPVB-SAPB)	Support consistency model
Postoperative VAS at 24 hour	Consistent	No nodal inconsistency	No loop inconsistent	Support consistency model

Overall, all outcomes are associated with global consistency, and minor nodal or loop inconsistency.

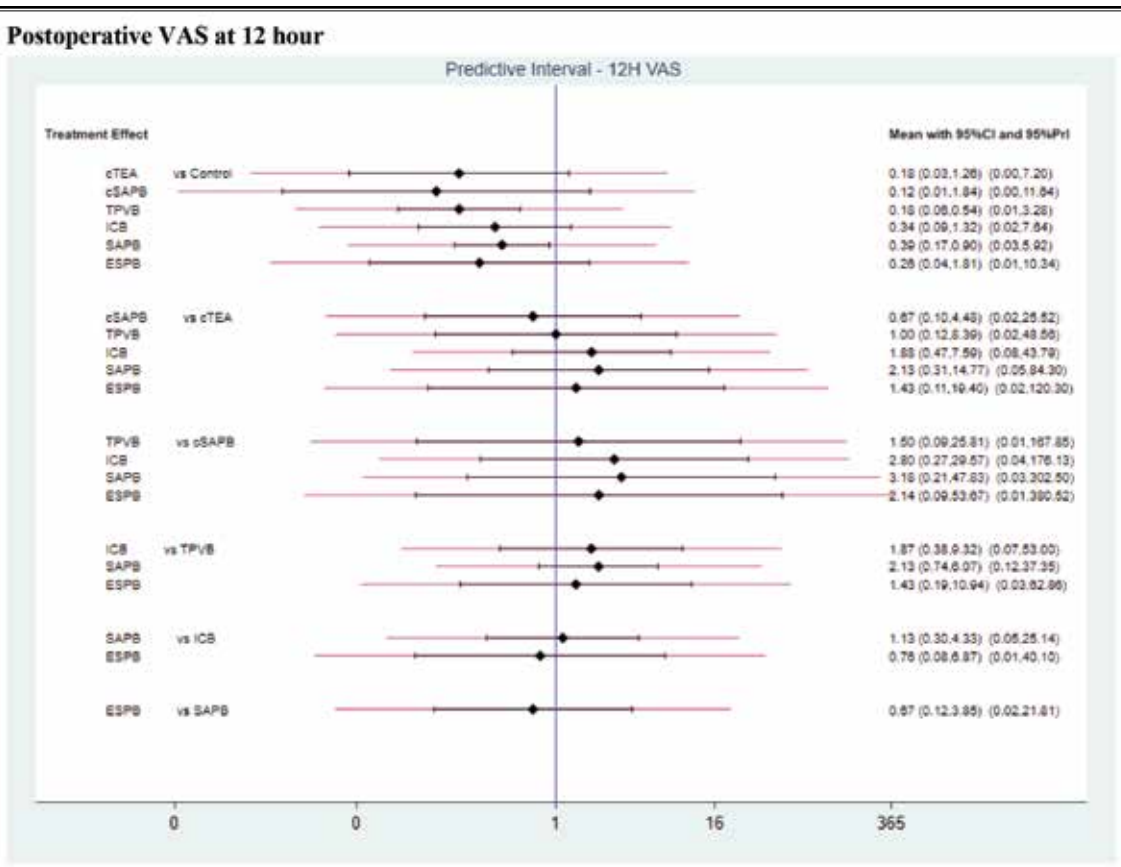
Cumulative opioids consumption within 24 hours



Supplementary Material 7. ***Predictive intervals (Interval plots)***
The interval plot produces a forest plot to estimate effect sizes and uncertainties for all pairwise comparisons. Meanwhile, it provides comparison specific estimates and 95% CI of mixed evidence with (red line) and without (black line) taking the comparison-specific heterogeneity into account.

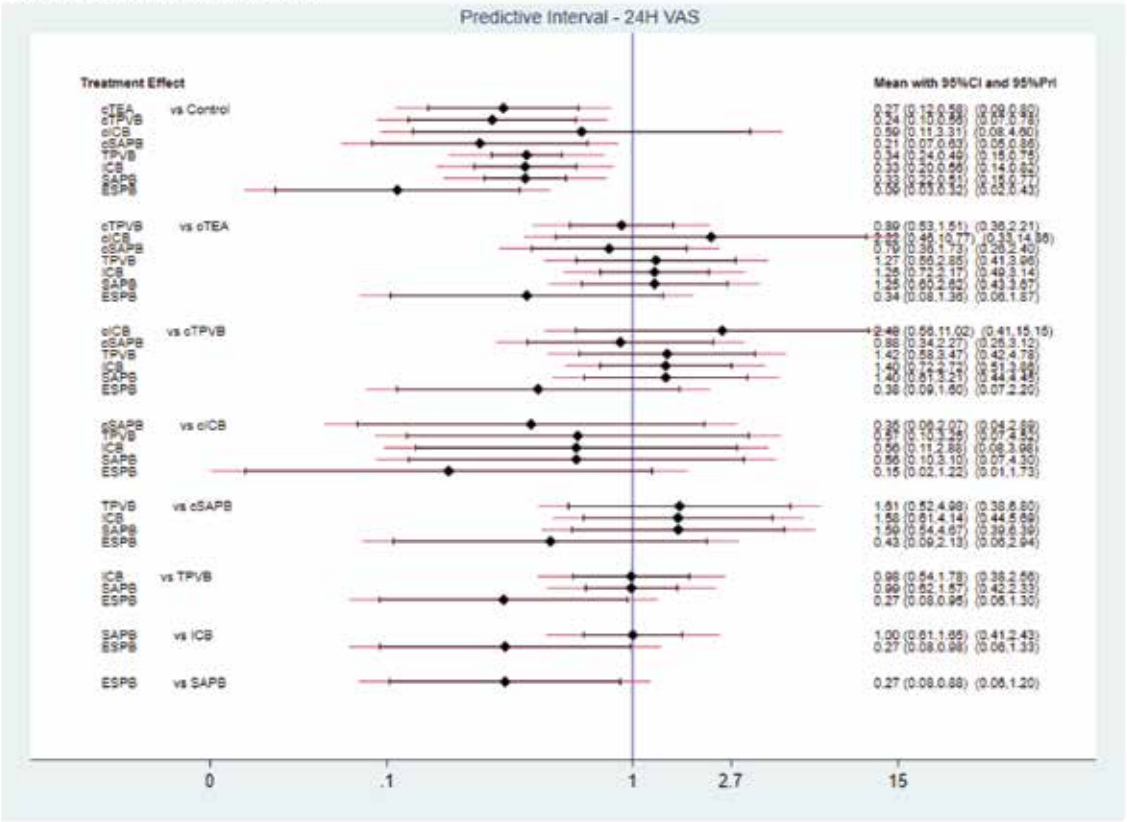


Supplementary Material 7 cont. ***Predictive intervals (Interval plots)***
The interval plot produces a forest plot to estimate effect sizes and uncertainties for all pairwise comparisons. Meanwhile, it provides comparison specific estimates and 95% CI of mixed evidence with (red line) and without (black line) taking the comparison-specific heterogeneity into account.



Supplementary Material 7 cont. ***Predictive intervals (Interval plots)***
The interval plot produces a forest plot to estimate effect sizes and uncertainties for all pairwise comparisons. Meanwhile, it provides comparison specific estimates and 95% CI of mixed evidence with (red line) and without (black line) taking the comparison-specific heterogeneity into account.

Postoperative VAS at 24 hour



Supplementary Material 7 cont. ***Predictive intervals (Interval plots)***
The interval plot produces a forest plot to estimate effect sizes and uncertainties for all pairwise comparisons. Meanwhile, it provides comparison specific estimates and 95% CI of mixed evidence with (red line) and without (black line) taking the comparison-specific heterogeneity into account.

Cumulative opioids consumption within 24 hours										
Control	6.63 (-5.99,19.25)	-4.73 (-10.94,1.48)	-8.07 (-12.58,-3.56)	-6.80 (-11.84,-1.77)	-12.97 (-17.21,-8.74)	-3.51 (-7.88,0.86)	-19.06 (-27.29,-10.82)	-21.16 (-30.21,-12.10)	-13.03 (-17.24,-8.83)	-19.76 (-25.53,-13.99)
	WI	-11.36 (-24.25,1.52)	-14.70 (-27.08,-2.32)	-13.44 (-25.83,-1.04)	-19.60 (-31.49,-7.71)	-10.14 (-23.45,3.16)	-25.69 (-40.62,-10.76)	-27.79 (-43.18,-12.39)	-19.66 (-32.86,-6.46)	-26.39 (-40.12,-12.67)
		ESPB	-3.34 (-9.02,2.34)	-2.07 (-7.15,3.00)	-8.24 (-13.21,-3.28)	1.22 (-6.25,8.68)	-14.33 (-24.36,-4.29)	-16.43 (-27.14,-5.71)	-8.30 (-15.54,-1.06)	-15.03 (-23.16,-6.90)
			SAPB	1.27 (-2.60,5.13)	-4.90 (-8.35,-1.46)	4.56 (-1.63,10.74)	-10.99 (-20.17,-1.80)	-13.09 (-23.01,-3.16)	-4.96 (-10.93,1.01)	-11.69 (-18.75,-4.63)
				ICB	-6.17 (-9.68,-2.66)	3.29 (-3.19,9.78)	-12.25 (-21.52,-2.98)	-14.35 (-24.35,-4.35)	-6.23 (-12.41,-0.04)	-12.96 (-20.13,-5.79)
					TPVB	9.46 (3.49,15.43)	-6.08 (-15.11,2.95)	-8.18 (-17.96,1.60)	-0.06 (-5.79,5.68)	-6.79 (-13.64,0.07)
						cWI	-15.54 (-23.93,-7.16)	-17.64 (-26.83,-8.46)	-9.52 (-13.89,-5.15)	-16.25 (-22.22,-10.28)
							cSAPB	-2.10 (-11.23,7.03)	6.02 (-1.20,13.24)	-0.71 (-6.59,5.18)
								cEPB	8.12 (-0.02,16.26)	1.39 (-5.59,8.37)
									cTPVB	-6.73 (-10.92,-2.54)
										cTEA

Supplementary Material 8. *Netleague tables of mixed estimates*
The diagonal cells include all of the competing treatments in each outcome, and green box indicates statistically significant results (95% CI does not cross null value of 0 VAS) while red boxes indicate statistically insignificant result (95% CI does cross null value of 0 VAS).

Postoperative VAS at 6 hour								
Control	-1.81 (-3.02,-0.60)	-1.66 (-2.25,-1.07)	-1.20 (-1.90,-0.49)	-1.85 (-2.41,-1.29)	-0.72 (-3.15,1.71)	-0.58 (-2.68,1.52)	-1.28 (-2.58,0.02)	-1.82 (-2.93,-0.71)
	ESPB	0.15 (-0.90,1.20)	0.61 (-0.72,1.95)	-0.04 (-1.32,1.24)	1.09 (-1.59,3.77)	1.23 (-1.16,3.62)	0.53 (-1.20,2.26)	-0.01 (-1.59,1.58)
		SAPB	0.46 (-0.35,1.28)	-0.19 (-0.91,0.53)	0.94 (-1.52,3.41)	1.08 (-1.06,3.22)	0.38 (-0.99,1.75)	-0.16 (-1.34,1.03)
			ICB	-0.65 (-1.53,0.23)	0.48 (-1.84,2.80)	0.62 (-1.37,2.60)	-0.08 (-1.18,1.01)	-0.62 (-1.48,0.24)
				TPVB	1.13 (-1.35,3.62)	1.27 (-0.90,3.44)	0.57 (-0.84,1.98)	0.03 (-1.20,1.26)
					cSAPB	0.14 (-2.72,3.00)	-0.56 (-2.90,1.77)	-1.10 (-3.26,1.06)
						cICB	-0.70 (-2.35,0.95)	-1.24 (-3.11,0.64)
							cTPVB	-0.54 (-1.43,0.35)
								cTEA

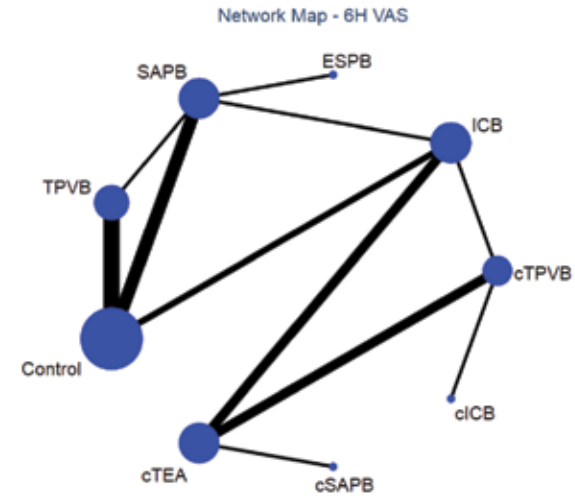
Postoperative VAS at 12 hour						
Control	-1.34 (-3.28,0.59)	-0.94 (-1.78,-0.11)	-1.07 (-2.41,0.27)	-1.70 (-2.77,-0.62)	-2.10 (-4.81,0.61)	-1.70 (-3.64,0.23)
	ESPB	0.40 (-1.35,2.15)	0.27 (-1.93,2.48)	-0.35 (-2.39,1.68)	-0.76 (-3.99,2.47)	-0.36 (-2.97,2.25)
		SAPB	-0.13 (-1.47,1.21)	-0.75 (-1.80,0.30)	-1.16 (-3.87,1.55)	-0.76 (-2.70,1.18)
			ICB	-0.63 (-2.23,0.98)	-1.03 (-3.39,1.33)	-0.63 (-2.03,0.76)
				TPVB	-0.41 (-3.26,2.45)	-0.01 (-2.13,2.12)
					cSAPB	0.40 (-1.50,2.30)
						cTEA

Supplementary Material 8 cont. *Netleague tables of mixed estimates*
The diagonal cells include all of the competing treatments in each outcome, and green box indicates statistically significant results (95% CI does not cross null value of 0 VAS) while red boxes indicate statistically insignificant result (95% CI does cross null value of 0 VAS).

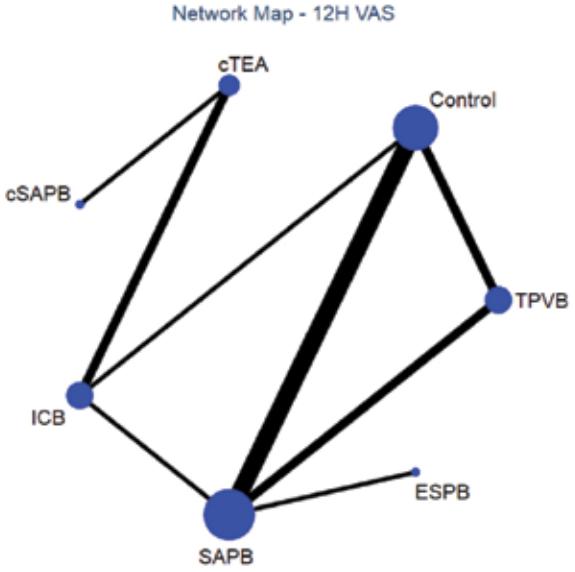
Postoperative VAS at 24 hour								
Control	-2.40 (-3.64,-1.15)	-1.10 (-1.51,-0.68)	-1.10 (-1.62,-0.58)	-1.08 (-1.44,-0.72)	-1.56 (-2.66,-0.46)	-0.52 (-2.24,1.19)	-1.43 (-2.28,-0.58)	-1.32 (-2.08,-0.55)
	ESPB	1.30 (0.13,2.47)	1.30 (0.02,2.57)	1.32 (0.05,2.58)	0.84 (-0.76,2.43)	1.87 (-0.20,3.94)	0.96 (-0.47,2.40)	1.08 (-0.31,2.46)
		SAPB	-0.00 (-0.50,0.50)	0.02 (-0.45,0.48)	-0.46 (-1.54,0.62)	0.57 (-1.13,2.28)	-0.34 (-1.17,0.49)	-0.22 (-0.96,0.52)
			ICB	0.02 (-0.58,0.61)	-0.46 (-1.42,0.50)	0.58 (-1.06,2.21)	-0.33 (-1.00,0.33)	-0.22 (-0.77,0.33)
				TPVB	-0.48 (-1.61,0.65)	0.56 (-1.18,2.30)	-0.35 (-1.25,0.54)	-0.24 (-1.05,0.57)
					cSAPB	1.04 (-0.73,2.80)	0.13 (-0.82,1.07)	0.24 (-0.55,1.03)
						cICB	-0.91 (-2.40,0.58)	-0.80 (-2.38,0.78)
							cTPVB	0.11 (-0.41,0.64)
								cTEA

Supplementary Material 8 cont. ***Netleague tables of mixed estimates***
The diagonal cells include all of the competing treatments in each outcome, and green box indicates statistically significant results (95% CI does not cross null value of 0 VAS) while red boxes indicate statistically insignificant result (95% CI does cross null value of 0 VAS).

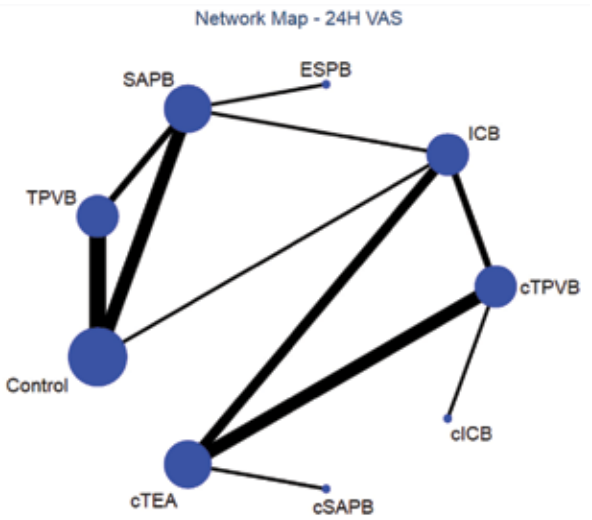
Supplementary Material 9. ***Network Geometry***
Network geometry maps were used to represent all available direct comparisons between treatments for each outcome visually; nodes of the network map corresponded to analgesic treatments; line thickness within the network map corresponded to the number of direct comparisons available for that outcome.



Supplementary Material 9 cont. ***Postoperative VAS at 6 hour***
Twenty RCTs (n=1134) reported VAS at 6 hour (Figure 1). This included comparisons of Control vs TPVB (5 RCTs), cTEA vs cSAPB (1 RCT), ICB vs cTEA (3 RCTs), cTPVB vs cICB (1 RCT), TPVB vs SAPB (1 RCT), SAPB vs ESPB (1 RCT), Control vs ICB (1 RCT), Control vs SAPB (3 RCT), cTEA vs cTPVB (3 RCTs), cTPVB vs ICB (1 RCT), ICB vs SAPB (1 RCT). The network was partly disconnected and control arm as the largest comparator. Consequently, many arms yielded only indirect estimates.



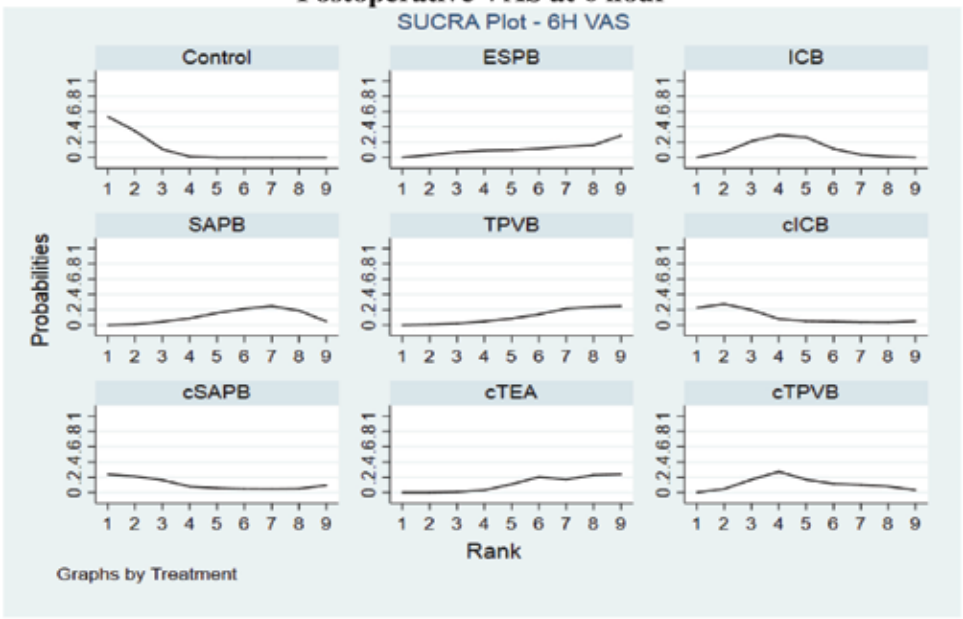
Supplementary Material 9 cont. ***Postoperative VAS at 12 hour***
Twelve RCTs (n=776) reported VAS at 12 hour (Figure 2). This included comparisons of Control vs SAPB (4 RCTs), cTEA vs cSAPB (1 RCT), TPVB vs SAPB (2 RCTs), ESPB vs SAPB (1 RCT), Control vsTPVB (2 RCTs), Control vs ICB (1 RCT), cTEA vs ICB (2 RCTs), SAPB vs ESPB (1 RCT). The network was partly disconnected and control arm as the largest comparator. Consequently, many arms yielded only indirect estimates.



Supplementary Material 9 cont. ***Postoperative VAS at 24 hour***

Twenty RCTs (n=1155) reported VAS at 24 hour (Figure 3). This included comparisons of Control vs TPVB (5 RCTs), cTEA vs cSAPB (1 RCT) , TPVB vs SAPB (2 RCTs), ESPB vs SAPB (1 RCT), Control vs SAPB (4 RCTs), cTEA vs ICB (3 RCTs), cTPVB vs cICB(1 RCT) , Control vs ICB (1 RCT), cTEA vs cTPVB (4 RCTs), cTPVB vs ICB (2 RCTs), ICB vs SAPB (1 RCT). The network was partly disconnected and control arm as the largest comparator. Consequently, many arms yielded only indirect estimates.

Postoperative VAS at 6 hour

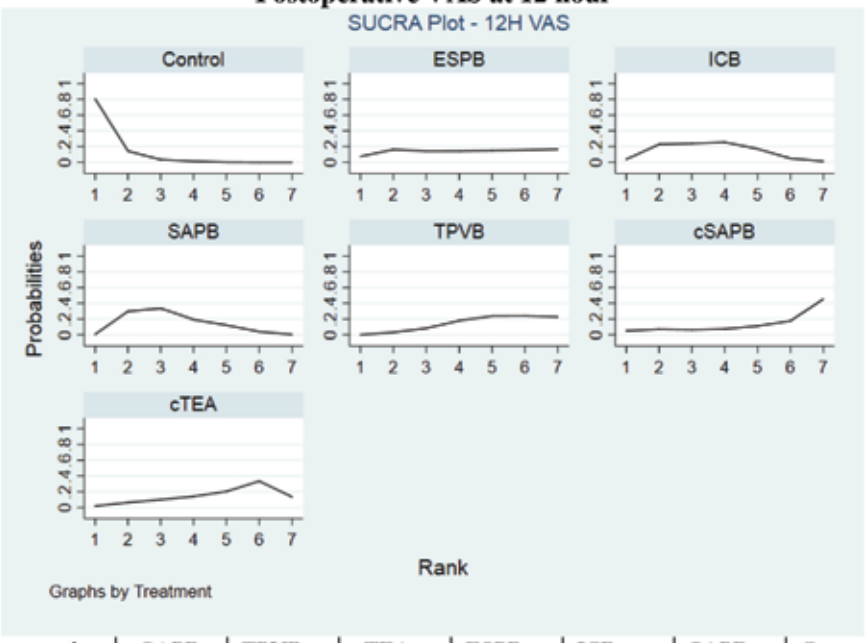


Intervention	cTEA	TPVB	ESPB	SAPB	cTPVB	ICB	cSAPB	cICB	Control
Probability	3.1%	23.3%	28.8%	34.3%	50.9%	58.7%	17.8%	66.5%	71.9%

Supplementary Material 10. ***SUCRA rankings***

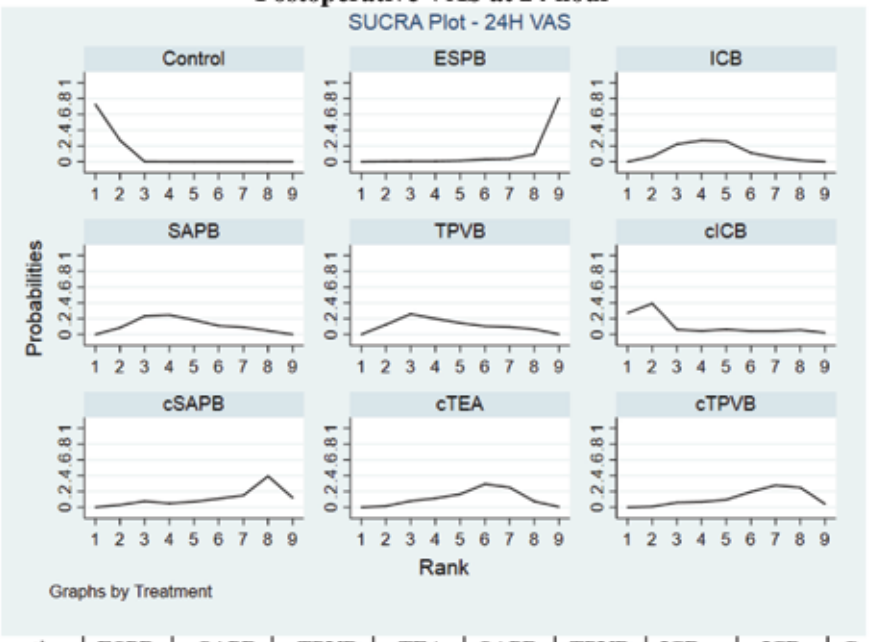
Surface under the cumulative ranking curve (SUCRA) produces rankograms and cumulative ranking plots for all treatments of each outcome. The results yields a probability (percentage) of an intervention being among the best options and a mean rank.

Postoperative VAS at 12 hour



Intervention	cSAPB	TPVB	cTEA	ESPB	ICB	SAPB	Control
Probability	25.5%	29.1%	33.5%	45.6%	58.4%	62.3%	95.7%

Postoperative VAS at 24 hour



Intervention	ESPB	cSAPB	cTPVB	cTEA	SAPB	TPVB	ICB	cICB	Control
Probability	5.2%	27.9%	31.7%	40.9%	56.6%	57.4%	58.1%	75.6%	96.6%

Supplementary Material 10 cont. *SUCRA rankings*
Surface under the cumulative ranking curve (SUCRA) produces rankograms and cumulative ranking plots for all treatments of each outcome. The results yields a probability (percentage) of an intervention being among the best options and a mean rank.