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REVIEW ARTICLE/BRIEF REVIEW

Efficacy of regional anesthesia techniques for postoperative analgesia in patients undergoing major oncologic breast surgeries: a systematic review and network meta-analysis of randomized controlled trials

Efficacité des techniques d'anesthésie régionale pour l'analgésie postopératoire chez les patientes subissant des chirurgies mammaires oncologiques majeures: une revue systématique et une méta-analyse en réseau d'études randomisées contrôlées

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Abstract

Background *The optimal regional technique to control pain after breast cancer surgery remains unclear. We sought to synthesize available data from randomized controlled trials comparing pain-related outcomes following various regional techniques for major oncologic breast surgery.*

Methods *In a systematic review and network meta-analysis, we searched trials in PubMed, Embase Scopus, Medline, Cochrane Central and Google Scholar, from inception to 31 July 2020, for commonly used regional techniques. The primary outcome was the 24-hr resting pain score measured on a numerical rating score of 0–10. We used surface under the cumulative ranking curve (SUCRA) to establish the probability of an intervention ranking highest. The analysis was performed using the Bayesian random effects model, and effect sizes are reported as 95% credible interval (Crl). We conducted cluster-rank analysis by combining 24-hr pain ranking with 24-hr opioid use or incidence of postoperative nausea and vomiting.*

Results *Seventy-nine randomized controlled trials containing 11 different interventions in 5,686 patients were included. The SUCRA values of the interventions for 24-hr resting pain score were continuous paravertebral block (0.83), serratus anterior plane block (0.76), continuous wound infusion (0.76), single-level paravertebral block (0.68), erector spinae plane block (0.59), modified pectoral block (0.49), intercostal block (0.45), multilevel paravertebral block (0.41), wound infiltration (0.33), no intervention (0.12), and placebo (0.08). When compared with placebo, the continuous paravertebral block (mean difference, 1.26; 95% Crl, 0.43 to 2.12) and serratus anterior plane block (mean*

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difference, 1.12; 95% Crl, 0.32 to 1.9) had the highest estimated probability of decreasing 24-hr resting pain scores. Cluster ranking analysis combining 24-hr resting pain scores and opioid use showed that most regional analgesia techniques were more effective than no intervention or placebo. Nevertheless, wound infiltration and continuous wound infusion may be the least effective active interventions for reducing postoperative nausea and vomiting.

Conclusion *Continuous paravertebral block and serratus anterior plane block had a high probability of reducing pain at 24 hr after major oncologic breast surgery. The certainty of evidence was moderate to very low. Future studies should compare different regional anesthesia techniques, including surgeon-administered techniques such as wound infiltration or catheters. Trials comparing active intervention with placebo are unlikely to change clinical practice.*

Study registration: *PROSPERO (CRD42020198244); registered 19 October 2020.*

Résumé

Contexte *La technique régionale optimale pour contrôler la douleur après une chirurgie de cancer du sein n'a pas encore été clairement établie. Nous avons cherché à synthétiser les données disponibles provenant d'études randomisées contrôlées comparant les issues liées à la douleur à la suite de diverses techniques régionales pour la chirurgie mammaire oncologique majeure.*

Méthode *Dans une revue systématique et une méta-analyse de réseau, nous avons recherché les études portant sur les techniques régionales couramment utilisées dans les bases de données PubMed, Embase Scopus, Medline, Cochrane Central et Google Scholar, de leur création au 31 juillet 2020. Le critère d'évaluation principal était le score de douleur au repos à 24 heures mesuré sur une échelle d'évaluation numérique de 0 à 10. Nous avons utilisé la surface sous la courbe de classement cumulatif (SUCRA) afin d'établir la probabilité qu'une intervention soit cotée plus haut. L'analyse a été réalisée à l'aide d'un modèle bayésien à effets aléatoires, et les tailles d'effet sont rapportées comme intervalle crédible à 95 % (ICr). Nous avons effectué une analyse de classement en grappes en combinant le classement de douleur sur 24 heures avec la consommation d'opioïdes sur 24 heures ou l'incidence des nausées et vomissements postopératoires.*

Résultats *Soixante-dix-neuf études randomisées contrôlées comportant 11 interventions différentes chez 5686 patientes ont été incluses. Les valeurs SUCRA des interventions pour le score de douleur au repos à 24 heures étaient le bloc paravertébral continu (0,83), le bloc du plan antérieur du serratus (0,76), la perfusion continue de la plaie (0,76), le bloc paravertébral à un seul niveau (0,68), le bloc du plan des muscles érecteurs du rachis (0,59), le bloc pectoral modifié (0,49), le bloc intercostal (0,45), le bloc paravertébral multiniveau (0,41), l'infiltration de plaie (0,33), l'absence d'intervention (0,12) et le placebo (0,08). Par rapport au placebo, le bloc paravertébral continu (différence moyenne, 1,26; ICr 95 %, 0,43 à 2,12) et le bloc du plan antérieur du serratus (différence moyenne, 1,12; ICr 95 %, 0,32 à 1,9) ont affiché la probabilité estimée la plus élevée de diminuer les scores de douleur au repos à 24 heures. L'analyse du classement des grappes combinant les scores de douleur au repos et la consommation d'opioïdes à 24 heures a montré que la plupart des techniques d'analgésie régionale étaient plus efficaces que l'absence d'intervention ou un placebo. Néanmoins, l'infiltration de la plaie et la perfusion continue de la plaie semblaient être les interventions actives les moins efficaces pour réduire les nausées et vomissements postopératoires.*

Conclusion *Le bloc paravertébral continu et le bloc du plan antérieur du serratus ont affiché une forte probabilité de réduire la douleur 24 heures après une chirurgie mammaire oncologique majeure. La fiabilité des données probantes allait de modérée à très faible. Les études futures devraient comparer différentes techniques d'anesthésie régionale, y compris les techniques administrées par le chirurgien telles que l'infiltration de plaie ou les cathéters. Il est peu probable que les études comparant une intervention active à un placebo modifient la pratique clinique.*

Enregistrement de l'étude : *PROSPERO (CRD42020198244); enregistrée le 19 octobre 2020.*

Keywords oncologic breast surgery · postoperative analgesia · regional technique · erector spinae block · modified pectoral nerve block · paravertebral block · serratus anterior plane block · wound infiltration

Breast cancer is the second most common malignancy, affecting nearly 10% of women during their lifetime.[1] Surgery remains the primary treatment for breast cancer. Over 30% of patients report inadequate control of their acute postoperative pain after surgery.[2,3] Inadequately managed pain after breast surgery not only has psychological, physiologic, and socio-economic consequences but also delays discharge from the postoperative recovery area and hospital.[4] Further, uncontrolled acute postoperative pain has been associated with increased chronic postsurgical pain after oncologic breast surgery.[5] Therefore, effective management of postoperative pain is critical.

Most of the pain during breast surgery arises from the sensory nerves of the thoracic wall. There is increasing interest in the use of peripheral nerve blockade techniques to prevent and treat postoperative pain.[6] Increased availability of ultrasound has improved the safety and efficacy of blocks. This has led to the development of an array of safer and easier new fascial plane blocks, including pectoral, serratus anterior plane, and erector spinae plane (ESP) blocks. These nerves can also be blocked at a more proximal level via paravertebral blocks or at the peripheral level through wound infiltrations (WI). These techniques have become an essential component of multimodal analgesia for major oncologic breast surgery. They can potentially improve patient outcomes with regards to acute and persistent postsurgical pain and enhance recovery.[7]

Given the variety of available blocks and the lack of data directly comparing these techniques, the optimal choice remains unclear. Previous attempts to synthesize relevant data have been limited to pairwise comparisons of two or three techniques only.[8,9] Recently, Wong *et al.* published a network meta-analysis (NMA) comparing pain scores for different regional anesthesia modalities.[10] Nevertheless, treatment rankings or combination of outcomes for best clinical decision-making had not been explored. Thus, we sought to aggregate data from published randomized controlled trials (RCTs) to compare pain-related outcomes following the use of commonly described regional techniques in patients undergoing major oncologic breast surgery under general anesthesia.

Methods

We conducted a systematic review and NMA of RCTs comparing different regional analgesic techniques used for major oncologic breast surgery. This review was registered with PROSPERO (registration number CRD42020198244) and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Network Meta-analysis (PRISMA) guidelines.[11]

Eligibility criteria

We included RCTs involving adult female patients undergoing major oncologic breast surgery under general anesthesia. Interventions were compared with alternative active interventions, placebo block, or no intervention. We considered an intervention as a "placebo" if a sham block or inactive intervention was performed (placebo effect) and "no intervention" if no block was attempted. The evaluated interventions included ESP block, intercostal nerve block (ICB), modified pectoral (PECS) block, serratus anterior plane block (SAPB), single injection WI, continuous wound infusion (CWI), and thoracic paravertebral block (PVB), including single injection single level (SL_TPVB), single injection multiple level (ML_TPVB), and continuous paravertebral (CTPVB).

Figure 1 shows the included regional analgesic techniques and important anatomical correlations. The modified PECS block, also known as the PECS2 block, includes two injections—an interpectoral injection (PECS1) and a pectoserratus plane injection.[12]

A study was included if it reported any of the following postoperative outcomes: opioid consumption, pain scores, time to rescue analgesia, and postoperative nausea/vomiting. Trials that evaluated two or more different volumes or concentrations of local anesthetics or any additive on the same intervention were included, as long as the interventions were compared with a control. In such cases, the active arms were combined to provide comparative data for the regional technique with control. We excluded trials or treatment arms, evaluating the role of supplementary drugs alone in regional injectate. We also excluded non-randomized comparisons, trials examining different approaches of the same block, and trials comparing primary regional techniques with general anesthesia.

Search strategy and selection criteria

PubMed, Google Scholar, Embase, Scopus, and the Cochrane central registers of the controlled trial were searched for RCTs comparing the above-described regional techniques for oncologic breast surgery from inception until 31 July 2020. No language restrictions were applied. To identify additional trials, reviewers also hand-searched cross-references of included trials, meta-analyses, systematic reviews, and published guidelines. Both free text and MeSH terms were used individually and in various combinations to maximize the results yielded. Our search strategy is outlined in the Electronic Supplementary Material (ESM), eAppendix.

Two investigators (N.P.S. and J.K.M.) independently assessed the abstracts, followed by full-text screening. Any disagreements between authors regarding the eligibility of a trial were resolved by discussion or by another author (A.K.).

Data collection process and data items

Two reviewers (N.P.S. and J.K.M.) extracted the data independently from each included study on standardized Excel 2018 forms (Microsoft Corporation, Redmond, WA, USA). The extracted items included**:** the trial

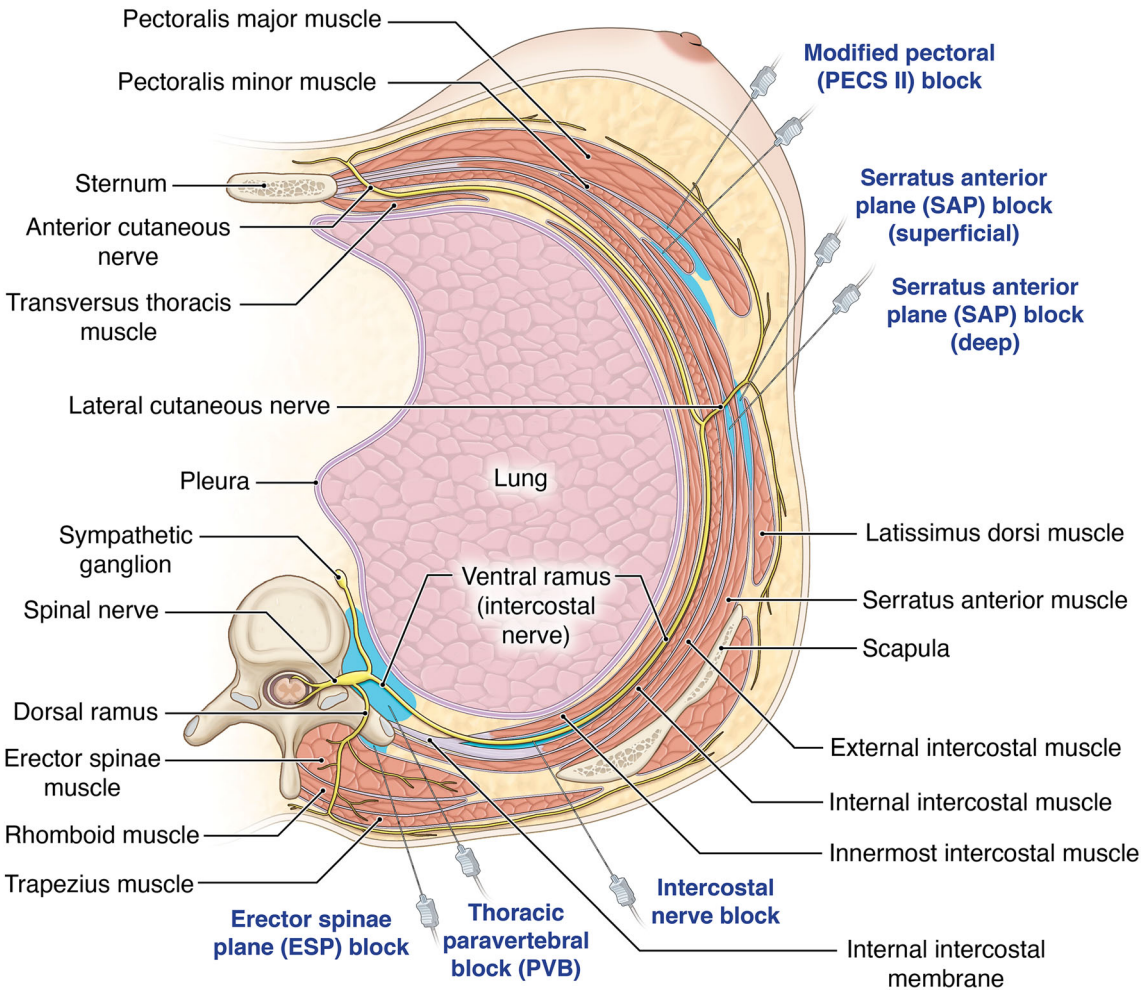


Figure 1 Important anatomical correlations of the regional techniques included in this systematic review. Dr. V. Uppal holds the copyright of this image. This image has not been published before and appears with the permission from Dr. V. Uppal, Dalhousie University, Halifax, NS, Canada.

characteristics (country, year of publication), study design, participants (sample size, age), type of surgery, type of regional technique, unilateral or bilateral surgery, single injection or catheter technique, use of ultrasound guidance, local anesthetic bolus and infusion regimen, perioperative analgesic regimen, and outcome measures. Data were extracted from graphs using the online tool, graphreader.com. Study authors were contacted if information was missing or unclear.

The geometry of the network

We analyzed published RCTs comparing different regional analgesic techniques (or inactive control) for major oncologic breast surgery. Each active or inactive comparator formed a node, and the randomized comparison between the interventions is shown by the link (edges) between nodes. Different variations of the same block technique or dosage regimen were lumped into the same node (e.g., superficial and deep SAP blocks formed a single node).

Summary measures

For continuous variables, means and standard deviations (SD) were extracted, while proportions were extracted for dichotomous outcomes. Data provided as the median and interquartile range were converted to mean and SD using Cochrane validated Hozo's formula.[13] Based on the Cochrane Collaboration recommendation, missing SDs were imputed by using the mean SD of the remaining studies.[14] Pain scores reported as visual, verbal, or numeric rating scales were standardized to 0–10 for quantitative pooling.

We estimated the probability of each treatment option being ranked higher for a particular outcome using surface

under the cumulative ranking curves (SUCRA). The SUCRA values ranged from 0 to 1 (100%). The higher the SUCRA value and closer to 1 (100%), the higher the likelihood that therapy was top-ranked and therefore more desirable.[15]

Statistical analysis

The primary outcome for this review was resting pain score at 24 hr postoperatively. The secondary outcomes were mean pain score at 4–6 hr, opioid consumption at 24 hr, time to first rescue analgesic supplementation, and opioid-related adverse effects. Cumulative intravenous consumption of morphine was calculated, with opioids other than morphine converted to morphine equivalent doses using a published equivalence formula.[16]

The analysis was performed using Bayesian statistics (random effects model). We used the "Gemtc" package for R (R Foundation, Vienna, Austria) for numerical data analysis, which uses vague priors [normal (0, 0.0001)] for estimating the trial baselines, treatment differences, and the random effects SD [uniform (0.2)]. The Bayesian concept defines the use of a credible interval, which is more practical than the confidence interval because indirect effects introduce some degree of uncertainty in pooled outcomes. For a 95% credible interval (Crl), the value of interest (e.g., size of treatment effect) lies with a 95% probability in the interval. Unlike the confidence interval, which defines boundaries for point estimate values, the Crl defines boundaries for probability values.

We ran 5,000 adaptations and 20,000 iterations with a thinning factor of 10. This resulted in a potential scale reduction factor of less than 1.05. We assigned the "no intervention" group as the study-level reference treatment for regression modelling.

Assessment of inconsistency

We evaluated the configuration of the network of comparisons by constructing a graphical representation (network diagram) of its geometry using the R software package ("netmeta"). The direct and indirect estimates were compared by fitting the consistency model, determining only the effects between each agent and the reference (no intervention), and acquiring the indirect treatment effects by consistency equation and the inconsistency model, which provides prior distribution for all treatment combinations possible.

We explored network inconsistency using net heat plots and a global test of inconsistency. The net heat plot allows visual estimation of the contribution of direct estimates from pairwise comparisons and quantifies the inconsistency contributed to the network by each individual pairwise comparison.

Risk of bias within individual studies and publication bias

Two independent reviewers reviewed the publications included in the analysis. The risk of bias was assessed according to five domains: randomization process, deviation from intended interventions, missing data outcomes, measurement of outcome, and selection of reported results, and the overall bias was based on the criteria recommended by the Cochrane Collaboration (Version 2 of the Cochrane risk-of-bias tool for randomized trials [RoB 2]).[17] Response options for each domain were assessed as "yes," "probably yes," "probably no," "no," and "no information. The overall risk of bias generally corresponded to the highest risk of bias in any of the domains. If a study was judged to have "some concerns" about the risk of bias for multiple domains, it was judged at a high risk of bias overall. The possibility of publication bias was estimated by a comparison-adjusted funnel plot and quantified by Egger's test.

Certainty of the evidence

We had originally planned to use the Grading of Recommendations Assessment, Development and Evaluation approach for assessing the certainty of evidence. Nevertheless, after the recent publication of the *Confidence in Network Meta-Analysis* (CINeMA)[A] approach specifically designed to evaluate the overall evidence quality for NMA, we decided to use this approach to evaluate the certainty of evidence.[18] Although there is little guidance regarding which approach is better, it was our opinion that the CINeMA approach (Cochrane Collaboration) was less tedious and more objective for evaluation in the context of NMA. It assesses evidence in six domains: (1) within-study bias (impact of risk of bias in the included trials), (2) reporting bias (publication and other reporting bias), (3) indirectness, (4) imprecision, (5) heterogeneity, and (6) incoherence. Trials were assessed for the indirectness of evidence individually. Indirectness refers to the relevance of the included trials to the research question. Included studies were scored on the basis of uniformity across parameters, including study participants, interventions, and outcome characteristics. The more divergence was noted in the above three parameters, the more indirectness was assumed.

For analysis, a widely accepted one-point difference in numeric rating scale pain scores was used as the minimal

[A] *Confidence in Network Meta-Analysis.* Available from https://cinema.ispm.unibe.ch (accessed November 2021).

clinically important difference when making decisions regarding imprecision and heterogeneity.[19,20] The certainty of the evidence was graded as high, moderate, low, and very low based on the CINeMA approach. The certainty of evidence was downgraded by one level if there were "some concerns" in one or two domains. If there were "some concerns" in more than two domains or "major concerns" in one domain, the certainty of the evidence was downgraded by two levels.

Additional analysis

An exploratory analysis was undertaken by pairing SUCRA values of two different outcomes using clustering methods to obtain meaningful treatment groups. In addition, we performed a sensitivity analysis to evaluate the effect of the invasiveness of surgery on the rank probability of techniques being evaluated. We collated the data from trials, including the patients undergoing modified radical mastectomy (MRM) only. The trials that enrolled a mixed surgical population along with MRM and did not report results separately were not used to evaluate it.

Results

Study selection

We identified 3,207 references from various databases. A PRISMA flowchart showing the studies identified, screened, eligible, and included is shown in Figure 2. Of the 260 full-text manuscripts we reviewed, 79 studies published from 2000 to 2020 were deemed eligible for our final network analysis.[7,21–98] Of these, two trials were not published in English. A total of 5,686 patients with 11 different analgesic interventions were included. Most of the participants underwent MRM, mastectomy, or resection of the tumour with sentinel lymph node biopsy or axillary lymph node dissection.

Presentation of network geometry

The primary outcome (resting pain score at 24 hr) was reported in 59 RCTs with 3,888 participants. Figure 3 shows the network plot for the primary outcome. Each node represents one intervention. The size of the node is proportional to the number of participants randomized to

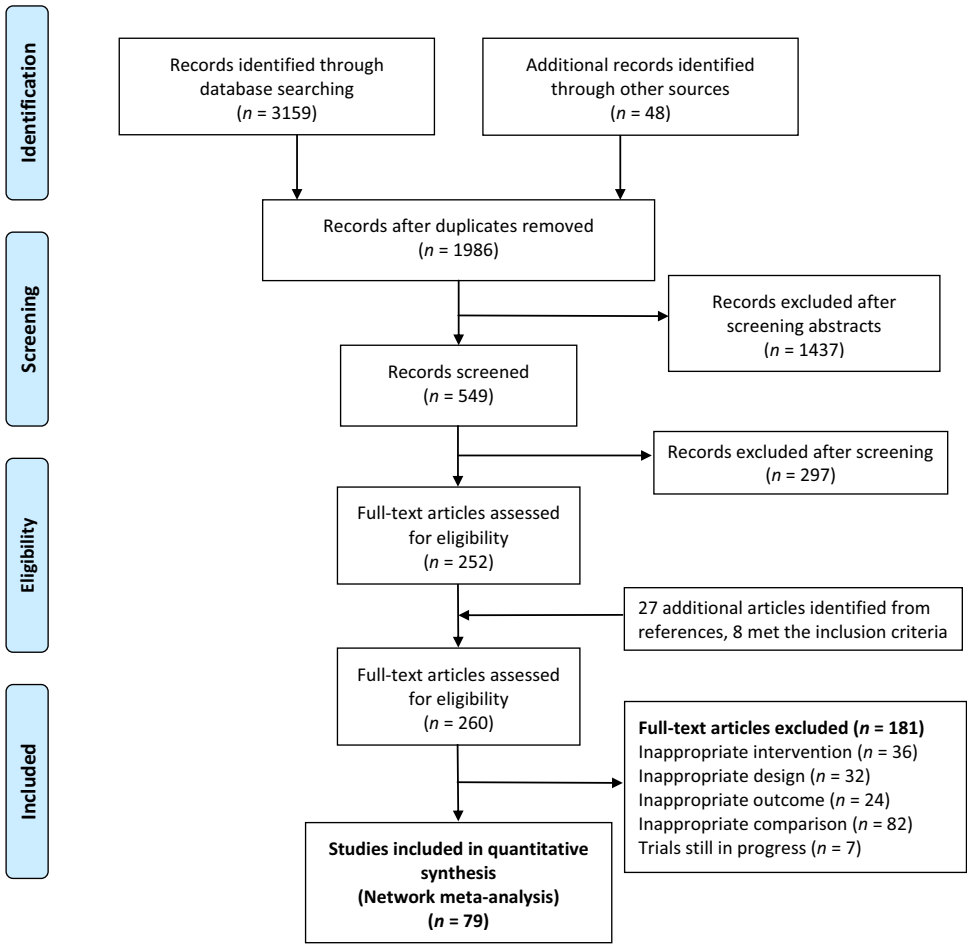


Figure 2 PRISMA flow diagram showing the flow of information through the different phases of a systematic review. PRISMA = Preferred Reporting Items for Systematic Reviews and Network Meta-analysis[11]

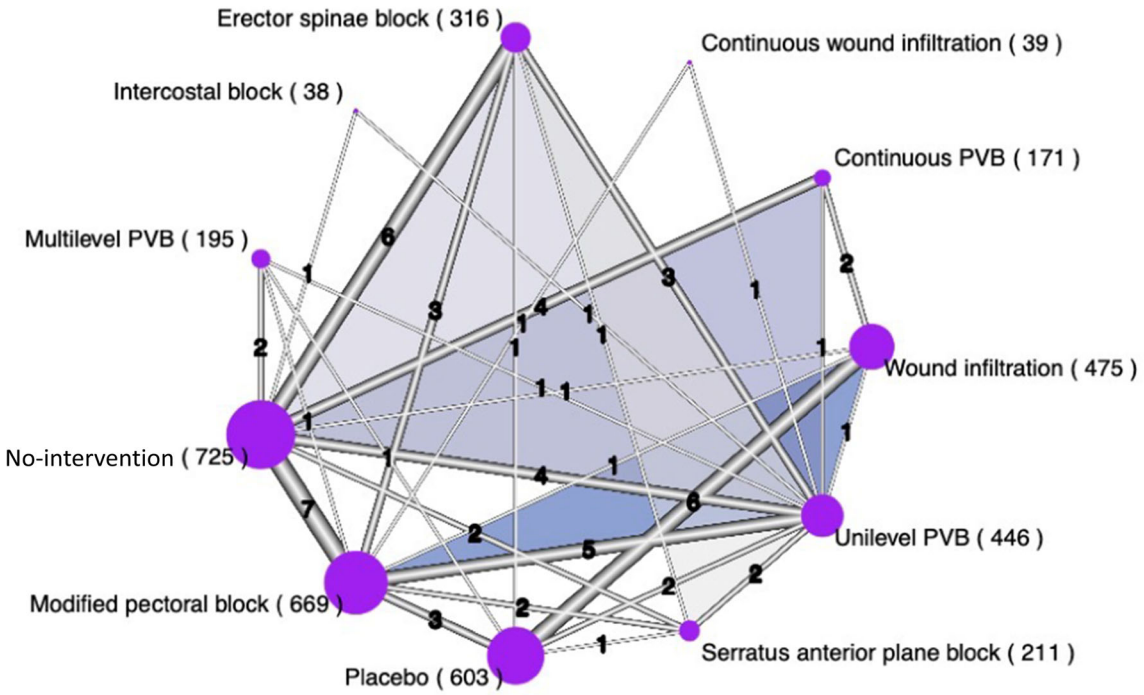


Figure 3 Network plot showing the network geometry for the primary outcome (24 hr resting pain score). The size of the node corresponds to the sample size of the treatment group (reported in parentheses). Lines connecting the nodes show the number of trials (in parentheses) comparing the connected nodes. The width of each line corresponds to the number of RCTs comparing the two interventions. PVB = paravertebral block

that intervention, and the width of the edge is proportional to the number of trials comparing two interventions. The most common comparators were modified PECS block, wound infiltration, single level PVB, placebo, and no intervention. Head-to-head trials (direct comparisons) were missing for many interventions, such as ESP block and CWI.

All secondary outcomes displayed geometry similar to the primary network and were connected. The mean study sample size was 35 patients per arm. Sixty-seven studies had two arms, nine compared three treatments, and three compared four interventions.

Characteristics of included trials

Table 1 includes detailed information about surgical procedures, analgesic intervention, and outcomes reported of included trials. It shows the preponderance of studies comparing modified PECS block (seven direct comparisons), ESP block (six direct comparisons) with no intervention, and WI (six direct comparisons) with placebo. Fifty-one trials utilized the ultrasound guidance for the performance of block, while the rest of the studies used landmark techniques. Long-acting local anesthetics, i.e., bupivacaine (32), ropivacaine (29), and levobupivacaine (13) were administered in the majority of trials, whereas articaine and lidocaine were used in one trial each. Thirty-nine trials evaluated the patients undergoing MRM, 15 trials included patients undergoing mastectomy (total or partial) with or without lymph node dissection, and 25 trials included patients undergoing mixed cancer surgical procedures.

Risk of bias within studies

eFigure 1 in the ESM shows the risk of bias using the Cochrane RoB 2 tool for each included study. Fifty-six studies were assessed as low risk of bias in all domains. Thirteen studies were assessed as high risk of bias in at least one domain. The remaining ten studies had some concerns regarding the risk of bias in at least one domain. These findings were incorporated into CINeMA analysis when determining the certainty of evidence.

Synthesis of outcomes

We used a random effects model, as the deviance information criterion values were lower with the random effects model. The data for the following outcomes were pooled for synthesis.

Table 1 Characteristics of included randomized controlled trials

S no.	Author year	Study group	Surgical procedure	Drug concentration (dose)	Postoperative analgesia	Primary outcome
1	Abdallah 2014[21]	1 T1–5 TPVB (33) 2 Sham block (31)	Major breast cancer surgery	0.5% Ropivacaine (25 mL) 1% Lidocaine skin wheals	Morphine *iv* PRN Hydromorphone *iv* PRN	QoR
2	Abdel-halim 2011[22]	1 CTPVB (20) 2 No intervention (20)	Major breast cancer surgery	2% Lidocaine with epinephrine (20 mL) and 5 mL bolus PRN and infusion of 5 $mL{\cdot}hr^{-1}$ Nothing	Morphine *iv* PRN	Intraoperative and postoperative analgesia
3	Abdelaziz Ahmed 2018[23]	1 PECS block (30) 2 PECS block (30) 3 No intervention (30)	MRM	0.25% Bupivacaine + 0.9% normal saline (30 mL) 0.25% Bupivacaine + magnesium 100 mg (30 mL) Nothing	Pethidine *iv* PRN	Postoperative pain scores
4	Aksu 2019[24]	1 ESP block (25) 2 No intervention (25)	MRM, mastectomy + LND, lumpectomy + LND	0.25% Bupivacaine (20 mL) Nothing	Morphine PCA	Morphine consumption in 24 hr
5	Albi-Feldzer 2013[25]	1 Wound infiltration (117) 2 Placebo (119)	MRM or breast-conserving surgery + LND	0.375% Ropivacaine (3 $mL{\cdot}kg^{-1}$) 0.9% Normal saline (0.8 $mL{\cdot}kg^{-1}$)	PCM I g *po* 6 hourly Ketoprofen 50 mg *po* 6 hourly Morphine PCA	Incidence of chronic pain
6	Al Ja'bari 2019[26]	1 PECS block (20) 2 No intervention (22)	MRM	0.5% Ropivacaine (30 mL) Nothing	PCM 1 g *iv* 6 hourly Ibuprofen 400 mg *iv* 8 hourly Morphine *iv* PRN	Morphine consumption in 24 hr
7	Altıparmak 2019[27]	1 ESP block (20) 2 PECS block (18)	MRM	0.25% Bupivacaine (20 mL) 0.25% Bupivacaine (30 mL)	Tramadol PCA, morphine *iv* PRN	Tramadol consumption in 24 hr
8	Altiparmak 2020[28]	1 IC block (28) 2 No intervention (28)	MRM	0.25% Bupivacaine (30 mL) Nothing	Morphine PCA, dexketoprofen *iv* PRN	QoR 40
9	Annamalai 2017[29]	1 PECS block (30) 2 T4 TPVB (30)	MRM	0.25% Bupivacaine (30 mL) 0.25% Bupivacaine (15–20 mL)	Not stated	Duration of analgesia
10	Arunakul 2010[30]	1 T4 TPVB (10) 2 No intervention (100)	MRM	0.5% Bupivacaine (3 $mL{\cdot}kg^{-1}$) Nothing	Morphine PCA	Morphine consumption in 24 hr
11	Bansal 2012[31]	1 CTPVB (20) 2 Wound infiltration (20)	MRM	0.25% Bupivacaine (3 $mL{\cdot}kg^{-1}$) followed by 0.2 $mL{\cdot}kg^{-1}{\cdot}hr^{-1}$ 0.25% Bupivacaine (3 $mL{\cdot}kg^{-1}$)	Tramadol IM PRN Morphine PCA PRN	Postoperative analgesia
12	Barrington 2020[32]	1 PECS block (53) 2 Wound infiltration (51)	WLE or mastectomy ± LND	0.475% Ropivacaine 0.45 $mL{\cdot}kg^{-1}$ (max 40 mL) 0.475% Ropivacaine 0.45 $mL{\cdot}kg^{-1}$ (max 40 mL)	PCM 1 g *po* 6 hourly Tapentadol *po* PRN Oxycodone *po* PRN Fentanyl *iv* PRN	QoR 15 at 24 hr

Table 1 continued

S no.	Author year	Study group	Surgical procedure	Drug concentration (dose)	Postoperative analgesia	Primary outcome
13	Bashandy 2015[33]	1 PECS block (60) 2 No intervention (60)	MRM	0.25% Bupivacaine (30 mL) Nothing	PCM I g *po* 8 hourly Ketoprofen 100 mg *po* 8 hourly Morphine PCA	VAS at various time intervals
14	Baudry 2008[34]	1 Wound infiltration (40) 2 Placebo (38)	Lumpectomy or total mastectomy + LND	0.475% Ropivacaine (40 mL) 0.9% Normal saline (40 mL)	PCM I g *po* 6 hourly Ketoprofen 50 mg *po* 12 hourly Nalbuphine *iv* PRN	VAS at 24 hr
15	Bhuvaneswari 2012[35]	1 T3 TPVB (12) 2 T3 TPVB (12) 3 T3 TPVB (12) 4 Placebo (12)	Total mastectomy + LND	0.25% Bupivacaine + epinephrine (0.3 mL·kg^{-1}) 0.25% Bupivacaine + epinephrine + fentanyl (0.3 mL·kg^{-1}) 0.5% Bupivacaine + epinephrine (0.3 mL·kg^{-1}) 0.9% Normal saline (0.3 mL·kg^{-1})	Morphine *iv* PRN	Morphine consumption in 24 hr
16	Boughey 2009[36]	1 T1–5 TPVB (39) 2 No intervention (41)	Breast cancer surgery	0.5 to 1% ropivacaine (15–30 mL max 5 mg·kg^{-1}) Nothing	Fentanyl *iv* PRN, Hydromorphone *iv* PRN	Pain scores after surgery
17	Bouman 2014[37]	1 CTPVB (18) 2 Wound infiltration (18)	WLE + LND with reconstruction, total mastectomy ± LND, MRM	0.75% Ropivacaine (0.25 mL·kg^{-1}) followed by PCA 0.25% Bupivacaine (10 mL)	PCM 1 g 6 hourly Naproxen/diclofenac PRN Piritramide PRN	VAS at 24 hr
18	Burlacu 2006[38]	1 CTPVB (13) 2 CTPVB (13) 3 CTPVB (12) 4 No intervention (14)	WLE or mastectomy + LND with reconstruction	0.25% Levobupivacaine + normal saline (20 mL) followed by infusion 0.25% Levobupivacaine + fentanyl 50 µg (20 mL) followed by infusion 0.25% Levobupivacaine + clonidine 150 µg (20 mL) followed by infusion Nothing	Morphine PCA	Morphine consumption in 24 hr
19	Campbell 2015[39]	1 Wound infiltration (45) 2 No intervention (34)	WLE or mastectomy + LND	0.25% Bupivacaine (40 mL) Nothing	PCM *po* PRN Oxynorm *po* PRN Morphine *iv*/SC/PCA PRN	Postoperative pain and/or analgesic consumption
20	Eldemrdash 2019[40]	1 ESP block (23) 2 T4 TPVB (23) 3 SAP block (24)	MRM	2% Articaine with epinephrine (20 mL) 2% Articaine with epinephrine (20 mL) 2% Articaine with epinephrine (20 mL)	Morphine PCA	Duration of analgesia VAS at various time intervals
21	El-Sheikh 2017[41]	1 PECS block (20) 2 T4 TPVB (20)	Mastectomy	Local anesthetic (30 mL) Local anesthetic (10–20 mL)	Morphine *iv* PRN	Perioperative analgesia

Table 1 continued

S no.	Author year	Study group	Surgical procedure	Drug concentration (dose)	Postoperative analgesia	Primary outcome
22	Fallatah 2016[42]	1 T2–6 TPVB (20) 2 No intervention (20)	Lumpectomy + LND	0.5% Bupivacaine (20 mL) Nothing	PCM 1 g *iv* 6 hourly Lornoxicam *iv* PRN Morphine *iv* PRN	Dynamic pain scores at various time intervals
23	Fujii 2019[43]	1 PECS block (40) 2 SAP block (40)	Mastectomy	0.5% Ropivacaine (30 mL) 0.5% Ropivacaine (30 mL)	Morphine PCA	Pain at 6 months after surgery
24	Gad 2019[44]	1 ESP block (24) 2 PECS block (24)	MRM	0.25% Levobupivacaine + dexmedetomidine 0.5 $\mu g \cdot kg^{-1}$ (20 mL) 0.25% Levobupivacaine + dexmedetomidine 0.5 $\mu g \cdot kg^{-1}$ (20 mL)	Ketorolac *iv* PRN Morphine *iv* PRN	Morphine consumption in 24 hr
25	El Ghamry 2019[45]	1 T4 TPVB (35) 2 ESP block (35)	MRM	0.25% Bupivacaine (20 mL) 0.25% Bupivacaine (20 mL)	Morphine PCA	Morphine consumption in 24 hr
26	Gupta 2017[46]	1 T4 TPVB (25) 2 SAP block (25)	MRM	0.5% Bupivacaine (20 mL) 0.5% Bupivacaine (20 mL)	Morphine PCA	Duration of analgesia
27	Gurkan 2018[47]	1 ESP block (25) 2 No intervention (25)	Breast cancer surgery	0.25% Bupivacaine (20 mL) Nothing	Morphine PCA	Morphine consumption in 24 hr
28	Gurkan 2020[48]	1 ESP block (25) 2 T4 TPVB (25) 3 No intervention (25)	Breast cancer surgery	0.25% Bupivacaine (20 mL) 0.25% Bupivacaine (20 mL) Nothing	PCM 1 g *iv* 6 hourly Morphine PCA	Morphine consumption in 24 hr
29	Ali Hassn 2016[49]	1 PECS block (30) 2 Placebo (30)	MRM	0.5% Bupivacaine + dexmedetomidine I $\mu g \cdot kg^{-1}$ (30 mL) 0.9% Normal saline (30 mL)	Morphine PRN	Incidence of chronic pain at 6 months
30	He 2020[50]	1 ESP block (20) 2 No intervention (20)	MRM	0.5% Ropivacaine (20 mL) Nothing	Flurbiprofen axetil *iv* PRN	VAS at various time intervals
31	Ilfeld 2014[51]	1 CTPVB (30) 2 T3 TPVB (30)	U/L OR B/L Mastectomy ± LND	0.5% Ropivacaine with epinephrine (15 mL) followed by 5 $mL \cdot hr^{-1}$ 0.5% Ropivacaine with epinephrine (15 mL)	PCM *po* 975 mg 6 hourly Oxycodone *po* PRN Morphine *iv* PRN	Pain scores at 1 week
32	Johansson 2000[52]	1 Wound infiltration (30) 2 Placebo (29)	Partial mastectomy ± LND	0.375% Ropivacaine (0.6 $mL \cdot kg^{-1}$) 0.9% Normal saline (0.6 $mL \cdot kg^{-1}$)	Dexketoprofen 100 mg *po* 6 hourly Ketobemidone *iv* PRN	VAS at various time intervals
33	Jonnavithula 2015[53]	1 Wound infiltration (20) 2 Placebo (20) 3 No intervention (20)	MRM	0.25% Bupivacaine (40 mL) 0.9% Normal saline (40 mL) Nothing	Tramadol *im* PRN	Duration of analgesia
34	Kairalouma 2004[54]	1 T3 TPVB (30) 2 Sham block (30)	Lumpectomy or Mastectomy ± LND	0.5% Bupivacaine (0.3 $mL \cdot kg^{-1}$) 0.9% Normal saline (2 mL)	PCM 1 g *po* 8 hourly Ibuprofen 10 $mL \cdot kg^{-1}$ *po* 8 hourly Oxycodone *iv* followed by IM PRN	Oxycodone consumption in postoperative

Table 1 continued

S no.	Author year	Study group	Surgical procedure	Drug concentration (dose)	Postoperative analgesia	Primary outcome
35	Kamiya 2018[55]	1 PECS block (24) 2 Placebo (21)	Mastectomy ± LND	0.25% Levobupivacaine (30 mL) 0.9% Normal saline (30 mL)	Diclofenac *pr* PRN Pentazocine *iv* PRN	NRS at 6 hr
36	Karmakar 2014[7]	1 TPVB (57) 2 CTPVB (60) 3 No intervention (60)	MRM	Ropivacaine 2 mL·kg^{-1} + epinephrine (20 mL) Ropivacaine 2 mL·kg^{-1} + epinephrine (20 mL) followed by 0.25% Ropivacaine 0.1 mL·kg^{-1}·hr^{-1} Nothing	Diclofenac 75 mg *po* 12 hourly Morphine *iv*/*im* PRN PCM and dextropropoxyphene *po* PRN	Incidence of chronic pain
37	Kasimahanti 2016[56]	1 T4 TPVB (28) 2 T2 & 5 TPVB (30)	Total mastectomy + LND	0.5% Ropivacaine (0.3 mL·kg^{-1}) 0.5% Ropivacaine (0.3 mL·kg^{-1})	Diclofenac *iv* PRN Tramadol *iv* PRN	Analgesic consumption in 24 hr
38	Khemka 2019[57]	1 PECS block (50) 2 No intervention (50)	Breast cancer surgery + LND	0.25% Levobupivacaine (30 mL) Nothing	PCM 1 g *iv* 8 hourly Morphine PCA	Morphine consumption in 24 hr
39	Kim 2018[58]	1 PECS block (40) 2 No intervention (38)	Breast cancer surgery + LND	0.25% Ropivacaine (30 mL) Nothing	Ketorolac 30 mg *iv* Fentanyl *iv* PRN Pethidine or tramadol *iv* PRN	Opioid consumption in 24 hr
40	Kulhari 2016[59]	1 T3 TPVB (20) 2 PECS block (20)	MRM	0.5% Ropivacaine (25 mL) 0.5% Ropivacaine (25 mL)	Morphine PCA	Duration of analgesia Morphine consumption in 24 hr
41	Kumar 2018[60]	1 PECS block (25) 2 No intervention (25)	MRM	0.25% Bupivacaine (30 mL) Nothing	PCM 1 g *iv* 8 hourly Tramadol *iv* PRN	Static VAS at various time intervals
42	Ferreira Laso 2014[61]	1 Wound infiltration (34) 2 Placebo (39)	MRM	0.25% Levobupivacaine (30 mL) followed by 0.5% Levobupivacaine 2 mL·hr^{-1} 0.9% Normal saline 2 mL·hr^{-1}	PCM I g *iv* PRN Metamizole *iv* PRN Dexketoprofen *iv* PRN Morphine *sc* PRN	NRS at various time intervals
43	Li 2011[62]	1 T2–5 TPVB (15) 2 No intervention (25)	Breast cancer surgery	0.5% Bupivacaine (12–20 mL) Nothing	PCM *iv* PRN Ketorolac *iv* PRN Morphine *iv* PRN	QoR
44	Mazzinari 2019[63]	1 SAP block (28) 2 No intervention (30)	MRM or breast-conserving surgery	0.25% Levobupivacaine (30 mL) Nothing	PCM 1 g *iv* 8 hourly Dexketoprofen 50 mg *iv* 8 hourly Morphine PCA	Morphine consumption in 24 hr
45	Mohamed 2013[64]	1 Wound infiltration (35) 2 Wound infiltration (35) 3 Wound infiltration (35) 4 Placebo (35)	MRM	0.5% Bupivacaine + 0.9% normal saline (15 mL) 0.5% Bupivacaine + Clonidine 150 µg (15 mL) 0.5% Bupivacaine + clonidine 250 µg (15 mL) 0.9% Normal saline (15 mL)	Tramadol *iv* PRN	Tramadol consumption in 48 hr

Table 1 continued

S no.	Author year	Study group	Surgical procedure	Drug concentration (dose)	Postoperative analgesia	Primary outcome
46	Mohta 2016[65]	1 T3 TPVB (15) 2 T3 TPVB (15) 3 No intervention (15)	MRM or breast-conserving surgery + LND	0.5% Bupivacaine (0.3 $mL{\cdot}kg^{-1}$) + 0.9% normal saline (1 mL) 0.5% Bupivacaine (0.3 $mL{\cdot}kg^{-1}$) + Dexmedetomidine 1 $\mu g{\cdot}kg^{-1}$ (1 mL)	Morphine PCA	Morphine consumption in 24 hr
47	Moller 2007[66]	1 T1–5 TPVB (38) 2 Placebo (41)	Lumpectomy or mastectomy ± LND	0.5% Levobupivacaine (30 mL) 0.9% Normal saline (30 mL)	PCM *po* 6 hourly Ibuprofen *po* PRN, Oxycodone *po* PRN	Fentanyl consumption in PACU
48	Moustafa 2020[67]	1 T4 TPVB (45) 2 ESP block (45)	MRM	0.25% Bupivacaine (30 mL) 0.25% Bupivacaine (20 mL)	PCM *iv* 6 hourly Morphine PRN	Success rate of the block
49	Neethu 2018[68]	1 PECS block (30) 2 No intervention (30)	MRM	0.25% Ropivacaine (20 mL) Nothing	Fentanyl PCA PCM *iv* PRN	Fentanyl consumption in 24 hr
50	O'Riain 2005[69]	1 CTPVB (15) 2 No intervention (15)	Mastectomy + LND	0.25% Bupivacaine 15 mL followed by 10 $mL{\cdot}hr^{-1}$ Nothing	Morphine PCA	Vascular endothelial growth factor levels
51	O'Scanaill 2018[70]	1 PECS block (15) 2 CWI (15) 3 PECS block + CWI (15)	WLE or mastectomy ± LND	0.25% Levobupivacaine (30 mL) 0.25% Levobupivacaine (20 mL) followed by 0.1% levobupivacaine 10 $mL{\cdot}hr^{-1}$ combination	PCM *iv*/*po* 6 hourly Ibuprofen *po* 400 mg 8 hourly Oxycodone *po* PRN	Area under curve of VAS on movement
52	Pillai 2015[71]	1 T1–5 TPVB (121) 2 Sham (126)	Mastectomy ± LND	0.75% Ropivacaine (25 mL) subcutaneous LA	Not stated	Anesthetic requirement and most severe pain in 2 hr
53	Pillai 2018[72]	1 PECS block (19) 2 T2–4 TPVB (20)	MRM	0.5% Bupivacaine (30 mL) 0.5% Bupivacaine (20 mL)	Morphine PRN PCM *iv* PRN	Morphine consumption in 24 hr
54	Qian 2019[73]	1 T1–5 TPVB (86) 2 Placebo (86)	Partial mastectomy ± LND	0.5% Ropivacaine (25 mL) 0.9% Normal saline (25 mL)	Flurbiprofen 50 mg *iv* 12 hourly Sufentanil PCA	Pain at 3 months after surgery
55	Rahimzadeh 2018[74]	1 SAP block (30) 2 No intervention (30)	MRM	0.2% Bupivacaine (0.33 $mL{\cdot}kg^{-1}$) Nothing	PCM *iv* PRN Fentanyl *iv* PCA	Postmastectomy acute pain
56	Razek 2018[75]	1 PECS block (30) 2 SAP block (30)	Nonreconstructive surgery	0.25% Levobupivacaine + epinephrine (40 mL) 0.25% Levobupivacaine + epinephrine (30 mL)	Ketorolac 30 mg *iv* 8 hourly Fentanyl *iv* PRN	Intraoperative and postoperative analgesic effect
57	Seelam 2020[76]	1 ESP block (50) 2 No intervention (50)	MRM	0.25% Bupivacaine (30 mL) Nothing	PCM *iv* 8 hourly Morphine *iv* PRN	Morphine consumption in 24 hr
58	Senapathi 2019[77]	1 PECS block (25) 2 Placebo (25)	MRM	0.25% Bupivacaine (30 mL) 0.9% Normal saline (30 mL)	Ketorolac 30 mg *iv* 8 hourly Morphine PCA	Intraoperative fentanyl consumption

Table 1 continued

S no.	Author year	Study group	Surgical procedure	Drug concentration (dose)	Postoperative analgesia	Primary outcome
59	Sharma 2020[78]	1 ESP block (30) 2 No intervention (30)	Total mastectomy + LND	0.5% Ropivacaine (0.4 mL·kg^{-1}) Nothing	Morphine PRN PCM *iv* PRN	Morphine consumption in 24 hr
60	Siddeshwara 2019[79]	1 PECS block (20) 2 T3 TPVB (20)	MRM	0.25% Levobupivacaine + dexamethasone 4 mg (25 mL) 0.25% Levobupivacaine + dexamethasone 4 mg (25 mL)	Morphine *iv* PRN	Duration of analgesia
61	Sidiropoulou 2008[80]	1 T4 TPVB (24) 2 CWI (24)	MRM	0.2% Ropivacaine (20 mL) 0.2% Ropivacaine 2 mL·hr^{-1}	Morphine PCA	Morphine consumption in 24 hr
62	Singh 2019[81]	1 ESP block (20) 2 No intervention (20)	MRM	0.5% Bupivacaine (20 mL) Nothing	Diclofenac 1.5 mL·kg^{-1} *iv* 8 hourly Morphine *iv* PRN	Morphine consumption in 24 hr
63	Sinha 2019[82]	1 ESP block (30) 2 PECS block (30)	MRM	0.2% Ropivacaine (20 mL) 0.2% Ropivacaine (25 mL)	Morphine PCA	Morphine consumption in 24 hr
64	Strazisar 2013[83]	1 CWI (30) 2 Placebo (30)	Breast cancer surgery + LND	0.25% Levobupivacaine 15 mL followed by 2 mL·hr^{-1} Nothing	Piritramide *iv* PRN	Incidence of acute and chronic pain
65	Syal 2017[84]	1 Wound infiltration (20) 2 T4 TPVB (20) 3 PECS block (20)	MRM	0.5% Bupivacaine + epinephrine (20 mL) 0.5% Bupivacaine + epinephrine (20 mL) 0.5% Bupivacaine + epinephrine (30 mL)	Diclofenac *iv* 8 hourly Fentanyl *iv* PRN	VAS at the various time interval
66	Thomas 2018[85]	1 PECS block (28) 2 Placebo (30)	MRM	0.25% Ropivacaine (30 mL) 0.9% Normal saline (30 mL)	PCM *iv* PRN, fentanyl *iv* PRN	Duration of analgesia Analgesic requirement in 24 hr
67	Tripathy 2019[86]	1 PECS block (29) 2 T4 TPVB (29)	MRM	0.5% Bupivacaine + 2% lidocane + dexmedetomidine (30 mL) 0.5% Bupivacaine + 2% lidocane + Dexmedetomidine (30 mL)	PCM *iv* PRN Diclofenac *iv* PRN	PCM consumption in 24 hr
68	Uppal 2017[87]	1 T4 TPVB (32) 2 T1–5 TPVB (36)	Mastectomy ± LND	0.5% Ropivacaine (25 mL) 0.5% Ropivacaine (25 mL)	PCM 975 mg *po* 6 hourly Hydromorphone *po* PRN	Sensory dermatomal spread at 20 min
69	Versyck 2017[88]	1 PECS block (35) 2 Placebo (30)	Lumpectomy or mastectomy ± LND	0.25% Levobupivacaine (30 mL) 0.9% Normal saline (30 mL)	PCM 1 g *iv* 6 hourly Tramadol *iv* PRN Pitramidine *iv* PRN	Intraoperative and postoperative opioid consumption
70	Vigneau 2011[89]	1 Wound infiltration (22) 2 Placebo (24)	Lumpectomy or mastectomy ± LND	0.75% Ropivacaine (20 mL) 0.9% Normal saline (20 mL)	PCM 1 g *po* 6 hourly Morphine SC PRN	Dynamic VAS at various time intervals

Table 1 continued

S no.	Author year	Study group	Surgical procedure	Drug concentration (dose)	Postoperative analgesia	Primary outcome
71	Vlassakov 2020[90]	1 T4 TPVB (10) 2 IC block (10)	Unilateral or bilateral mastectomy ± reconstruction	0.375/0.5% Ropivacaine (2.5 mL·kg^{-1}) 0.375/0.5% Ropivacaine (2.5 mL·kg^{-1})	Not stated	USG image quality
72	Wahba 2013[91]	1 T4 TPVB (30) 2 PECS block (30)	MRM	0.25% Levobupivacaine (15-20 mL) 0.25% Levobupivacaine (30 mL)	Morphine PCA	Morphine consumption at 24 hr
73	Wang 2018[92]	1 PECS block (30) 2 No intervention (30)	MRM + reconstruction	0.5% Ropivacaine (30 mL) Nothing	Morphine *iv* PRN	Morphine consumption at 24 hr
74	Wu 2015[93]	1 T1–5 TPVB (187) 2 No intervention (191)	Partial or total mastectomy ± LND	0.25% Levobupivacaine (30 mL) Nothing	Morphine *iv* PRN Morphine PCA	Postoperative pain and opioid consumption
75	Xu 2016[94]	1 T4 TPVB (30) 2 Placebo (30)	MRM	0.5% Ropivacaine (20 mL) 0.9% Normal saline (20 mL)	Sufentanil PCA	Postoperative analgesia
76	Yao 2020[95]	1 ESP block (39) 2 Placebo (40)	MRM	0.5% Ropivacaine (25 mL) 0.9% Normal saline (25 mL)	Flurbiprofen 50 mg *iv* 12 hourly Sufentanil PCA	QoR at 24 hr
77	Yao 2019[96]	1 SAP block (34) 2 Placebo (34)	Mastectomy ± LND	0.5% Ropivacaine (25 mL) 0.9% Normal saline (25 mL)	Flurbiprofen 50 mg *iv* 12 hourly Sufentanil PCA	QoR at 24 hr
78	Yayik 2019[97]	1 SAP block (24) 2 Sham (24)	MRM	0.25% Levobupivacaine (30 mL) 0.9% Normal saline (2 mL)	Dexketoprofen 50 mg *iv* 12 hourly Fentanyl PCA Pethidine *iv* PRN	Fentanyl consumption at 24 hr
79	Zielinski 2011[98]	1 Wound infiltration (54) 2 Placebo (52)	MRM	0.25% Bupivacaine (40 mL) 0.9% Normal saline (40 mL)	Metramizole 1 g *iv* 6 hourly Morphine PCA	VAS at various time intervals

CTPVB = continuous paravertebral block; CWI = continuous wound infusion; ESP = erector spinae plane; IC = intercostal; *im* = intramuscular; *iv* = intravenous; LA = local anesthetic; LND = lymph node dissection; MRM = modified radical mastectomy; NRS = numeric rating scale; NS= normal saline; PECS = modified pectoral block; PCA = patient-controlled analgesia; PCM = paracetamol; *po* = per oral; *pr* = per rectal; PRN = as needed; QoR = quality of recovery; SA = serratus anterior plane; TPVB = paravertebral block; USG = ultrasound-guided ; VAS = visual analogue scale; WLE = wide local excision.

Primary outcome

Resting pain score at 24 hr

Data comparing the resting pain score at 24 hr were available from 59 trials including 3,888 patients. The SUCRA values of the interventions for 24-hr rest pain were: CTPVB, 0.83; SAPB, 0.76; CWI, 0.76; SL_TPVB, 0.68; ESP block, 0.59; PECS block, 0.49; ICB, 0.45; ML_TPVB, 0.41; WI, 0.33; no intervention, 0.12; and placebo, 0.08. When compared with no intervention and placebo, we observed clinically significant mean differences for CTPVB, SAPB, and CWI.

The lower-left diagonal half of Table 2 (league table) shows the mean difference with 95% Crl for each pairwise comparison for resting pain scores at 24 hr with clinically significant values in bold font; positive values favour row intervention and negative values favour column intervention. The pairwise comparison of network estimates showed a mean difference of 1.26 (95% Crl, 0.43 to 2.12) for resting pain score at 24 hr between the highest (CTPVB) and lowest SUCRA value intervention (placebo).

A sensitivity analysis that enrolled only MRM surgery population included 30 trials with 1,879 patients. The SUCRA scores for interventions for resting pain scores at 24 hr were CWI, 0.79; SL_TPVB, 0.72; CTPVB, 0.69; ESP

block, 0.63; PECS block, 0.57; SAPB, 0.53; ML_TPVB, 0.52; ICB, 0.50; no intervention, 0.23; WI, 0.2; and placebo, 0.12.

Secondary outcomes

Early pain scores (4–6 hr)

Fifty-five trials, including 3,721 patients, reported this outcome. The SUCRA values of the interventions for early pain scores were: SL_TPVB, 0.73; ESP block, 0.72; CTPVB, 0.70; SAPB, 0.65; PECS block, 0.63; ML_TPVB, 0.61; CWI, 0.56; WI, 0.44; ICB, 0.21; placebo, 0.16; and no intervention, 0.09. SL_TPVB, ESP block, and CTPVB were the three best interventions for early pain scores. When compared with no intervention, clinically significant mean differences were observed for all active interventions except ICB and WI. Compared with placebo, clinically significant mean differences were observed for SL_TPVB, ESP block, CTPVB, SAPB, and PECS block. Additionally, ICB showed significantly higher six-hour pain scores than all active interventions except WI.

The upper-right diagonal half of Table 2 (league table) shows the mean difference with 95% Crl for each pairwise comparison for six-hour pain scores with clinically significant mean differences shown in bold. The pairwise comparison of network estimates showed a mean difference of − 1.35 (95% Crl, − 2 to − 0.71) for pain scores between the highest (SL_TPVB) and lowest SUCRA value intervention (no intervention).

Twenty-four-hour parenteral morphine equivalent consumption

Fifty-four RCTs with a total of 3,428 patients reported this outcome. The SUCRA values of the interventions for 24-hr parenteral morphine equivalent consumption were: ML_TPVB, 0.882; CWI, 0.878; PECS bock, 0.73; SAPB, 0.64; SL_PVB, 0.55; ESP block, 0.51; WI, 0.41; ICB, 0.38; CTPVB, 0.33; placebo, 0.14; and no intervention, 0.05.

The lower-left diagonal half of Table 3 (league table) shows the mean difference with 95% Crl for each pairwise comparison for 24-hr opioid consumption. The pairwise comparison of network estimates showed a mean difference of 14.0 (95% Crl, 5.0 to 23.0) mg parenteral morphine between the highest (ML_TPVB) and lowest SUCRA value intervention (no intervention).

Time to the first analgesia

Data comparing time to first analgesic supplementation were available from 34 trials including 2,077 patients. The SUCRA values of the interventions for delaying time to request first analgesia were: ESP block, 0.84; SL_TPVB, 0.76; PECS block, 0.66; WI, 0.59; SAPB, 0.57; ML_TPVB, 0.56; placebo, 0.24; CTPVB, 0.24; no intervention, 0.04. eTable 1 in the ESM (league table) shows the mean difference with 95% Crl for each pairwise comparison for time to the first analgesia. The pairwise comparison of network estimates showed a mean difference of 552 (95% Crl, 857.52 to 275.23) min for the time to first analgesia request between the highest (ESP block) and the lowest SUCRA value intervention (no intervention).

Postoperative nausea and vomiting

Postoperative nausea and vomiting (PONV) was the only adverse effect consistently reported. Data comparing PONV were available from 39 trials including 2,728 patients. The SUCRA values of the interventions for reducing PONV were: CTPVB, 0.97; SL_TPVB, 0.77; SAPB, 0.76; PECS block, 0.70; ICB, 0.65; ML_TPVB, 0.53; ESP block, 0.53; CWI, 0.29; WI, 0.20; placebo, 0.16; and no intervention, 0.13. The upper-right diagonal half of Table 3 (league table) shows the odds ratio with 95% Crl for each pairwise comparison for PONV. The pairwise comparison of network estimates showed an odds ratio of 6.41 (95% Crl, 1.05 to 48.65) for PONV between the highest (CTPVB) and lowest SUCRA value intervention (no intervention).

Block-related complications

Forty-one included trials explicitly reported not having encountered any block-related complication, whereas 30 studies did not include complication data. Most complications related to regional techniques were reported with PVBs. Two patients of the 639 (0.3%) receiving an SL_TPVB developed pneumothorax,[41,45] whereas two out of 625 (0.3%) in the ML_TPVB group encountered vascular puncture,[42] and another two had pleural puncture without pneumothorax.[56] In the continuous PVB group comprising 201 participants, three had transient Horner's syndrome (0.5%)[71] and another had epidural extension of local anesthetic.[51] One trial reported an unusually high rate of complications with PECS block, including transient neurologic complications (paresthesia or numbness) in the upper extremity in five participants and bruising at the injection site in three patients.[32] One patient had wound hematoma in the placebo WI group.

Exploration for inconsistency

The quality of evidence generated for resting pain scores at 24 hr was evaluated using the CINeMA approach. The

Table 2 League table showing resting pain scores at 24 hr and pain scores at 4–6 hr

Pain 24 hr												Pain 4-6 hr
	TPVB	0.28 (-1.54 to 2.09)	0 (-1.13 to 1.12)	**1.34 (-0.91 to 3.63)**	0.19 (-1.08 to 1.45)	**1.35 (0.4 to 2.29)**	0.13 (-0.92 to 1.18)	**1.13 (-0.01 to 2.26)**	0.11 (-1.16 to 1.37)	0 (-1.06 to 1.06)	0.5 (-0.66 to 1.66)	
	-0.03 (-1.46 to 1.42)	CWI	-0.28 (-1.95 to 1.36)	**1.07 (-1.53 to 3.69)**	-0.09 (-1.85 to 1.65)	**1.07 (-0.54 to 2.66)**	-0.15 (-1.69 to 1.38)	0.85 (-0.82 to 2.51)	-0.17 (-1.93 to 1.58)	-0.28 (-1.83 to 1.25)	0.22 (-1.53 to 1.96)	
	-0.41 (-1.28 to 0.44)	-0.39 (-1.72 to 0.94)	ESPB	**1.35 (-0.82 to 3.54)**	0.19 (-0.86 to 1.24)	**1.36 (0.69 to 2.03)**	0.14 (-0.59 to 0.87)	**1.14 (0.26 to 2.02)**	0.11 (-0.9 to 1.13)	0.01 (-0.76 to 0.76)	0.5 (-0.52 to 1.53)	
	-0.64 (-2.09 to 0.81)	-0.61 (-2.39 to 1.15)	-0.22 (-1.57 to 1.13)	ICB	**-1.17 (-3.42 to 1.09)**	0 (-2.07 to 2.07)	**-1.22 (-3.36 to 0.93)**	-0.22 (-2.44 to 1.99)	**-1.25 (-3.5 to 1.02)**	**-1.35 (-3.52 to 0.81)**	-0.86 (-3.12 to 1.39)	
	-0.69 (-1.73 to 0.35)	-0.66 (-2.11 to 0.78)	-0.27 (-1.17 to 0.63)	-0.05 (-1.52 to 1.42)	ML_TPVB	**1.16 (0.27 to 2.06)**	-0.05 (-0.98 to 0.89)	0.95 (-0.08 to 1.98)	-0.08 (-1.29 to 1.12)	-0.19 (-1.15 to 0.78)	0.31 (-0.85 to 1.48)	
	-1.16 (-1.89 to -0.44)	**-1.14 (-2.42 to 0.16)**	-0.74 (-1.28 to -0.22)	-0.52 (-1.79 to 0.75)	-0.47 (-1.27 to 0.32)	No intervention	**-1.22 (-1.79 to -0.65)**	-0.22 (-1 to 0.56)	**-1.24 (-2.16 to -0.33)**	**-1.35 (-2 to -0.71)**	-0.85 (-1.76 to 0.05)	
	-0.54 (-1.34 to 0.26)	-0.51 (-1.76 to 0.73)	-0.12 (-0.69 to 0.44)	0.1 (-1.21 to 1.41)	0.15 (-0.68 to 0.97)	0.62 (0.17 to 1.07)	PECS	**1 (0.25 to 1.74)**	-0.02 (-0.96 to 0.91)	-0.13 (-0.74 to 0.47)	0.37 (-0.54 to 1.26)	
	-1.26 (-2.12 to -0.43)	**-1.24 (-2.58 to 0.1)**	-0.85 (-1.55 to -0.15)	-0.62 (-2.01 to 0.75)	-0.58 (-1.46 to 0.3)	-0.11 (-0.72 to 0.52)	-0.73 (-1.32 to -0.13)	Placebo	**-1.02 (-2.05 to 0.01)**	**-1.13 (-1.91 to -0.36)**	-0.63 (-1.41 to 0.14)	
	-0.15 (-1.12 to 0.82)	-0.12 (-1.52 to 1.27)	0.26 (-0.52 to 1.04)	0.49 (-0.93 to 1.91)	0.54 (-0.46 to 1.53)	**1.01 (0.31 to 1.71)**	0.39 (-0.3 to 1.08)	**1.12 (0.32 to 1.9)**	SAPB	-0.11 (-1.05 to 0.83)	0.39 (-0.77 to 1.55)	
	-0.3 (-1.11 to 0.5)	-0.27 (-1.52 to 0.97)	0.12 (-0.49 to 0.72)	0.34 (-0.95 to 1.62)	0.39 (-0.45 to 1.22)	0.86 (0.36 to 1.37)	0.24 (-0.26 to 0.74)	0.96 (0.34 to 1.59)	-0.15 (-0.87 to 0.57)	SL_TPVB	0.5 (-0.42 to 1.42)	
	-0.81 (-1.63 to 0.01)	-0.78 (-2.17 to 0.62)	-0.39 (-1.18 to 0.4)	-0.16 (-1.58 to 1.25)	-0.12 (-1.08 to 0.85)	0.35 (-0.33 to 1.05)	-0.27 (-0.96 to 0.43)	0.46 (-0.13 to 1.05)	-0.65 (-1.54 to 0.22)	-0.51 (-1.22 to 0.22)	WI	

Each cell gives the relative 0–10 numeric rating scale pain scores. The left side of the table shows resting pain scores at 24 hr values in mean difference (95% credibility interval). The right side of the table shows pain scores at 4–6 hr values in mean difference (95% credibility interval). Bold value indicates indicate clinically significant mean difference. Positive values indicate that the analgesic method in the corresponding column has a higher pain score than the corresponding row. Green highlights indicate compared interventions.
CTPVB = continuous paravertebral block; CWI = continuous wound infusion; ESPB = erector spinae plane block; IC = intercostal; ML_TPVB = multiple level paravertebral block; PECS = modified pectoral block; SAPB = serratus anterior plane block; SL_TPVB = single-level paravertebral block; WI = wound infiltration

inconsistency of the network was explored graphically using heat plots (ESM eFigure 2).[99] The net heat plot is coloured yellow and red. The red colours indicate that the contribution of the evidence is inconsistent with other evidence in the network. Global test of inconsistency based on a random effects design-by-treatment interaction model showed a *P* value of 0.70. No major statistical inconsistencies were identified using any of the above approaches.

Publication bias (risk of bias across studies)

The risk of publication bias in the primary outcome was found to be low by visualization of funnel plot and Egger's test (ESM eFigure 3). The trials appeared symmetrically distributed, and the regression test gave non-significant results ($P = 0.07$).

Certainty of the evidence

The overall certainty of evidence with the effect size for each pairwise comparison is shown in ESM eTable 2. The certainty of evidence for pairwise comparison ranged from moderate to very low. Major concerns were identified in heterogeneity and impression domains in some pairwise comparisons.

Cluster ranking analysis

Figure 4 shows the two-dimensional cluster plots that combine SUCRA ranking for two outcomes. The same colour represents the clusters with similar efficacy for the combination of both outcomes. The cluster of treatments on the right upper corner group ranked highest for both outcomes, while treatments on the left lower corner group ranked lowest.

Clustered ranking plots for analgesic outcome 24-hr parenteral morphine equivalent and pain score showed all active interventions are significantly superior to no intervention or placebo (Figure 4a). Further, when analgesic outcomes (24-hr pain), were clustered with PONV, the most reported side effect, WI and CWI appeared to be less effective (Figure 4b).

Discussion

Summary of evidence

This NMA provides the most comprehensive synthesis of evidence to date for the analgesic efficacy of various regional techniques in patients undergoing oncologic breast

Table 3 League table showing pain scores at 4–6 hr and postoperative nausea and vomiting

24-hr parenteral morphine equivalent consumption												PONV
	CTPVB	4.91 (0.42 to 62.58)	2.38 (0.35 to 19.02)	1.54 (0.06 to 29.51)	2.47 (0.36 to 19.79)	6.41 (1.05 to 48.65)	1.59 (0.24 to 12.77)	7.19 (1.2 to 55.2)	1.05 (0.05 to 18.44)	1.37 (0.19 to 10.97)	6.13 (1.07 to 46.19)	
	8.56 (-0.86 to 17.94)	CWi	0.48 (0.09 to 2.82)	0.31 (0.02 to 5.05)	0.5 (0.08 to 3.25)	1.31 (0.26 to 7.26)	0.33 (0.07 to 1.6)	1.46 (0.25 to 9.48)	0.21 (0.01 to 3.59)	0.28 (0.06 to 1.26)	1.25 (0.19 to 9.53)	
	2.55 (-4.16 to 9.21)	-6 (-14.01 to 2.04)	ESPB	0.64 (0.05 to 6.55)	1.03 (0.31 to 3.43)	2.67 (1.34 to 5.73)	0.66 (0.26 to 1.74)	3 (1.02 to 9.64)	0.43 (0.03 to 4.77)	0.58 (0.22 to 1.41)	2.58 (0.7 to 10.48)	
	0.12 (-13.24 to 13.45)	-8.45 (-22.51 to 5.82)	-2.42 (-14.91 to 10.07)	ICB	1.63 (0.13 to 25.61)	4.22 (0.48 to 51.59)	1.05 (0.1 to 14.5)	4.74 (0.42 to 73.48)	0.69 (0.02 to 20.98)	0.91 (0.08 to 12.17)	4.06 (0.33 to 68.93)	
	9.1 (-1.36 to 19.56)	0.53 (-10.81 to 11.76)	6.53 (-2.72 to 15.78)	8.95 (-5.84 to 23.91)	ML_TPVB	2.6 (0.87 to 8.21)	0.65 (0.2 to 2.07)	2.9 (1.41 to 6.57)	0.42 (0.03 to 4)	0.56 (0.17 to 1.75)	2.48 (0.88 to 7.98)	
	-4.87 (-10.91 to 1.07)	-13.44 (-20.96 to -5.85)	-7.43 (-11.13 to -3.74)	-5.02 (-16.91 to 6.97)	-13.96 (-23.05 to -4.98)	No intervention	0.25 (0.11 to 0.52)	1.12 (0.4 to 3.23)	0.16 (0.01 to 1.67)	0.22 (0.09 to 0.47)	0.96 (0.28 to 3.49)	
	4.88 (-1.46 to 11.16)	-3.68 (-11.17 to 3.87)	2.33 (-1.58 to 6.18)	4.75 (-7.57 to 17.07)	-4.21 (-12.84 to 4.4)	9.76 (6.57 to 12.94)	PECS	4.5 (1.64 to 13.21)	0.66 (0.05 to 6.88)	0.87 (0.37 to 1.86)	3.85 (1.11 to 14.71)	
	-3.09 (-9.85 to 3.56)	-11.67 (-19.86 to -3.46)	-5.67 (-10.47 to -0.94)	-3.23 (-15.89 to 9.41)	-12.2 (-20.84 to -3.54)	1.79 (-2.61 to 6.11)	-7.98 (-11.99 to -4.05)	Placebo	0.14 (0.01 to 1.15)	0.19 (0.06 to 0.56)	0.86 (0.39 to 1.92)	
	4.08 (-3.53 to 11.8)	-4.47 (-13.27 to 4.47)	1.52 (-4.22 to 7.39)	3.94 (-9.08 to 17.15)	-5.01 (-14.83 to 4.86)	8.95 (3.53 to 14.52)	-0.81 (-6.12 to 4.61)	7.19 (1.61 to 12.84)	SAPB	1.33 (0.12 to 18.29)	5.96 (0.64 to 77.8)	
	3.04 (-3.33 to 9.43)	-5.51 (-13.16 to 2.2)	0.48 (-3.66 to 4.58)	2.91 (-9.61 to 15.45)	-6.04 (-15.21 to 3.14)	7.92 (4.08 to 11.76)	-1.84 (-5.54 to 1.84)	6.15 (1.68 to 10.69)	-1.04 (-6.57 to 4.38)	SL_TPVB	4.47 (1.25 to 18.94)	
	1.17 (-5.22 to 7.45)	-7.4 (-16.33 to 1.56)	-1.4 (-7.37 to 4.55)	1.04 (-11.97 to 14.06)	-7.93 (-17.74 to 1.78)	6.04 (0.74 to 11.35)	-3.72 (-9.12 to 1.63)	4.28 (-1.09 to 9.62)	-2.91 (-9.9 to 3.94)	-1.87 (-7.72 to 3.88)	Wi	

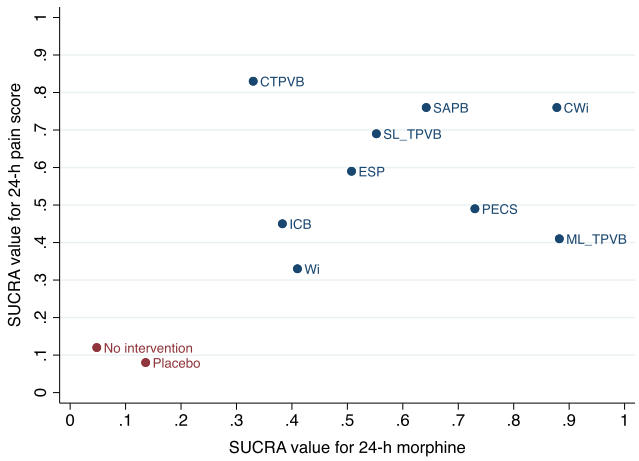
The left side of the table shows the mean difference in cumulative opiate consumption at 24 hr. A positive value indicates the row intervention is favourable and a negative value indicates the column intervention is favourable. The right side of the table shows the odds ratio for PONV. A value more than 1.0 favours row intervention to a value less than 1.0 favours column intervention. Green highlights indicate compared interventions. CTPVB = continuous paravertebral block; CWI = continuous wound infusion; ESPB = erector spinae plane block; IC = intercostal; ML_TPVB = multiple level paravertebral block; PECS = modified pectoral block; PONV = postoperative nausea and vomiting; SAPB = serratus anterior plane block; SL_TPVB = single level paravertebral block; WI = wound infiltration

surgery. The data consistently showed that most regional analgesia techniques are more effective than no intervention or placebo for major oncologic breast surgery. Further, for 24-hr resting pain scores, continuous techniques such as continuous PVB and CWI unsurprisingly had high SUCRA scores, as the effect of single injection techniques is unlikely to last beyond the 12-hr mark. Nevertheless, the certainty of evidence for CWI was judged low or very low because of imprecision and heterogeneity.

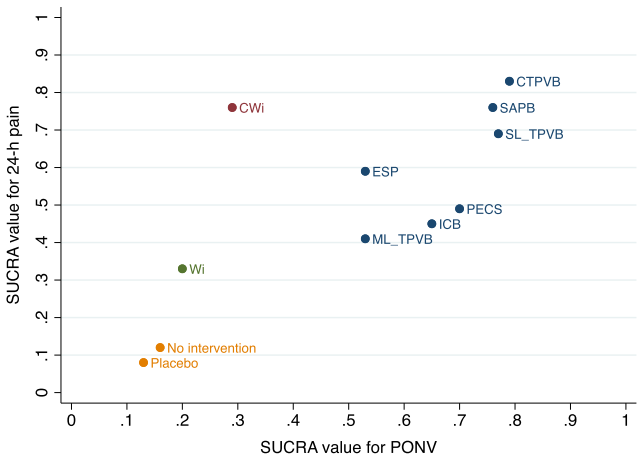
Although the mean difference between the various active comparators and no intervention for 24-hr resting pain scores ranged from 0.6 to 1.2 points on a 10-cm scale, the odds ratio for PONV ranged from 2 to 6, favouring active interventions over no intervention. Therefore, improved analgesia along with a lower incidence of PONV may justify performing the active intervention.

Paravertebral blocks featured in the top three ranks and were the most efficacious interventions for multiple outcomes. Conclusions for the primary outcome did not substantially change with sensitivity analysis, including MRM surgical procedure only. When analgesia outcomes were simultaneously examined with the commonly reported adverse effect (PONV), WI and CWI appeared to be less effective among the active interventions. Interestingly, the CWI group had low opioid use but a high incidence of PONV. This is contradictory as PONV is a common side effect of opioids. Nevertheless, it is well known that PONV is multifactorial, especially during the perioperative period. Further, the evidence contribution to CWI was based on two to three small studies and the certainty of evidence was rated low for this finding. These findings require further exploration and should be viewed with caution until further evidence is available.

Like other outcomes, the time to first analgesic supplementation was significantly longer for the most active interventions compared with placebo or no intervention. Although the time to first analgesic request



(a) Clustered ranking plot, 24-h Pain-Morphine



(b) Clustered ranking plot, 24-h pain-PONV

Figure 4 The clustered ranking plot according to the efficacy of a) 24-hr parenteral morphine use and 24-hr resting pain scores b) 24-hr resting pain scores and PONV. The sum of the cumulative ranking (SUCRA) score is derived from the mean ranking of treatment in a network. A SUCRA value of 1 corresponds to a 100% probability that the treatment ranks first in that network for that outcome to whereas a value of 0 corresponds to a 100% probability that the treatment ranks last in that network for that outcome. Treatments in the upper-right quadrant represent the best treatments to corresponding to the lowest opiate consumption and the lowest pain scores. *CWI* continuous wound infiltration; *CTPVB* continuous paravertebral block; *ESP* erector spinae plane block; *IC* intercostal block; *ML_TPVB* multiple level paravertebral block; *PECS* modified pectoral block; *SAPB* serratus anterior plane block; *SL_TPVB* single-level paravertebral block; *WI* wound infiltration.

has been used as a surrogate for the duration of analgesia, cumulative opioid use may be more important as it determines the overall opioid-related side effects in the perioperative period.

Although the ranking of the active interventions varied for different outcomes, a consistent finding was the lack of significant differences between the comparisons that excluded placebo or no intervention for analgesic outcomes. In other words, the Crl of active interventions were overlapping, and the active interventions were generally significantly better than no intervention or placebo. In this respect, our findings are consistent with the recently published review by Wong *et al.* Although the rankings provide some measure of the comparative efficacy of the interventions, it does not account for the uncertainty of estimates. Not finding differences between the active interventions may be either due to the absence of a difference between them or lack of sufficient power to show a difference. Clearly, more head-to-head comparisons comparing active interventions may improve our understanding of the subject. Futures studies should compare different active comparisons rather than comparing active interventions to either placebo or no intervention.

Implications for patients, healthcare providers, and policymakers

A recent survey of the American Society of Breast Surgeons showed a marked practice variation in the administration of regional anesthesia (i.e., blocks), with 43% of surgeons reporting no blocks used for major breast surgery.[100] Although some of this variation in practice may be warranted, the possibility of unwarranted variation cannot be ruled out.[101] The evidence clearly indicates that most regional analgesia techniques are more effective than no intervention or placebo for major oncologic breast surgery. Nevertheless, which technique is offered to patient may depend on multiple factors such as extent of surgery, resources available, and patient preference.

Paravertebral blocks were consistently ranked higher than other regional techniques across the outcomes studied. This is in agreement with the recently published guidelines for oncologic breast surgery by Procedure Specific Postoperative Pain Management (PROSPECT) group that recommended PVB as the first-choice regional analgesic technique for major breast surgery.[102] Although the included trials were heterogeneous regarding the technique of PVB, ultrasound-guided single-level PVB has been shown to be noninferior to the multiple injection technique in other studies.[56,87] A potential advantage of PVBs over interfacial blocks is the ability to block the sympathetic and somatic components of pain. Nevertheless, the higher efficacy of PVBs comes at a risk of complications such as pneumothorax, hypotension, vagal reaction, and epidural hematoma. There were six reported cases of pneumothorax (0.9%) that happened after ultrasound-guided SL_TPVB insertion, and two suspected

cases of pleural puncture without pneumothorax that occurred with ultrasound-guided multiple-level PVB.[41,45,56] Epidural spread and vascular puncture were reported in three cases each after PVB.[42,51] These complications are likely under-reported.

Therefore, fascial plane blocks, including PECS, ESP, and SAP blocks, have gained popularity. Furthermore, patients may prefer a technique that can be easily performed under general anesthesia to avoid the discomfort of needle insertion. Healthcare workers may also prefer PECS or SAP blocks, which can be rapidly performed without repositioning the patient after induction of general anesthesia. Similarly, WI or CWI can be quickly performed during surgery and were associated with the fewest reported complications. Nevertheless, WI was ranked low for most outcomes after major breast surgery. It may be adequate for minor breast surgery without axillary involvement. Furthermore, both WI and CWI may be less effective in reducing the risk of PONV. Additionally, wound catheters may be associated with increased risk of wound infection and may impair mobilization. From a policymaker's perspective, the cost of the wound catheter pump, supplies, and follow-up may not be worth the potential additional benefit. Overall, the PECS block or SAPB might be the best approach as these blocks can be easily performed after general anesthesia in the supine position; nevertheless, clinicians should choose a technique that they are most comfortable with and that suits their hospital setting.

Strengths and limitations

This NMA is strengthened by the inclusive and thorough nature of the systematic review, enhancing its external validity. For the primary outcome alone, it included comparative data from 59 trials and 3,888 participants. Most of the trials were homogeneous with regard to investigating major oncologic breast surgeries known to be associated with moderate-to-severe pain. We were able to compare all frequently used regional techniques together on an identical scale, unlike previous reviews that were limited to pairwise comparisons. The robustness of the probability ranking was confirmed by sensitivity analysis, including for MRM surgical procedure only. In addition, no intervention and placebo are often grouped together for meta-analysis; however, open label no block, unlike placebo, lacks any potential positive psychological benefits and may better represent pain scores and opioid use when a patient is not offered a nerve block in clinical practice. Analyzing these interventions separately improves the accuracy and robustness of our results. Nevertheless, our results did not show any significant differences between no block and placebo.

Our analysis has several limitations. Outcomes were characterized by a high degree of heterogeneity; possible reasons for this may be accredited to the subtle disparity in surgical technique and anesthetic practice and postoperative analgesic regimens at the different centres. There was also variability in drug concentrations, combinations with various additives, and type of local anesthetics administered. Although we attempted to include major oncologic breast surgeries in this review, there was a variation in the type of surgeries and surgical techniques among the studies. Further, the reporting, type, and number of antiemetic agents used varied between the studies. Therefore, we downgraded the certainty of evidence based on these factors.

Many included studies were small and did not report important outcomes such as dynamic pain score, quality of recovery, functional outcomes, or the incidence of chronic pain. Adverse outcomes, such as procedure-related hematoma, infection, and local anesthetic systemic toxicity, were likely under-reported. Also, the results of the NMA have to be interpreted with caution because network analysis provides probability ranking, not the absolute rank order, because of overlapping credible intervals.

Conclusion

Our analysis indicates that all regional analgesia techniques were more effective than no intervention or placebo for major oncologic breast surgery. When analgesia outcomes were simultaneously examined with PONV, WI and CWI appeared to be less effective among the active interventions. Paravertebral blocks were consistently the most effective in the outcomes evaluated but were associated with a higher risk of complications. Alternatively, SAPB had a high estimated probability of reducing 24-hr resting pain with a low risk of complications. The certainty of the evidence was moderate to very low, mainly because of heterogeneity and imprecision for some comparisons. Future studies should compare different regional anesthesia techniques with each other, including surgeon-administered techniques such as WI or catheters. Trials comparing active intervention with placebo are unlikely to change clinical practice.

Author contributions NPS, JKM, and VU contributed to the conception of the study and drafted the protocol. NPS, JKM, and AK screened the studies and extracted the data. VU and NPS analyzed the results. VU and NPS drafted the manuscript. JKM, AK, and RG critically edited the manuscript. All authors contributed to the study design and interpretation of data.

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