ANESTHESIOLOGY

Pectoralis-II Myofascial Block and Analgesia in Breast Cancer Surgery

A Systematic Review and Meta-analysis

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Pectoralis-II block is a potential alternative to paravertebral blocks to provide regional analgesia for breast cancer surgery

What This Article Tells Us That Is New

- This meta-analysis includes 14 randomized trials comparing pectoralis-II block with paravertebral blocks and found that there were no differences in pain scores or opioid consumption between the two groups in patients having surgery for breast cancer
- Pectoralis-II blocks were noninferior to paravertebral blocks in reducing pain intensity and morphine consumption for the first 24 h after surgery and both were superior to systemic analgesia alone

ABSTRACT

Background: Thoracic paravertebral block is the preferred regional anesthetic technique for breast cancer surgery, but concerns over its invasiveness and risks have prompted search for alternatives. Pectoralis-II block is a promising analgesic technique and potential alternative to paravertebral block, but evidence of its absolute and relative effectiveness *versus* systemic analgesia (Control) and paravertebral block, respectively, is conflicting. This meta-analysis evaluates the analgesic effectiveness of Pectoralis-II *versus* Control and paravertebral block for breast cancer surgery.

Methods: Databases were searched for breast cancer surgery trials comparing Pectoralis-II with Control or paravertebral block. Postoperative oral morphine consumption and difference in area under curve for pooled rest pain scores more than 24 h were designated as coprimary outcomes. Opioid-related side effects, effects on long-term outcomes, such as chronic pain and opioid dependence, were also examined. Results were pooled using random-effects modeling.

Results: Fourteen randomized trials (887 patients) were analyzed. Compared with Control, Pectoralis-II provided clinically important reductions in 24-h morphine consumption (at least 30.0 mg), by a weighted mean difference [95% CI] of −30.5 mg [−42.2, −18.8] ($P < 0.00001$), and in rest pain area under the curve more than 24 h, by −4.7cm · h [−5.1, −4.2] or −1.2cm [−1.3, −1.1] per measurement. Compared with paravertebral block, Pectoralis-II was not statistically worse (not different) for 24-h morphine consumption, and not clinically worse for rest pain area under curve more than 24 h. No differences were observed in opioid-related side effects or any other outcomes.

Conclusions: We found that Pectoralis-II reduces pain intensity and morphine consumption during the first 24 h postoperatively when compared with systemic analgesia alone; and it also offers analgesic benefits noninferior to those of paravertebral block after breast cancer surgery. Evidence supports incorporating Pectoralis-II into multimodal analgesia and also using it as a paravertebral block alternative in this population.

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Breast cancer affects one in nine females during their lifetime,[1] and more than 40% of women diagnosed with this cancer undergo tumor resection.[2,3] The procedure is associated with moderate-to-severe acute postoperative pain[4]; failure to provide adequate acute pain control is associated with increased opioid requirements, poor quality of recovery,[5] and chronic postsurgical pain.[6,7] Indeed, the risks of chronic postsurgical pain and long-term opioid dependence after breast cancer surgery are 29%[8] and 11%,[9] respectively. Consequently, anesthesiologists are well-positioned to provide safe and reliable perioperative interventions that optimize acute pain control and enhance long-term outcomes.[3,10]

Thoracic paravertebral block has been described as the gold standard analgesic modality for breast cancer surgery.[11] The benefits of paravertebral block have been well

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established, including reduced postoperative pain, decreased opioid requirements, and lower risks of postoperative nausea and vomiting.[12] Paravertebral block also enhances quality of recovery[5] and seems to protect against chronic postsurgical pain.[7] However, paravertebral block is considered an invasive[13] block requiring advanced skill[14] and deep needling in close vicinity to the pleura, neuraxis, and intercostal neurovascular bundles such that the risks of pneumothorax, neuraxial spread, and systemic toxicity persist.[13,15,16] These concerns seem to prompt the quest for paravertebral block alternatives.

Described by Blanco *et al.*[17] in 2012, the Pectoralis-II fascial block promises a simple, superficial and safe alternative to anesthetize the hemithorax. It involves depositing local anesthetics between (1) pectoralis major and pectoralis minor muscles and (2) pectoralis minor and serratus anterior muscles, at the levels of the third and fourth ribs, along the mid-axillary line.[17] Pectoralis-II purportedly blocks the T2–T6 intercostal nerves, medial and lateral pectoral nerves, and intercostobrachial and long thoracic nerves.[15,18,19] However, reports suggest that the analgesic effectiveness of Pectoralis-II is modest, at best, when compared with systemic analgesia alone,[20,21] whereas comparisons between Pectoralis-II and paravertebral block have yielded conflicting results with some trials suggesting Pectoralis-II superiority,[22,23] and others reporting no difference.[15]

We undertook this systematic review and meta-analysis to identify the potential clinical role of Pectoralis-II block. We aimed to quantify the absolute and relative analgesic benefits of the Pectoralis-II block by comparisons with systemic analgesia alone (Control) and to paravertebral block, respectively, in adult females having breast cancer surgery. Postoperative pain severity and analgesic consumption during the first 24 h were designated as coprimary outcomes. For secondary objectives, we aimed to compare Pectoralis-II and paravertebral block for noninferiority over the primary outcomes, and we also examined the effects on immediate quality of recovery, as well as on long-term quality of life, risk of chronic postsurgical pain, and persistent opioid consumption.

Materials and Methods

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) in preparing this manuscript.[24] Randomized controlled trials that compared the effects of Pectoralis-II block to systemic analgesia alone (Control) or to paravertebral block on analgesic outcomes (or at least postoperative pain severity scores) in patients undergoing breast cancer surgery were sought. Studies were evaluated using a pre-designed protocol. The protocol was not published, and the review was not registered with the International prospective register of systematic reviews (PROSPERO).

Eligibility Criteria

Randomized or quasi-randomized studies that allocated adult patients (at least 18 yr old) undergoing breast cancer surgery to receive Pectoralis-II were considered for inclusion. All types of breast tumor resection or axillary interventions were considered for eligibility. This included mastectomies or partial mastectomies with or without axillary lymph node dissection or sentinel lymph node biopsy. Because of the great variability of cosmetic procedures and associated tumescence techniques used, trials were excluded if cosmetic procedures were performed (*e.g.*, breast augmentation, reduction mammoplasty, or breast reconstruction), but we did not exclude procedures that combined breast tumor reduction with immediate reconstruction. We accepted all variations of the Pectoralis-II technique if the description explicitly described deposition of local anesthetics between the pectoralis major and minor muscles (Pectoralis-I component) as well as in the plane between the pectoralis minor and serratus anterior muscles. Trials were excluded if Pectoralis-II was performed in conjunction with other blocks (*e.g.*, serratus anterior plane block) precluding the identification of analgesic effects of the Pectoralis-II block alone.[25,26] Eligible comparators included systemic analgesia alone (*i.e.*, no block or sham block, as Control) or paravertebral block. Studies that used local anesthesia infiltration as a Control group were excluded because this intervention is considered an effective active comparator that improves pain control after breast cancer surgery.[20,21] Trials of volunteers or those not reporting analgesic outcomes were excluded. No language restrictions were placed on study inclusion; any non-English studies were translated using an online translator.

Search Methods

A systematic search strategy was created for the U.S. National Library of Medicine database, MEDLINE; the MEDLINE In-process and Other Non-Indexed citations database; the ExcerptaMedica database, EMBASE; and the Cochrane Database of Systematic Reviews. These databases were searched from November 2012 (date of the original Pectoralis-II block description[27]) to August 25, 2018. The search strategy was developed using medical subject headings and key words relating to the central research question of this paper. Specifically, the search terms included in the search strategy revolved around the following key domains: breast cancer surgery, Pectoralis-II, Pectoralis block, pectoralis block, pectoral nerve, postoperative pain, pain control, and postoperative analgesia. The complete search strategy was based on an initial MEDLINE search, which can be viewed in appendix A (Supplemental Digital Content, http://links.lww.com/ALN/B978). This strategy was modified as needed for the remaining databases. The citations and bibliographies of included articles were hand-searched to identify any potentially relevant trials. The proceedings of the following international conferences also had their published abstracts electronically searched: American Society of Anesthesiologists 2011–2017, American Society of Regional Anesthesia and Pain Medicine 2013–2017,

the European Society of Regional Anesthesia 2014–2017, American Association of Cancer Research 2014–2016, and the European Society of Anesthesiology 2015–2017. We also reviewed the clinical trial registry at the Web site ClinicalTrials.gov,[28] and contacted authors of any potentially relevant completed or ongoing trials.

Selection of Included Studies

Two independent reviewers (N.H. and N.K.) initially assessed the results from the literature search based on title and abstract alone. The full-text citations of potentially eligible articles were subsequently retrieved and reviewed again by the same two independent reviewers. In case of disagreement between the two reviewers on eligibility, a discussion was initiated. If consensus could not be reached after discussion, a third reviewer (F.W.A.) assessed the study in question and made the final decision. The initial agreement on full-text eligibility between the two independent reviewers was assessed using an unweighted kappa (κ).

Data Extraction

A standardized data extraction form was used, and all data extraction was carried out in duplicate by two independent reviewers (N.H. and N.K.). In cases of discrepancy in data extraction, a discussion was initiated. If a consensus could not be reached, a third reviewer (F.W.A.) assessed the data point in question and made the final decision. The primary source of all data was numerical data reported in tables or figures. A graph digitizing software (GraphClick, Arizona Software, USA) was used to extract data in studies that reported data in purely graphical form.

Data collected included information relating to the year of publication, number of patients, intervention and comparator groups, type of breast cancer surgery performed, average age of participants, Pectoralis-II technique, and assessment of block success. We also extracted data and measures of variance at all reported times for interval postoperative pain scores; interval postoperative analgesic consumption, functional assessments, time to analgesic request (hours), level of patient satisfaction with pain relief, postanesthesia care unit and hospital discharge times (hours), incidence of chronic postsurgical pain, quality of postoperative recovery and quality of life, opioid dependence after discharge, level of disability after discharge, block-related side-effects (*i.e.*, local anesthetic systematic toxicity, bleeding or hematoma formation, pneumothorax, or block failure), and opioid-related side effects (*i.e.*, hypotension, respiratory depression, sedation, pruritis, constipation, or urinary retention).

Assessment of Methodologic Quality of Individual Trials

The methodologic quality of each included trial was assessed using the Cochrane Collaboration tool for risk of bias assessment.[29] This tool evaluates bias in six predefined domains that assess the quality of different components of study methodology in randomized trials. These included adequacy random sequence generation, allocation concealment, level of blinding of study personnel and outcome assessors, loss to follow-up, and selective outcome data reporting.[30] Each included study was rated as having either a low, unclear, or high risk of bias for each domain by two independent reviewers (N.H. and F.W.A.). For all risk of bias assessments relating to patient and outcome assessor blinding, we *a priori* assigned a moderate to high risk of detection bias to all studies that lacked (a) a sham Pectoralis II (invasive placebo) or (2) an active comparator, such as paravertebral block.

Methodologic Quality across Trials

The overall methodologic quality of evidence across pooled outcomes was also assessed using the Grades of Recommendation, Assessment, Development, and Evaluation guidelines.[31,32] These guidelines classify the evidence for pooled outcomes based on predefined criteria based on study quality, consistency, directness, precision, and publication bias.[32] Based on the level of bias across these criteria, the overall pooled outcome is classified as follows: (1) high quality: further research is very unlikely to change the confidence in the estimate of effect; (2) moderate quality: further research is very likely to have an important impact on the confidence of the estimate of effect and may change the estimate; (3) low quality: further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate; or (4) very low quality: there is uncertainty surrounding the estimate.[31,32]

Primary and Secondary Outcomes

The two coprimary outcomes of this meta-analysis were (1) difference in the area under the curve of the weighted pooled rest pain scores and (2) the cumulative postoperative oral morphine equivalent consumption (mg) during the first 24-h interval[33] in patients receiving Pectoralis-II and Control or paravertebral block. We chose to evaluate these primary outcomes because examining either of these two outcomes in isolation of the other does not provide a definitive assessment of the analgesic effect of the Pectoralis-II block. For the area under the curve analysis, the weighted pool rest pain scores for 1 h (postanesthesia care unit), 6 h, 12 h, and 24 h postoperatively were used. The area under the curve analysis was selected because it is a representative way of describing the patients' pain control experience more than 24 h; it captures pain severity as well as the duration of this severity. We also anticipated variations in the analgesic effectiveness of Pectoralis-II block, with block onset and offset within 6 to 12 h postoperatively, compared with an anticipated more prolonged analgesic effect of paravertebral block.[12]

Secondary outcomes examined included cumulative postoperative oral morphine consumption (mg) at 2 h (postanesthesia care unit)[33] and during the 24 to 48 h time interval[33]; postoperative pain severity (Visual Analog Scale pain scores) at 1 h (postanesthesia care unit), 6 h, 12 h, 24 h, 36 h, and 48 h postoperatively; time to first analgesic request (hours) and to hospital discharge (hours); and quality of recovery. We also evaluated block success rate, defined as a presence of any sensory changes indicative of block onset in the hemithorax. Safety outcomes assessed included postoperative opioid related side-effects (postoperative nausea and vomiting, sedation/respiratory depression, pruritis, hypotension, urinary retention, or constipation), and nerve block–related complications (pneumothorax, block failure, or local anesthetic systemic toxicity). Finally, we examined several long-term secondary outcomes, including the incidence of chronic postsurgical pain, quality of life, opioid dependence, and level of disability.

Measurement of Outcome Data

Postoperative surgical pain may be measured using a wide variety of standardized tools, including the Visual Analog Scale, numeric rating scale, and the verbal rating scale.[34–36] The Visual Analog Scale commonly measures pain severity on a 0 to 10 cm or 0 to 100 cm Visual Analog Scale pain scale. Higher scores on this tool are associated with increased pain.[35] For the purposes of this review, all postoperative pain scores were converted to an equivalent score on the 0 to 10 cm Visual Analog Scale.[37]

For secondary outcomes, all postoperative opioid analgesics administered were converted to oral morphine equivalents in milligrams.[33] All measures of patient satisfaction were also converted to a Visual Analog Scale equivalent score (0 equals *least satisfied*, and 10 equals *most satisfied*).[37] All time-to-event data are presented in hours.

Statistical Analyses

For continuous outcomes, we extracted the mean and SD. In situations where these are not reported, the median and interquartile range were used to approximate these values.[38] Similarly, in situations where the mean and 95% CI are reported, statistical conversions were used to estimate the mean and SD.[39] When SD values are not reported, these values were imputed by the methods described by Furukawa *et al.*[40] In situations where the mean could not be derived, the median was used to estimate the mean. If required for statistical pooling, categorical data (patient satisfaction) was converted to continuous form with means and SD.[41] For dichotomous outcomes (side effects, complications), data were converted to overall incidence numbers. In cases where separate pain scores for different anatomical areas (*e.g.*, breast *vs.* axilla) were presented, the weighted mean for pain in these two areas was calculated. We pooled studies only if data were available from three or more studies; we summarized the evidence qualitatively (without pooling), when possible, if data were available from fewer than three trials.

Meta-analysis

We anticipated the presence of heterogeneity among the studies. Therefore, continuous data were pooled using the inverse variance method with random-effects modeling, whereas dichotomous data were pooled using Mantel–Haenszel with random-effects modeling.[42]

For the continuous secondary outcomes, a mean difference with 99% CI was calculated. For the dichotomous secondary outcomes, an odds ratio with 99% CI was calculated. A 99% CI was selected for secondary outcomes to reduce the risk of type-I error associated with multiple testing. We designated a P value < 0.025 as a threshold of statistical significance for the two primary outcomes, and $P < 0.01$ for all other secondary outcomes. All tests of were two-tailed.

Interpretation

We used different approaches in analyzing and interpreting the two coprimary outcomes. For cumulative postoperative oral morphine consumption during the first 24 h postoperatively, we calculated a mean difference [95% CI]. The results for cumulative postoperative oral morphine consumption were interpreted in light of the minimal clinically important difference for oral morphine equivalent consumption. Analgesic outcomes research has not identified such a value; nonetheless, a 30-mg difference in oral morphine equivalent consumption (or 10-mg IV morphine equivalent) during the first 24 h postsurgery is generally considered as the least that can be considered clinically important. A corresponding noninferiority margin (Δ) of 27-mg oral morphine was selected *a priori*. For the one-sided test of noninferiority over this outcome, the lower boundary of the 95% CI of the mean difference should not cross Δ to declare noninferiority.

As for the area under the curve of rest pain scores in the first 24 h, we first pooled the rest pain scores at each of the designated time points (1, 6, 12, and 24 h) for each arm of the comparisons. The pooled scores were then used to estimate the area under the curve (expressed in cm · h) of rest pain score during the first 24-h postoperatively for each arm; and a mean difference of the area under the curve was calculated for each comparison. This difference in area under the curve was interpreted in light of the minimal clinically important difference[43] in the Visual Analog Scale pain scale for the breast cancer population, 1.1 cm for each time point,[44,45] or 3.3 cm · h for the 24 h period. A Δ of 3.0 cm · h was selected *a priori* for this analysis. For the one-sided test of noninferiority over this outcome, the lower boundary of the 95% CI of the mean difference should not cross Δ to declare noninferiority.

Exploring Heterogeneity

An I^2 statistic was calculated for all outcomes in this review to evaluate for heterogeneity. An I^2 value greater than 50% was considered an indicator of significant heterogeneity in the pooled estimate of effect.[39] If this threshold was obtained for cumulative postoperative oral morphine consumption during the first 24 h (coprimary outcome), we conducted additional metaregression analysis using mixed effects modeling to examine whether the results were influenced by *a priori* specified clinical predictors of treatment effect. We reported R^2 values (coefficient of determination) to quantify the extent to which each covariate explains the variability of data. The value of $R^2 = 1$ means that the covariate explains all the variability, whereas an $R^2 = 0$ means that the covariate does not explain any of the variability. This analysis was performed only if each subgroup within a covariate had at least two trials. The following covariates we considered for our metaregression analysis: (1) invasiveness of surgery (mastectomy *vs.* mastectomy with sentinel node biopsy *vs.* mastectomy with axillary dissection; (2) localization technique (ultrasound *vs.* ultrasound and nerve-stimulator combined)[46]; (3) short-acting (lidocaine and mepivacaine) *versus* intermediate/long-acting (bupivacaine, levobupivacaine, and ropivacaine) local anesthetics[47]; (4) dose of local anesthetic used (converted to mg of bupivacaine); (5) postoperative analgesic modality (multimodal, inclusive of opioid and other adjuvants *vs.* opioid-based)[48,49]; and (6) the addition of adjuvants that can prolong analgesic or block duration (*e.g.*, epinephrine, dexamethasone, or dexmedetomidine).[50,51] For each covariate, a coefficient of determination (R^2) was calculated. This coefficient ranges between 0 to 1, where a value of 0 means that 0% of the model is explained by the covariate, and a value of 1 means that 100% of the model is explained by the covariate.[52] Sensitivity analysis was performed through the sequential exclusion of studies with the above covariates in situations where metaregression analysis could not be performed (*i.e.*, fewer than two trials available for a specific covariate). Further sensitivity analysis was planned to examine the effect of excluding studies that were (1) published in nonindexed journals; (2) available as abstracts; and (3) had a high-risk of bias in one or more domains of the Cochrane risk of bias assessment tool.

Assessment of Publication Bias

The risk of publication bias was assessed using the Egger's Regression test,[53] and also by visual inspection of a funnel plot. An inverted, symmetrically shaped funnel is indicative of low risk of publication bias.[39]

Data Management

Review Manager Software (RevMan version 5.2; Nordic Cochrane Center, Cochrane Collaboration) was used to create all forest and funnel plots for this review. Meta-regression was performed using Comprehensive Meta-Analysis 3.0 (Engelwood, USA). Agreement between the reviewers, as assessed through the un-weighted κ, was calculated using SPSS software (version 24.0; SPSS Inc., USA).

Results

Our search strategy identified 292 unique citations. Searching international conference proceedings yielded an additional six potentially eligible abstracts. Of these, 275 were excluded based on title and abstract screening, because of incorrect intervention (n = 22), irrelevant comparator (n = 29), or for not being a randomized controlled trial (n = 224). The remaining 23 potentially eligible citations had their full-text versions reviewed. Of these, six were excluded for the following reasons: different population (cosmetic breast augmentation surgery, n = 2),[26,54] incorrect intervention (Pectoralis-I[55] or Pectoralis-II combined with Serratus anterior plane[25] block, n = 2), and irrelevant comparator (thoracic spinal anesthesia[56] or local anesthetic infusion,[57] n = 2). Correspondence with the authors of completed and ongoing trials found in clinical trial registries did not yield any additional studies. Three abstracts were also excluded as they were never published as full manuscripts,[58–60] with no further data were available from authors. Thus a total of 14 randomized controlled trials were included in this systematic review and meta-analysis,[2,3,10,13,15,16,22,23,61–66] including 12 full-text manuscripts,[2,3,10,13,15,16,22,61–65] and abstracts of two studies where full data and/or manuscripts under review were provided by the authors.[23,66] None of the included studies was a quasi-randomized trial. The unweighted κ for agreement on full-text eligibility between the two independent reviewers was 0.82; and a third reviewer opinion needed for three trials.[16,23,66] Figure 1 depicts the study flow diagram in this review.

Study Characteristics

The characteristics of included studies and outcomes assessed in this review are presented in table 1. The surgical procedures performed in the trials reviewed included modified radical mastectomy in 13 of 14 trials,[2,3,10,13,15,16,22,23,61–66] with additional axillary dissection in three trials,[10,62,63] and additional immediate breast reconstruction in two trials.[23,64] One trial also included patients undergoing partial mastectomy.[19] The 14 randomized controlled trials involved a total of 887 patients, of which 443 received Pectoralis-II block, 102 received paravertebral block, and 342 received general anesthesia alone (Control). Nine studies (684 patients) compared Pectoralis-II to Control, and five studies (203 patients) compared Pectoralis-II to paravertebral block. All 14 studies[2,3,10,13,15,16,19,22,23,61–65] reported pain severity scores in the first 24 h (coprimary outcome), and 14 studies[2,3,10,13,15,16,19,22,23,59,61–64] reported cumulative 24-h analgesic consumption (co-primary outcome). Postoperative pain and analgesic consumption were assessed beyond 24 h in

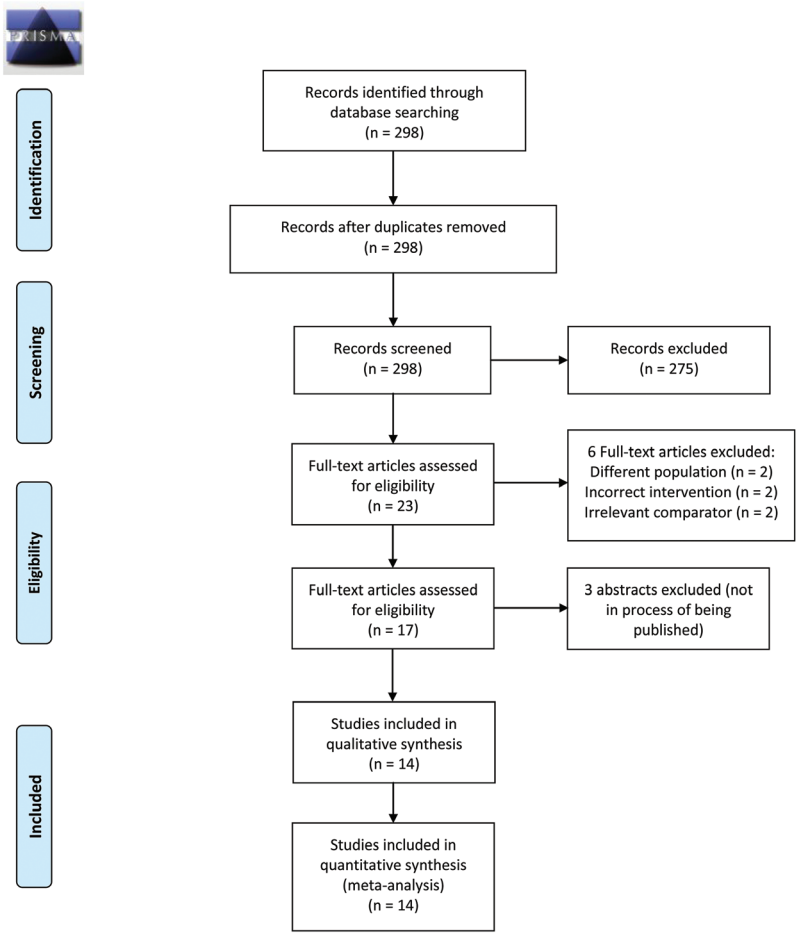

Fig. 1. Study flow diagram for study inclusion.

two studies only,[19,23] whereas long-term outcomes (quality of life or incidence of persistent postsurgical pain) were reported in one study only.[16]

The nerve block techniques and analgesic regimens used in the studies reviewed are presented in table 2. Pectoralis-II block was performed preoperatively in 11 studies,[2,3,10,13,15,16,22,23,61–63] intraoperatively (after the induction of general anesthesia) in two,[19,64] and block timing was not specified in one study.[65] The block technique was explicitly described as two injections (between pectoral major and minor muscles, and between pectoralis minor and serratus anterior muscles) in 12 studies,[2,3,10,13,15,16,19,22,61–64] whereas the remaining studies[23,65] cited Blanco's technique[17] without specifying that two injections were performed. In these two studies, we could not ascertain that two injections were performed, as some practitioners incorrectly refer to the injection between pectoralis minor and serratus anterior muscles as Pectoralis-II block. The level at which the Pectoralis-II block was performed was either T3[10,13,15,16,22,63] or between T3 and T4.[2,3,19,61,62,64] Only two studies[16,63] used adjuvants, dexmedetomidine[16] and epinephrine,[63] that could influence analgesic outcomes. The paravertebral block comparator in the five trials[15,22,23,61,63] comparing Pectoralis-II with paravertebral block involved a single-level single-injection technique performed at the T3[15,23,61] or T4[22,63] level using landmark guidance in one trial,[22] ultrasound-guided transverse in-plane approach in one trial,[15] and ultrasound-guided parasagittal in-plane approach in three trials.[23,61,63]

Risk of Bias Assessment

The risk of bias assessment for each individual study is presented in figure 2. Of the randomized controlled trials included, three[15,23,65] did not provide sufficient information about random sequence generation (unclear risk of detection bias) and six[10,13,15,23,64,65] did not provide sufficient information about allocation concealment (unclear risk of selection bias). Furthermore, nine studies[2,3,10,13,15,22,23,62,65] did not explicitly state that participants and operators performing blocks were blinded (unclear risk of performance bias), whereas one study[64] did not blind anesthesiologists

Table 1. Characteristics of Included Studies

Author/ Year	Surgery	N	Groups (n)	Surgical Anesthetic	Primary Outcome	Rest Pain Scores		Dynamic Pain Scores		Opioid Consumption		Time to First Analgesic Request	Block Success	Opioid-related Adverse Effects	Block-related Complications	Patient Satisfaction	PACU Discharge Time	Hospital Discharge Time	Functional Outcomes	Quality of Life Outcomes	Persistent Postsurgical Pain
						Early	Late	Early	Late	Early	Late										
Pectoralis II *versus* Control																					
Bashandy 2015	MRM	120	1. PECS + GA (60) 2. GA (60)	GA	Pain score at 24 h	•				•		•		•			•	•			
Hassn 2015	MRM	60	1. PECS + GA + Dexmed (30) 2. GA (30)	GA	N/S	•				•		•		•		•		•			•
Kanitkar 2016	MRM	50	1. PECS + GA (25) 2. GA (25)	GA	N/S	•															
Versyck 2017	MRM; Partial Mastectomy; SLNB; ALND	140	1. PECS + GA (70) 2. GA (70)	GA	Peri-operative analgesic consumption and pain score	•	•			•	•					•					
Ahmed 2018	MRM; ALND	90	1. PECS + GA (30) 2. PECS + GA + MgS (30) * 3. GA (30)	GA	N/S	•				•		•		•	•						
Kim 2018	MRM	80	1. PECS + GA (40) 2. GA (40)	GA	Analgesic consumption at 24 h	•				•				•	•						
Kumar 2018	MRM	50	1. PECS + GA (25) 2. GA (25)	GA	Pain score at 1h	•		•		•		•	•	•	•						
Neethu 2018	MRM; ALND	60	1. PECS + GA (30) 2. GA (30)	GA	Analgesic consumption at 24 h	•		•		•				•		•			•		
Wang 2018	MRM ± Immediate reconstruction	64	1. PECS + GA (32) 2. GA (32)	GA	Analgesic consumption at 24 h	•				•				•	•			•	•		
***PECS* II *versus* PVB**																					
Wahba 2014	MRM	60	1. PECS + GA (30) 2. PVB + GA (30)	GA	Analgesic consumption at 24 h	•		•		•		•	•	•	•	•					
Scimia 2016	MRM ± Immediate reconstruction	20	1. PECS + GA (10) 2. PVB + GA (10)	GA	N/S	•	•			•	•				•						
El-Sheikh 2016	MRM	40	1. PECS + GA (20) 2. PVB + GA (20)	GA	N/S	•				•		•		•	•			•			
Kulhari 2017	MRM	40	1. PECS + GA (20) 2. PVB + GA (20)	GA	Time to first analgesic request and analgesic consumption at 24 h	•				•		•	•	•	•						
Syal 2017	MRM; ALND	65	1. PECS + GA + Epi (21) 2. PVB + GA + Epi (22) 3. LA Infusion + GA + Epi (22)*	GA	Pain score up to 24 h	•				•		•			•						

Early was defined as less than 24 h; late was defined as more than 24 h.

*Group excluded from analysis

ALND, axillary lymph node dissection; Dexmed, dexmedetomidine; GA, general anesthesia; h, hour; LA, local anesthesia; MgS, magnesium sulfate; MRM, modified radical mastectomy; N/S, not specified; PACU, postanesthesia care unit; PECS, Pectoralis-II fascial plane block; PVB, paravertebral block; SLNB sentinel lymph node biopsy.

Table 2. Local Anesthetic Techniques for PECS-II and Analgesic Regiments of Included Studies

				PECS II					
Author/Yr	Pre-incisional Analgesia	Surgical Analgesia	Supplemental Postoperative Analgesia	Block Timing	Block technique 1. Injection between Pectoralis Major and Minor 2. Injection between Pectoralis Minor and Serratus Anterior	Level of Block	Localization	Assessment of Block Success	PECS Bolus
PECS II *versus* Control									
Bashandy 2015	1 – 2 mcg/kg IV fentanyl	1 – 2 mcg/kg IV fentanyl	PCA morphine; 1g PO paracetamol TID, 100 mg PO ketoprofen TID	Pre-Op	1, 2	T3	USG	N/S	30 mL 0.25% Bupivacaine
Hassn 2015	None	0.5 mcg/kg IV fentanyl	0.05 mg IV morphine; PO ketorolac for prn; 30mg IV ketorolac prn	Pre-Op	1, 2	T3	USG	N/S	30 mL 0.5% Bupivacaine + 1 mcg/kg Dexmed
Kanitkar 2016	N/S	N/S	N/S	N/S	N/S	N/S	N/S	N/S	N/S
Versyck 2017	5 mcg IV sufentanil	5 mcg IV sufentanil	15 mg/kg IV acetaminophen q6h; 200 mg IV tramadol prn; 1 mg IV piritramide q5min prn	Intra-Op	1, 2	T3, T4	USG	N/S	30 mL 0.25% Levobupivacaine
Ahmed 2018	1 mcg/kg IV fentanyl	1 mcg/kg IV fentanyl	50 mg IV pethidine	Pre-Op	1, 2	T3	USG	Y	28 mL 0.25% Bupivacaine +/- MgS
Kim 2018	0.6 mg/kg IV remifentanil	2 – 2.5 ng/ml remifentanil	IV fentanyl; 30mg Ketorolac; 25 mg meperidine prn; 50 mg tramadol prn	Pre-Op	1, 2	T3, T4	USG	N/S	30 mL 0.25% Ropivacaine
Kumar 2018	2 mcg/kg IV fentanyl	0.25 mcg/kg IV fentanyl	1 g IV paracetamol q8h; 2 mg/kg IV tramadol prn	Pre-Op	1, 2	T3, T4	USG	Y	30 mL 0.25% Bupivacaine
Neethu 2018	1 mcg/kg IV fentanyl	0.5 mcg/kg IV fentanyl	PCA fentanyl; 1 g IV paracetamol prn	Pre-Op	1, 2	T3, T4	USG	N	30 mL 0.25% Ropivacaine
Wang 2018	IV fentanyl	IV fentanyl	2 mg IV morphine q5min prn	Intra-Op	1, 2	T3, T4	USG	N/S	30 mL 0.5% Ropivacaine
PECS II *versus* PVB									
Wahba 2014	1 mcg/kg IV fentanyl	25 mcg IV fentanyl	PCA morphine	Pre-Op	1, 2	T3	USG	Y	10 mL 0.25% Levobupivacaine; 20 mL 0.25% Bupivacaine
Scimia 2016	N/S	N/S	IV morphine	Pre-Op	N/S	N/S	USG	N/S	N/S
El-Sheikh 2016	1-2 mcg/kg IV fentanyl	0.5 – 1 mcg/kg IV fentanyl	3 mg IV morphine prn	Pre-Op	1, 2	T3	USG	N/S	30 mL N/S concentration of LA
Kulhari 2017	1 mcg/kg IV fentanyl	1 mcg/kg IV fentanyl	PCA morphine	Pre-Op	1, 2	T3, T4	USG	Y	25 mL 0.5% Ropivacaine
Syal 2017	75 mg IV diclofenac; 2 mcg/kg IV fentanyl	2 mcg/kg IV fentanyl	75 mg IV diclofenac q8h prn; 1 mcg/kg IV fentanyl once	Pre-Op	1, 2	T3	USG	N/S	30 mL 0.5% Bupivacaine + Epi

Dexmed, dexmedetomidine; Epi, epinephrine; h, hour; Intra-Op, intraoperative; IV, intravenous; LA, local anesthesia; mcg, microgram; min, minute; mL, milliliter; MgS, magnesium sulfate; N, No; n, nanogram; N/A, not applicable; N/S, not specified; N-Stim, nerve stimulator; PCA, patient-controlled analgesia; PECS, pectoralis-II fascial plane block; prn, as needed; Pre-Op, preoperative; PVB, paravertebral block; q, every; USG, ultrasound guidance; Y, yes.

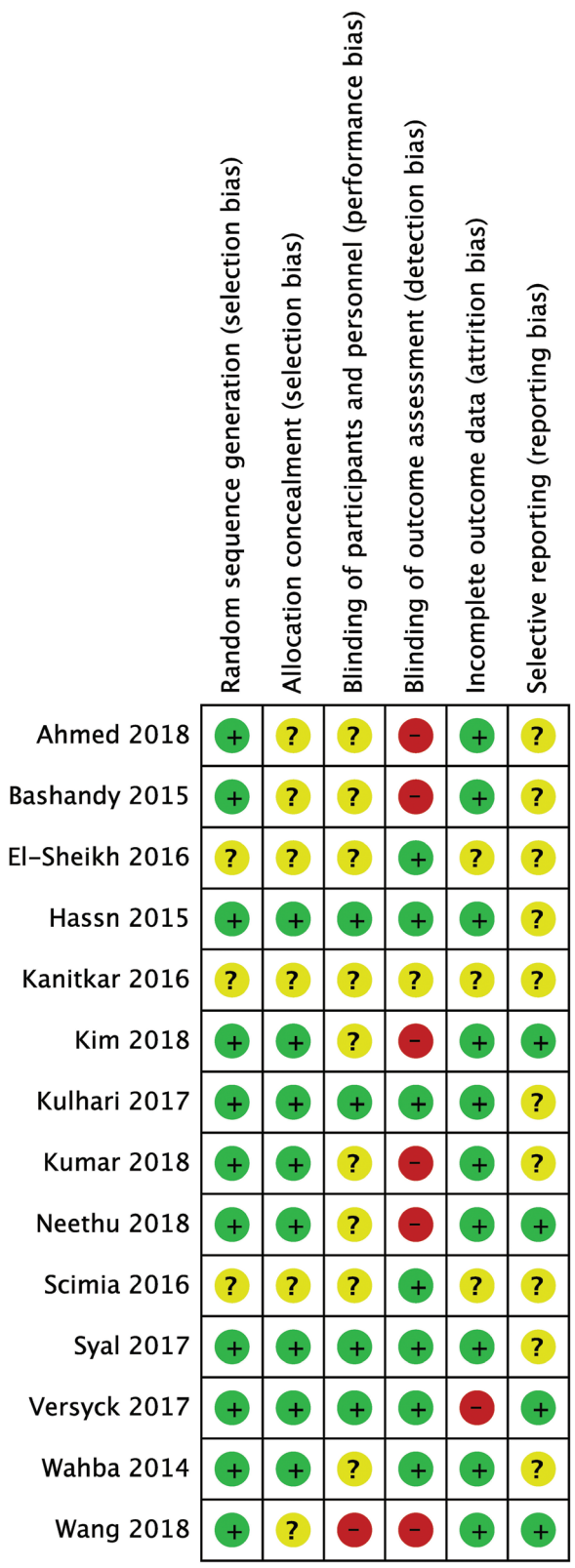

Fig. 2. The Cochrane risk of bias assessment for included studies.

performing Pectoralis-II (high risk of performance bias). One study[65] did not provide sufficient details regarding the sham blocks used (unclear risk of detection bias), and another six[2,3,10,13,62,64] did not use sham blocks at all (high risk of detection bias). Three studies[15,23,65] did not provide sufficient details to assess patient loss (unclear risk of attrition bias), whereas another study[19] had less than 20% loss and did not conduct any *post hoc* analysis (high risk of attrition bias). Finally, only four studies[2,19,62,64] were preregistered with clinical trial registries; thus, all other studies were assigned an unclear risk of reporting bias.

Primary Outcomes

Cumulative 24-h Oral Morphine Equivalent Consumption. For Pectoralis-II *versus* Control, all eight studies[2,3,10,13,16,19,62,65] (575 patients; Pectoralis II: 290, Control: 285) that reported cumulative 24-h oral morphine consumption provided sufficient reporting to allow for statistical pooling. Overall, Pectoralis-II block significantly reduced the cumulative 24-h oral morphine consumption by a mean difference [95% CI] of 30.5 mg [−42.2, −18.8], ($P < 0.00001$, $I^2 = 98\%$) compared with Control. Based on an minimal clinically important difference of 30 mg of oral morphine, this difference met the threshold of clinical importance, and the mean difference was not different from the minimal clinically important difference ($P = 0.951$). This outcome was characterized by high heterogeneity, and metaregression analysis performed to explore the sources of heterogeneity using predefined covariates suggested that cumulative 24-h oral morphine consumption was independent of (1) invasiveness of surgery (mastectomy *vs.* mastectomy with sentinel node biopsy *vs.* mastectomy with axillary dissection; $R^2 = 0.00$, $P = 0.532$); (2) localization technique (ultrasound alone *vs.* ultrasound and nerve-stimulator to elicit a pectoral twitch; $R^2 = 0.00$, $P = 0.072$); (3) postoperative analgesic modality (multimodal, inclusive of opioid and other adjuvants *vs.* opioid-based; $R^2 = 0.00$, $P = 0.194$); and (4) dose of local anesthetic used ($R^2 = 0.00$, $P = 0.942$). Metaregression was not performed on the type of local anesthetic as all studies[2,3,10,13,16,19,62,64] used intermediate/long acting formulations. Furthermore, for covariates where fewer than two trials were available (use of adjuncts),[16] the results were robust to sensitivity analysis. Additionally, the direction and magnitude of treatment effect did not change with additional sensitivity analysis when studies that were (1) published in nonindexed journals[16] and (2) had a high risk of bias in one or more domains of the Cochrane risk of bias assessment tool,[2,3,10,13,19,62,64] were excluded from analysis. Sensitivity analysis was not performed on excluding studies available as abstracts, because all studies included in this comparison were published in full-text.[2,3,10,13,16,19,62,64] The risk of publication bias was low for this comparison ($P = 0.181$), and the quality of evidence, as assessed by Grades of Recommendation, Assessment, Development, and Evaluation guidelines, was moderate because of the risk of detection bias and heterogeneity in the pooled estimate.

For Pectoralis-II *versus* paravertebral block, cumulative 24-h oral morphine consumption data were reported and pooled from five studies[15,22,23,61,63] (200 patients; Pectoralis-II: 100, paravertebral block: 100). Overall, Pectoralis-II was not different from paravertebral block for cumulative 24-h oral morphine consumption, with a mean difference [95% CI] of −6.2 mg [−13.3, 0.8] ($P = 0.083$, $I^2 = 86\%$). Metaregression analysis could not be performed for this outcome as less than two trials were available in the prespecified covariates. We performed sensitivity analysis by excluding the single study[22] that did not use ultrasound guidance, but this did not change the significance of the primary results. However, sensitivity analysis by excluding the study that used multimodal analgesia[63] and the study that included patients having axillary dissection[63] altered the magnitude of effect to significantly favoring Pectoralis-II by 9.8 mg [−17.6, −1.9] ($P = 0.020$, $I^2 = 79\%$); nonetheless, this difference was not clinically important (*i.e.*, different from the minimal clinically important difference of 30 mg, $P = 0.004$). This suggests that Pectoralis-II may be marginally superior to paravertebral block for axillary interventions limited to sentinel node biopsy. Intermediate/long-acting local anesthetics were used in all trials; thus, sensitivity analysis was not performed for this covariate.[15,22,23,61,63] Additionally, the direction and magnitude of treatment effect did not change with additional sensitivity analysis when studies that were (1) published in nonindexed journals[15,22] and (2) available as abstracts[23] were excluded from analysis. Sensitivity analysis was not performed on excluding studies based on having high risk of bias because none of studies included in this comparison met this criterion. The risk of publication bias was low for the Pectoralis-II *versus* paravertebral block ($P = 0.663$) comparison, and the quality of evidence was low because of imprecision and heterogeneity in the pooled estimate.

Area under the Curve for Pain Severity at Rest. The area under the curve of rest pain over the first 24 h for each arm examined was used to estimate the mean difference in area under the curve for each of the two comparisons of interest.

For Pectoralis-II *versus* Control, the number of patients included at the 1-h comparison was 438 (Pectoralis-II: 245, Control: 243), and 538 (Pectoralis-II: 270, Control: 268) at the 6, 12, and 24-h comparisons. The mean difference in area under the curve for the pooled rest pain scores (Pectoralis-II − Control) favored the Pectoralis-II block by −4.7 cm · h [−5.1, -4.2] (fig. 3), or −1.2 cm [−1.3, −1.1] per measurement. The absolute value of this difference was significantly greater than ($P < 0.0001$) the minimal clinically important difference in area under the curve for 24 h (3.3 cm · h), exceeding the threshold of clinical importance and confirming that Pectoralis-II provides superior rest pain control during the first 24 h postoperatively, compared with Control.

For Pectoralis-II *versus* paravertebral block, the number patients included at each time point was 203 (Pectoralis-II: 101, paravertebral block: 102), 228 (Pectoralis-II: 116, paravertebral block: 112), 163 (Pectoralis-II: 81, paravertebral block: 82), and 203 (Pectoralis-II: 101, paravertebral block: 102) at 1, 6, 12, and 24 h, respectively. The mean difference in area under the curve for the pooled rest pain scores

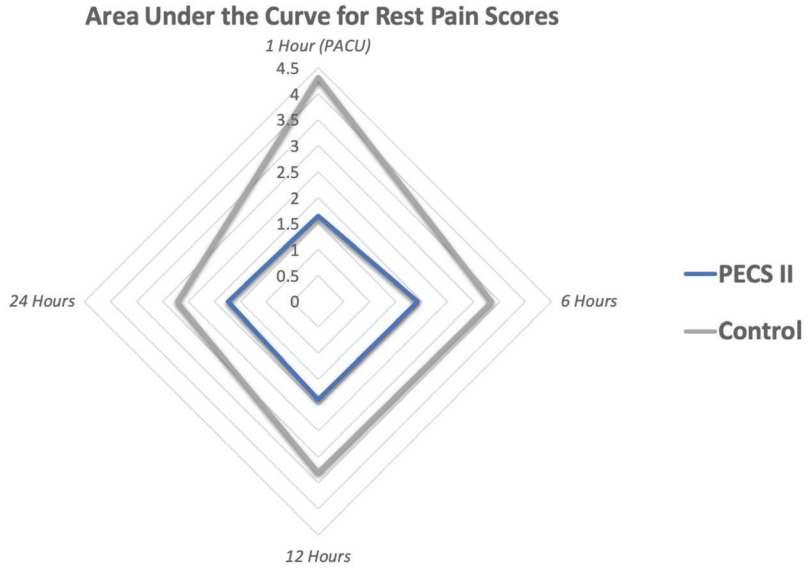

Fig. 3. Graphical representation (star plot) of the area under the curve of the pooled weighted mean pain scores at rest as measured by the visual analog scale (0–10 cm) over time (four time points) for each of Pectoralis II (PECS II) and Control (systemic analgesia). The axes depict pain scores at different time points. PACU, postanesthesia care unit.

(Pectoralis-II – paravertebral block) favored the Pectoralis-II block by −1.5 cm · h [−2.2, −0.8] (fig. 4), or −0.4 cm [−0.6, −0.2] per measurement. However, the absolute value of this difference was less than ($P < 0.0001$) the minimal clinically important difference area under the curve for 24 h (−3.3 cm · h).

Comparing Pectoralis-II and Paravertebral Block for Noninferiority

The mean difference between Pectoralis-II and paravertebral block in cumulative 24-h oral morphine consumption was −6.2 mg [−13.3, 0.8]; and the lower boundary of the 95% CI was significantly greater ($P = 0.002$) than the designated Δ (−27 mg), suggesting that Pectoralis-II is not statically or clinically worse than paravertebral block. Furthermore, the mean difference between Pectoralis-II and paravertebral block in area under the curve of rest pain scores over the first 24 h postoperatively was −1.5 cm · h [−2.2, −0.8], and both upper and lower boundaries of the 95% CI lied between zero and the designated Δ (−3.0 cm · h), suggesting that Pectoralis-II is not clinically worse than paravertebral block. These two comparisons suggest that Pectoralis-II is most likely not clinically worse than paravertebral block for analgesic outcomes during the first 24 h following breast cancer surgery.

Short-term Secondary Outcomes

Rest Pain Severity Scores at Individual Time Points. Compared with Control, Pectoralis-II improved pain control at 1, 6, 12, and 24 h postoperatively, by a mean difference [99% CI] equivalent to 2.5 cm [−3.5, −1.5] ($P < 0.00001$, $I^2 = 95\%$), 1.5 cm [−2.3, −0.7] ($P < 0.00001$, $I^2 = 93\%$), 1.4 cm [−2.3, −0.5] ($P = 0.0001$, $I^2 = 96\%$), and 0.9 cm [−1.8, −0.1] ($P = 0.006$, $I^2 = 97\%$), respectively (table 3). The risk of publication bias was low at 1- ($P = 0.251$), 6- ($P = 0.150$), 12- ($P = 0.093$), and 24-h ($P = 0.162$) assessments, and the quality of evidence was moderate for all time points due to the risk of detection bias and heterogeneity in the pooled estimate.

Compared with paravertebral block, Pectoralis-II improved pain control at 1 and 6 h postoperatively, by a mean difference [99% CI] equivalent to 1.1 cm [−1.5, −0.6] ($P < 0.00001$, $I^2 = 0\%$), and 0.7 cm [−1.3, −0.1] ($P = 0.002$, $I^2 = 37\%$), respectively. There were no differences in rest pain scores between the Pectoralis-II and paravertebral block groups at 12 and 24 h (table 3). The risk of publication bias was low at 1- ($P = 0.962$), 6- ($P = 0.932$), 12- ($P = 0.900$), and 24-h ($P = 0.553$) assessments, and the quality of evidence was low at all time points because of heterogeneity and imprecision in the pooled estimate.

Time to First Analgesic Request. For Pectoralis-II *versus* Control, the time to first analgesic request was assessed by four studies[3,10,13,62] (270 patients; Pectoralis-II: 125, Control: 145). Compared with Control, patients receiving Pectoralis-II block had a longer time to first analgesic request, by 5.02 h [2.55, 7.49] ($P < 0.00001$, $I^2 = 100\%$; table 3). The risk of publication bias was low for this comparison ($P = 0.120$), and the quality of evidence was low because of imprecision, heterogeneity, and a risk for detection bias in the pooled estimate.

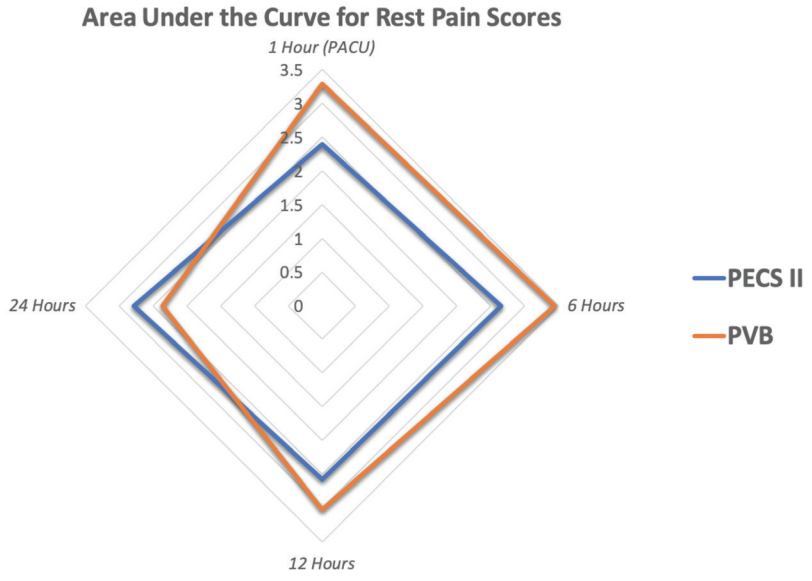

Fig. 4. Graphical representation (star plot) of the area under the curve of the pooled weighted mean pain scores at rest as measured by the visual analog scale (0–10 cm) over time (four time points) for each of Pectoralis-II (PECS II) and paravertebral block (PVB). The axes depict pain scores at different time points. PACU, postanesthesia care unit.

Table 3. Secondary Endpoint Results

Outcome	Studies Included	PECS II, Mean ± SD or n/N	Control or PVB, Mean ± SD or n/N	Mean Difference or Odds ratio (99% Confidence Interval)	*P* Value for Statistical Significance	*P* Value for Heterogeneity	I^2 Test for Heterogeneity	Quality of Evidence (GRADE)
PECS II *versus* Control								
Rest pain at 1 h (PACU) (cm)	7	1.64 ± 1.24	4.32 ± 1.63	-2.5 (-3.5 to -1.5)	< 0.00001	< 0.00001	95%	⊕⊕⊕⊖, Moderate
Rest pain at 6 h (cm)	8	1.92 ± 1.18	3.35 ± 1.75	-1.5 (-2.3 to -0.7)	< 0.00001	< 0.00001	93%	⊕⊕⊕⊖, Moderate
Rest pain at 12 h (cm)	8	1.90 ± 1.26	3.30 ± 1.69	-1.4 (-2.3 to -0.5)	0.0001	< 0.00001	96%	⊕⊕⊕⊖, Moderate
Rest pain at 24 h (cm)	8	1.74 ± 1.37	2.71 ± 1.69	-0.9 (-1.8 to -0.1)	0.006	< 0.00001	97%	⊕⊕⊕⊖, Moderate
Rest pain at 36 h (cm)*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Rest pain at 48 h (cm)*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Oral morphine consumption at 2 h (PACU) (mg)*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Oral morphine consumption at 24–48 h (mg)*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Time to analgesic request (h)	4	3.53 ± 3.50	1.83 ± 0.90	5.02 (2.55 to 7.49)	< 0.00001	< 0.00001	100%	⊕⊕⊕⊖, Moderate
Opioid-related side effects	6	35/185	62/185	0.3 (0.1 to 1.4)	0.050	0.022	67%	⊕⊕⊖⊖, Low
Block-related Complications	4	0/127	0/127	N/A	1.010	N/A	N/A	N/A
Patient satisfaction*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hospital discharge*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Chronic pain incidence*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Analgesic dependence after hospital discharge*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Functional outcomes*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Quality of life/quality of recovery*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PECS II *versus* PVB								
Rest pain at 1 h (PACU) (cm)	5	2.39 ± 1.33	3.29 ± 1.68	-1.1 (-1.5 to -0.6)	< 0.00001	0.513	0%	⊕⊕⊖⊖, Low
Rest pain at 6 h (cm)	4	2.65 ± 1.45	3.45 ± 1.84	-0.7 (-1.3 to -0.1)	0.002	0.192	37%	⊕⊕⊖⊖, Low
Rest pain at 12 h (cm)	4	2.57 ± 1.42	3.02 ± 1.42	-0.4 (-2.1 to 1.2)	0.511	< 0.00001	93%	⊕⊕⊖⊖, Low
Rest pain at 24 h (cm)	5	2.78 ± 1.79	2.36 ± 1.36	0.3 (-1.7 to 2.2)	0.743	< 0.00001	94%	⊕⊕⊖⊖, Low
Rest pain at 36 h (cm)*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Rest pain at 48 h (cm)*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Oral morphine consumption at 2 h (PACU) (mg)*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Oral morphine consumption at 24–48 h (mg)*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Time to analgesic request (h)	4	4.83 ± 2.92	5.09 ± 3.72	-0.32 (-2.70 to 2.05)	0.733	< 0.00001	97%	⊕⊕⊖⊖, Low
Opioid-related side effects	3	17/70	18/70	0.9 (0.3 to 3.1)	0.811	0.930	0%	⊕⊕⊖⊖, Low
Block-related complications	4	0/91	2/92	0.2 (0.0 to 10.6)	0.282	N/A	N/A	⊕⊕⊖⊖, Low
Patient satisfaction*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hospital discharge*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Chronic pain incidence*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Analgesic dependence after hospital discharge*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Functional outcomes*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Quality of life/quality of recovery*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

*Outcome reported by less than 3 studies or was not measured.

cm, centimeter; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; mg, milligrams; N/A, not applicable; PACU, postanesthesia care unit; PECS, pectoralis-II fascial plane block; PVB, paravertebral.

For Pectoralis-II *versus* paravertebral block, the time to first analgesic request was assessed by four studies[15,22,61,63] (183 patients; Pectoralis: 91, paravertebral block: 92). We found no difference between the Pectoralis-II and paravertebral block groups in the time to first analgesic request (table 3). The risk of publication bias was low for this comparison ($P = 0.652$), and the quality of evidence was low because of imprecision and heterogeneity in the pooled estimate.

Oral Morphine Consumption at 2 h (Postanesthesia Care Unit). Oral morphine consumption at 2 h (postanesthesia care unit stay) was assessed in one study comparing Pectoralis-II and Control,[19] and another comparing Pectoralis-II and paravertebral block.[23] Qualitatively, there were no differences in any of the comparisons for this outcome.

Oral Morphine Consumption during the 24- to 48-h Interval. Oral morphine consumption during the 24- to 48-h interval postoperatively was assessed by one study comparing Pectoralis-II and Control,[19] and another comparing Pectoralis-II and paravertebral block.[23] Qualitatively, there were no differences in any of the comparisons for this outcome.

Block Success. Assessment of sensory block onset was performed in three studies, two of which compared Pectoralis-II with paravertebral block[22,61] and one compared Pectoralis-II with Control.[3] Block success was reported for all of the Pectoralis-II and paravertebral block blocks performed in these studies.

Opioid-related Side Effects. For Pectoralis-II *versus* Control, six trials examined the risk of opioid-related side effects.[2,3,10,16,62,64] There were no differences between these two groups for this outcome (table 3). The risk of publication bias was low for this comparison ($P = 0.292$), and the quality of evidence was low because of heterogeneity and risk of detection bias in the pooled estimate.

For Pectoralis-II *versus* paravertebral block, three trials examined the risk of opioid-related side effects.[15,22,61] There were no differences between these two groups for this outcome (table 3). The risk of publication bias was low for this comparison ($P = 0.384$), and the quality of evidence was low because of imprecision in the pooled estimate.

Block-related Complications. For the Pectoralis-II *versus* Control, four studies[2,3,10,64] evaluated block-related complications. None of the patients involved in this comparison experienced any complications.

For Pectoralis-II *versus* paravertebral block, five studies[15,22,23,61,63] evaluated block-related complications. Although none of the patients in the Pectoralis-II group developed any block-related complications (pneumothorax, vascular puncture/hematoma, neuraxial spread, and local anesthetic systemic toxicity), two patients in the paravertebral block group developed a pneumothorax.[15] This difference did not reach statistical significance (table 3). Publication bias was not assessed for this outcome as complications occurred in one study only,[15] and the quality of evidence was low because of imprecision in the pooled estimate.

Quality of Recovery. None of the included studies assessed this outcome.

Long-term Secondary Outcomes

Incidence of Chronic Postsurgical Pain. Only one study comparing Pectoralis-II with Control assessed the incidence of chronic postsurgical pain at the 3- and 6-month postsurgery follow-ups.[16] Qualitatively, there were no difference in the risk of developing chronic postsurgical pain at three ($P = 0.160$) or six months ($P = 0.041$, adjusted threshold = 0.010) between the Pectoralis-II group (6 of 30 and 8 of 30 patients at 3 and 6 months, respectively) and the Control group (11 of 30 and 16 of 30 patients at 3 and 6 months, respectively).

Opioid Dependence. None of the included studies assessed long-term opioid dependence. Only one study comparing Pectoralis-II with Control assessed the need for analgesics at 2 weeks postsurgery.[16] Qualitatively, fewer patients ($P = 0.003$) in the Pectoralis-II group (9 of 30 patients) required analgesic at 2 weeks compared with the Control group (21 of 30 patients).

Quality of Life. None of the included studies assessed this outcome.

Level of Disability after Discharge. None of the included studies assessed this outcome.

Discussion

Our systematic review and meta-analysis is the first to demonstrate the absolute analgesic benefits of Pectoralis-II following breast cancer surgery, and to demonstrate the clinical utility of Pectoralis-II as an analgesic alternative to paravertebral block. Specifically, for analgesic consumption and area under the curve of rest pain scores during the first 24 h postoperatively, we found Pectoralis-II to be superior to Control by clinically important differences. Additionally, Pectoralis-II was noninferior and not clinically worse than paravertebral block for analgesic consumption and area under the curve of rest pain, respectively. Furthermore, there were no differences between the two techniques for all analgesic outcomes examined (time to first analgesic request, opioid-related side effects). These results support the analgesic utility of Pectoralis-II block in women having breast cancer surgery, as well as its use as a paravertebral block alternative in this population.

Ultrasound-guided anatomical descriptions of the Pectoralis-II block are consistent with our results. The Pectoralis-II block is associated with wide local anesthetic spread that blocks the T2–T5 dermatomes (*i.e.*, most of the breast tissue), a spread difficult to achieve with a single-injection paravertebral block.[27,66] Furthermore, by blocking the long thoracic, thoracodorsal, and medial and lateral pectoral, which are spared by the paravertebral block,[61]

Pectoralis-II theoretically provides effective analgesia to the axilla. Indeed, our review has provided novel evidence supporting the above anatomical hypothesis: we have observed that Pectoralis-II seemed to provide pain control that is superior to paravertebral block over the first 6 h postoperatively, but this difference is muted when the overall pain experience is evaluated using an area under the curve of pain more than 24 h. This observation can interpreted in the context of the nature of the surgical procedures examined, namely breast tumor resection inclusive of axillary interventions.[15,22,23,61,63] The unpooled data from the individual studies also corroborate this explanation; patients who received Pectoralis-II block had better control of pain localized to the axilla.[19,61] Therefore, it is important to confine the conclusion to the specific settings where the comparisons were conducted. Pectoralis-II is not clinically worse (noninferior) for analgesic outcomes to single-injection paravertebral block in patients having breast surgery procedures involving the axilla. Importantly, Pectoralis-II block enjoys several technical and clinical features that influence its desirability and acceptability by practitioners. As a superficial block targeting the fascial planes between thoracic wall muscles, Pectoralis-II is considered to be technically simpler and faster to perform compared to paravertebral block.[61,64] It is also believed to be associated with lower risks of local anesthetic systemic toxicity and pleural puncture,[61] and, if needed, could be performed after induction of general anesthesia.[19,64] These benefits of Pectoralis-II have made it an increasingly popular block, as evidenced by the publication of more than 26 studies[2,3,10,13,15,16,19,22,25,54,56,57,61–64,67–76] examining this block since its initial description in 2012.[27]

In contrast, there may be several safety and technical reasons why an effective paravertebral block alternative is desirable. From a safety perspective, success and quality of the paravertebral block depends on the levels of practitioner skill and experience,[12] which need to be high because of the paravertebral space proximity to the parietal pleura, intercostal nerves, neuraxis,[77–79] and major vessels (azygous vein and the descending aorta).[12,78] Conceivably, the risks of vascular puncture, neuraxial spread with symptomatic hypotension, and pleural puncture are not insignificant, and can be up to 5.4%, 4.6%,[67,78–80] and 1.1%,[80] respectively. Technically, dermatomal spread of single-level paravertebral block is unpredictable,[81] necessitating multiple paravertebral blocks,[7] with clear implications to risks, procedure time, and pain. Furthermore, the failure rate of paravertebral block is 5.6%[12] and is likely higher in obese patients.[82] Concerns regarding local anesthetic systemic toxicity have also been reported with bilateral paravertebral block;[83,84] and, owing to its depth, paravertebral block is also contraindicated in anticoagulated patients.[85] Not surprisingly, there has been an ongoing quest to identify simpler and safer paravertebral block alternatives to increase the acceptability of regional anesthesia for breast cancer surgery. To that end, all of the recently described fascial plane blocks, including erector spinae plane block,[86,87] retrolaminar block,[88,89] paraspinal block,[90] and the midpoint transverse process to pleura block[91] target more superficial endpoints that are outside the paravertebral space. However, unlike Pectoralis-II, these blocks currently lack supporting clinical evidence.

To present a balanced discussion, it is important to highlight the benefits of paravertebral block that were not examined in the trials reviewed, and where paravertebral block may continue to be advantageous (*i.e.*, superior), compared with the Pectoralis-II block. To start, paravertebral block is unique in its ability to provide surgical anesthesia,[5,92] whereas this has not been demonstrated yet with Pectoralis-II. Additionally, even for postoperative analgesia, the comparisons herein were conducted against single-level paravertebral block;[15,22,23,61,63] and conclusions are not necessarily generalizable to paravertebral block techniques involving injection at multiple thoracic levels. Another important advantage specific to paravertebral block but not Pectoralis-II is its combined somatic and sympathetic blockade of innervation to the breast, which may explain its prolonged analgesic effect lasting more than 48 h,[93–95] its impact on quality of recovery after surgery,[5] and its protective effect against chronic postsurgical pain.[96] Other technical advantages include the ability to administer paravertebral block in the absence of ultrasound equipment or relevant training, based on anatomical landmarks.[97,98] Additionally, patients who have had prior breast surgery or radiotherapy remain amenable to the paravertebral block; in contrast, Pectoralis-II block may not be feasible because of disruption of anatomical planes. Certain surgeons may also object to Pectoralis-II block, as it disrupts anatomical planes in the axilla and causes tissue edema, precluding effective use of cautery.[99] Finally, despite its anecdotal nature, evidence of improved survival with paravertebral block should also be considered.[100]

Our systematic review and meta-analysis has several notable strengths. First, our comprehensive search strategy that was limited to randomized controlled trials and incorporated non-English studies was able to identify a large number of full-text trials[2,3,10,13,15,16,19,22,61–64] and several relevant published abstracts.[23,58–60,66] Second, our assessment of the risk of performance and detection biases was conservative. Third, our review successfully pooled analgesic and pain data from a large number of trials on the topic and generated a moderate level of evidence supporting the analgesic role of the Pectoralis-II block for breast cancer surgery. Fourth, we used conservative thresholds of statistical significance and 99% CI for our secondary outcomes to reduce the risk of type-I error. Fifth, most of the trials were similar in regards to examining major breast cancer surgeries known to be associated with moderate-to-severe pain.[101] Sixth, our use of area under the curve analysis captured analgesic-time variation in the Pectoralis-II block in comparison to paravertebral block and Control, despite the limited number of observations available (four) and the

unequal distances between some observations. Using pain as one of two primary outcomes also partially adheres to the consensus definitions for the Standardized Endpoints in Perioperative Medicine initiative.[102] Finally, a *post hoc* power analysis performed to check whether the noninferiority comparisons had sufficient power revealed that 36 and 37 patients per group are needed to test for noninferiority over opioid consumption and area under the curve, respectively (with a significance level of 0.025, 90% power, zero allowable difference, and variances of 1,521 for opioid consumption and 15.5 for area under the curve). The sample size available (Pectoralis: 101, paravertebral block: 102) provided more than 99% power for the one-sided tests of noninferiority.

Our review also has several limitations. First, some outcomes were characterized by high levels of heterogeneity that was not resolved by metaregression or sensitivity analysis. Reasons for this may have been attributable to subtle variation in surgical technique and differences in anesthetic and analgesic regimens. Second, many of the included studies had small sample sizes, which decreases their effect and limits external validity. Third, given the limited evidence on other novel fascial plane blocks,[86–91] our focus was limited to only Pectoralis-II block in the specific clinical setting examined. Fourth, very few trials assessed sensory block onset,[3,22,61] precluding any conclusion on block success. Inconsistent reporting also precluded evaluating dynamic pain[3,22,62] and long-term outcomes (quality of life, disability), as included trials did not follow patients longitudinally. Prognosis and psychologic factors were also not reported in the source trials, impeding the evaluation of the impact[103] of these factors on pain and other analgesic outcomes. Fifth, all studies examined involved axillary interventions, thus pain originating from the axilla may have been a factor in favoring one intervention over the other. Sixth, this review did not include local infiltration, a technique that is gaining popularity, whether on its own or in combination with other blocks. Seventh, this review was unable to inform the incidence rate of rare events, such as serious complications; examining rare events requires much bigger sample sizes. Finally, Pectoralis-II is not necessarily complication-free[61] as our review did not have sufficient power to detect uncommon outcomes.[104] Similarly, our noninferiority analysis was a secondary objective and thus may not have been adequately powered.

Conclusions

In conclusion, Pectoralis-II is a beneficial analgesic technique that is clinically superior to Control, and not clinically worse than paravertebral block during the first 24 h after breast cancer surgery. These results encourage the incorporation of the Pectoralis-II block into a multimodal pain control strategy, as well its use as a paravertebral block alternative following breast tumor resection.

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Competing Interests

The authors declare no competing interests.

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