Journal of Clinical Anesthesia 63 (2020) 109744

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

journal homepage: www.elsevier.com/locate/jclinane

Analgesic efficacy of PECS and serratus plane blocks after breast surgery: A systematic review, meta-analysis and trial sequential analysis☆

Sina Grape[a], Eric Jaunin[a], Kariem El-Boghdadly[b,c], Vincent Chan[d], Eric Albrecht[e,*]

[a] Department of Anaesthesia, Valais Hospital, Sion, Switzerland
[b] Department of Anaesthesia, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom
[c] King's College London, London, United Kingdom
[d] Department of Anaesthesia, Toronto Western Hospital and University of Toronto, Toronto, Canada
[e] Department of Anaesthesia, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

ARTICLE INFO

Keywords:
Analgesia
Postoperative pain
Breast surgery
Peripheral nerve block

ABSTRACT

Study objective: To determine whether pectoral nerves (PECS) blocks provide effective postoperative analgesia when compared with no regional technique in patients undergoing breast surgery.
Design: Systematic review, meta-analysis and trial sequential analysis.
Setting: Operating room, postoperative recovery area and ward, up to 24 postoperative hours.
Patients: Patients undergoing breast surgery under general anaesthesia with either PECS block or no regional technique.
Interventions: We searched five electronic databases for randomized controlled trials comparing PECS block with no block or sham injection.
Measurements: The primary outcome was rest pain scores (analogue scale, 0–10) at 2 h, analysed according to surgery (mastectomy vs other breast surgery) and regional technique (PECS 2 vs other blocks), among others. Secondary outcomes included morphine equivalent consumption, and rate of postoperative nausea and vomiting at 24 h.
Main results: Sixteen trials including 1026 patients were identified. Rest pain scores at 2 h were decreased in the PECS blocks group, with a mean (95%CI) difference of −1.5 (−2.0, −1.0); I2 = 93%; p < 0.001, with no differences between surgery (mastectomy, mean difference [95%CI]: −1.8 [−2.4, −1.2], I^2 = 91%, p < 0.001; other breast surgery, mean difference [95%CI]: −1.1 [−2.1, −0.1], I^2 = 94%, p = 0.03; p for subgroup difference = 0.25), and regional technique (PECS 2, mean differences [95%CI]: −1.6 [−2.3, −1.0], I^2 = 94%, p < 0.001; other blocks, mean differences [95%CI]: −1.3 [−2.4, −0.1], I^2 = 74%, p = 0.04; p for subgroup difference = 0.57). The rate of postoperative nausea and vomiting was reduced from 30.8% (95%CI: 25.7%, 36.3%) to 18.7% (95%CI, 14.4%, 23.5%; p = 0.01). Similarly, secondary outcomes were significantly improved in the PECS blocks group. The overall quality of evidence was moderate-to-high.
Conclusions: There is moderate-to-high level evidence that PECS blocks provide postoperative analgesia after breast surgery when compared with no regional technique and reduce rate of PONV. This might provide the most benefit to those at high-risk of postoperative pain.

1. Introduction

Pain after breast surgery, radical mastectomy, in particular, is reported to be moderate to severe [1]. The pectoral nerves (PECS) blocks were developed to provide postoperative analgesia and include PECS 1, PECS 2 and serratus plane blocks. The PECS 1 block is achieved with a 10 ml injection of local anaesthetic between the pectoralis major and minor muscles at the third rib level in order to block the medial and lateral pectoral nerves [2]. The PECS 2 consists of a PECS 1 block plus a further injection of 20 ml of local anaesthetic between the pectoralis minor and serratus anterior muscles at the fourth rib level in order to block the intercostal nerves and the long thoracic nerve [3]. Finally, the

☆ Clinical trial number: PROSPERO – registration number: CRD42019131550.

* Corresponding author at: Department of Anaesthesia and Pain Medicine, Lausanne University Hospital, Rue du Bugnon 46, BH 05.311, 1011 Lausanne, Switzerland.
E-mail address: eric.albrecht@chuv.ch (E. Albrecht).
@DrEAlbrecht@elboghdadly (E. Albrecht)

https://doi.org/10.1016/j.jclinane.2020.109744
Received 10 September 2019; Received in revised form 7 January 2020; Accepted 15 February 2020

serratus plane block involves a 20 to 40 ml injection of local anaesthetic above or below the serratus anterior muscle at the 5th rib and blocks the intercostal nerves and thoracodorsal nerve [4]. The true analgesic efficacy of these techniques in the setting of breast oncological surgery is unclear.

Recent meta-analyses have attempted to resolve conflicting reports in the literature regarding the analgesic benefit of these blocks after breast surgery [5,6]. However, these studies, which included seven [5] and nine articles [6] for their primary outcome regarding the comparison between PECS blocks and control groups, either did not try to explain the high coefficient of heterogeneity [5], did not perform a trial sequential analysis to establish whether firm evidence was reached [5,6], or did not assess the quality of evidence [5,6]. Moreover, one of these two meta-analyses did not register prior to publication and therefore is prone to reporting bias [6]. We believe these issues do not allow physicians to rely on robust evidence to inform their clinical practice.

In order to resolve these drawbacks, and given that the literature has been bolstered by recent randomized clinical trials, we decided to undertake this systematic review, meta-analysis and trial sequential analysis with the objective of investigating whether PECS blocks improve postoperative pain-related outcomes, when compared with no regional anaesthesia, in patients having breast surgery.

2. Methods

2.1. Literature search and inclusion criteria

The conduct of this systematic review and meta-analysis adhered to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) statement [7], and we registered the protocol with PROSPERO (registration number: CRD42019131550). Our search strategy employed the following electronic databases up to July 15, 2019: MEDLINE, PUBMED, Embase, Cochrane Central Register of Controlled Clinical Trials and Web of Science. The population search words applied were: Breast or Breast surgery OR Breast diseases. The results from this initial search were merged with a subsequent search for the words Thoracic wall OR Thoracic nerves OR Nerve block. Several keywords were searched separately including: Mastectom*, Mammectom*, Lumpectom*, Mammoplast*, Tumorectom*, Quadrantectom*, Augmentation*, Implantation*, Reconstruction*, PEC*, Pector*, and Interfascial*. No language restriction or limit on subject age groups was placed on the search, however, the complete set of results were limited to only randomized controlled trials and human subjects. In addition, the authors scrutinized the references of all retrieved articles for any applicable trials that had not been captured by the above approach. Finally, Google Scholar™ was queried in order to identify any remaining relevant publications, and authors that registered clinical trials on Clinicaltrials.gov were contacted.

2.2. Population

This meta-analysis addresses female adults undergoing any breast surgical procedure.

2.3. Intervention and comparator

Trials comparing any PECS block with no block or sham injection were included. PECS block was defined as PECS 1, PECS 2 and serratus plane blocks in combination or alone.

2.4. Outcomes

Defined outcomes were extracted from each article following the routine approach that we previously described in meta-analyses on acute postoperative pain [8–11]. Our primary outcome was rest pain score at 2 postoperative hours. Secondary pain-related outcomes were rest pain at 12 and 24 postoperative hours; dynamic pain scores at 2, 12 and 24 postoperative hours; cumulative intravenous (iv) morphine equivalent consumption at 2, 12, and 24 postoperative hours; time to first analgesic request; and rates of postoperative nausea and vomiting (PONV) at 24 postoperative hours. We also sought to capture hospital length of stay, chronic pain (defined as persistent postoperative pain) at 6 postoperative months, and block-related infection.

2.5. Trial characteristics

Extracted trial characteristics included the type of breast surgery, type of PECS block, local anaesthetic injected, maintenance of anaesthesia, and perioperative analgesic treatment.

2.6. Rating of the studies

For each randomized trial, the methodologic quality was evaluated using the Cochrane Collaboration's Risk of Bias Tool [12]. Two authors (SG and EJ) employed this method to independently screen, review and score the items for each trial. A third author (EA), separately reviewed any instances of disagreement in scoring or extracted data.

2.7. Data extraction

The text, tables or images from the source articles were evaluated to extract the number of participants, number of events, means, standard deviations, standard error of means and 95% confidence intervals (CI). For articles that failed to describe the sample size or results as a mean and standard deviation or standard error of the mean and 95%CI, we contacted the corresponding author twice by email with a request for access to the relevant data or to the author's complete dataset. In the event of a corresponding author failing to reply, we employed the median and interquartile range as approximations of the mean and standard deviation, by estimating the mean as equivalent to the median and standard deviation as the interquartile range divided by 1.35, or the range divided by 4 [13]. All opioids were converted to equianalgesic iv morphine doses (iv morphine 10 mg = iv hydromorphone 1.5 mg = oral morphine 30 mg = oral oxycodone 20 mg = oral hydrocodone 30 mg = oral hydromorphone 7.5 mg = iv tramadol 100 mg = iv pethidine 75 mg = iv sufentanil 10 μg = iv fentanyl 100 μg) [14,15]. Pain scores employing a 11-graduation verbal, visual or numeric rating scale, results were transposed to a 0–10 scale to permit statistical evaluation. In addition, the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group system was applied to each outcome to evaluate the quality of evidence [16].

2.8. Statistical analysis

We utilised Review Manager (RevMan version 5.3.5; Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration 2014) for all meta-analyses. For continuous data, this software estimates the weighted mean differences, and similarly the risk ratio for categorical data between groups, with an overall estimate of the pooled effect. A meta-analysis could only be conducted when two or more trials reported any given outcome. We calculated the I^2 coefficient in order to assess heterogeneity and set predetermined limits for low (25–49%), moderate (50–74%), and high (> 75%) levels [17]. A random effects model was applied in circumstances when moderate or high heterogeneity was observed; otherwise, a fixed effects model was employed. As an attempt to account for sources of heterogeneity, subgroup analyses were conducted for our primary outcome according to the surgery (radical mastectomy versus other breast surgery), the anaesthetic maintenance (propofol vs volatile agent), the regional technique (PECS 2 block vs other PECS blocks) and perioperative analgesic strategy

(with or without multimodal analgesia treatment inclusive of acetaminophen and/or non-steroidal anti-inflammatory drugs and/or surgical infiltration with local anaesthetic). The anaesthetic maintenance subgroup analysis was determined to mitigate any potential influence of anaesthetic agent on analgesia, given that propofol has been shown to have analgesic properties [18]. Further, a sensitivity analysis on radical mastectomy with or without axillary lymph node dissection was also conducted. Finally, we performed a subgroup analysis on the rate of PONV within 24 h according to the administration of intraoperative PONV prophylaxis or not. The risk of publication bias associated with the primary outcome was estimated by creating a funnel plot of standard error of the mean difference in rest pain score at 2 postoperative hours (y-axis) as a function of the mean rest pain score difference at 2 postoperative hours (x-axis) and confirmed with Duval and Tweedie's trim and fill test [19] using Comprehensive Meta-analysis Version 2 software (Biostat, Englewood, NJ). Finally, we executed a trial sequential analysis on the primary outcome in order to evaluate whether firm evidence was reached for rest pain scores at 2 postoperative hours using TSA software version 0.9.5.10 Beta (Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark) [20]. We present results as the mean difference or relative risk (RR) with 95% CI and a 2-sided p-value < 0.05 was deemed to be significant.

3. Results

The literature search identified 615 trials, of which 16 met our inclusion criteria, comprising 1026 patients (Supplementary Fig. 1) [21–34]. The Cochrane Collaboration Risk of Bias tool (Fig. 1) revealed that most included articles had a low risk of bias. Eleven authors were contacted and 3 supplied the data [27–29]; means and standard deviations were approximated from median, interquartile range or range in six trials [22,23,25,26,31,36].

Trials characteristics are displayed in Table 1. Nine trials included patients who underwent radical mastectomy [21,22,24,27,28,30,34–36]. Anaesthesia was maintained with propofol in three studies [21,25,29]. All studies performed a PECS 2 block with 10 ml of local anaesthetics injected between the pectoralis major and minor muscles and 20 ml below the pectoralis minor muscle, except five studies that performed either a PECS 1 block [23], a PECS 1 with a serratus plane block [28], a PECS 2 with a serratus plane block [32], and a serratus plane block alone [29,35]. All blocks were performed with long-acting local anaesthetics. With the exception of 4 trials that performed the block before the induction of general anaesthesia [22,24,27,35], and one trial where block timing was not reported [28], all authors performed the block after induction of general anaesthesia but before surgery.

In total, six studies administered a routine intraoperative PONV prophylaxis consisting of a combination of ondansetron, dexamethasone and droperidol [21], a combination of ondansetron and dexamethasone [23,29,31,32,35], or dexamethasone alone [31]. In all trials except two, authors prescribed multimodal analgesia [28,34],

The mean (SD) rest pain scores at 2 postoperative hours was significantly reduced in the PECS blocks group (1.8 (1.2)) compared to the control group (3.3 (1.3); $p < 0.001$) without any differences observed between radical mastectomy and other breast surgery subgroups (Fig. 2). Similarly, there was no difference in the anaesthetic maintenance subgroup analysis as mean differences (95%CI) were -1.5 (-2.1, -1.0), $I^2 = 94\%$, $p < 0.001$ and -1.4 (-2.1, -0.7), $I^2 = 0\%$, $p < 0.001$ in the volatile agent and propofol subgroups, respectively ($p = 0.69$). The PECS 2 blocks and other PECS blocks subgroups had mean differences (95%CI) of -1.6 (-2.3, -1.0), $I^2 = 94\%$, $p < 0.001$ and -1.3 (-2.4, -0.1), $I^2 = 74\%$, $p = 0.04$, without subgroup difference, $p = 0.57$. Finally, the magnitude of the analgesic impact of PECS block vs control was reduced in the setting of multimodal analgesia (mean difference [95%CI]: -1.4 [-2.0, -0.9]; $I^2 = 94\%$; $p < 0.001$) when compared to no multimodal analgesia (mean difference [95%CI]: -2.2 [-2.7, -1.7]; $I^2 = 0\%$; $p < 0.001$; p for subgroup difference $= 0.04$). A sensitivity analysis of eight trials [22,24,27,28,30,33–35] revealed that the analgesic efficacy of the PECS block was more pronounced when a radical mastectomy was performed without axillary lymph node dissection [22,24,27] (mean difference (95%CI): -2.4 (-3.1, -1.8); $I^2 = 87\%$; $p < 0.001$) when compared with axillary dissection [28,30,33–35] (mean difference (95%CI): -1.1 (-2.0, -0.3); $I^2 = 92\%$; $p = 0.009$; p for subgroup difference $= 0.02$).

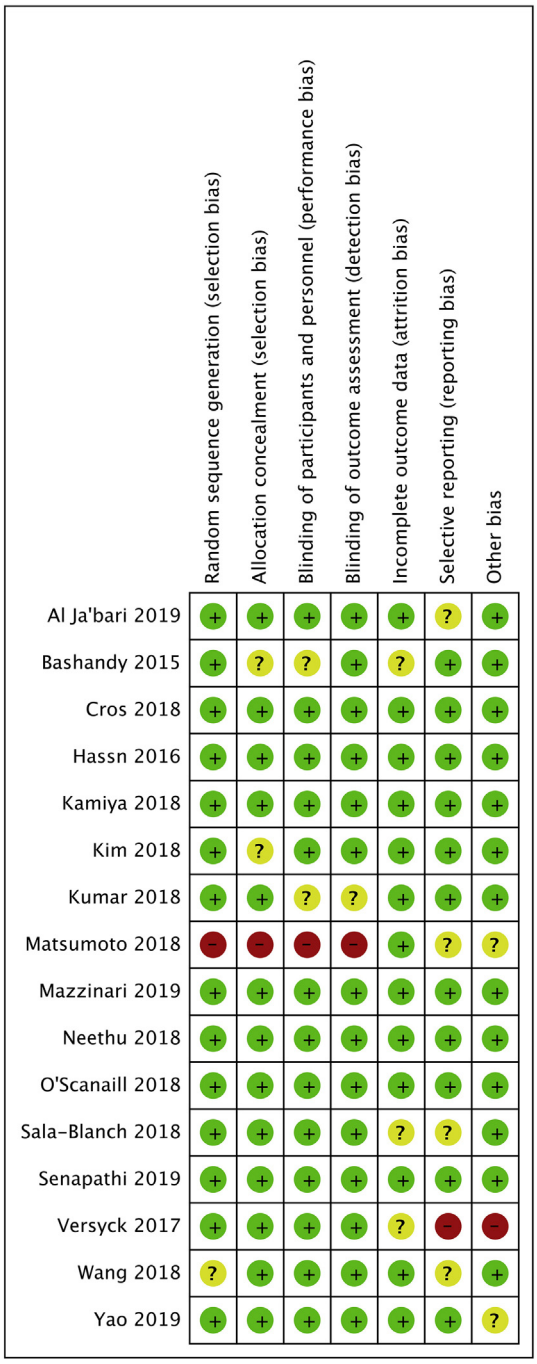

Fig. 1. Cochrane collaboration risk of bias summary: evaluation of bias risk items for each included study. Green circle, low risk of bias; red circle, high risk of bias; yellow circle, unclear risk of bias. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Characteristics of included studies (n = 15). Iv, intravenous; PCA, patient controlled-analgesia.

Reference	Group (n)	Surgery	Local anaesthetics regimen		Anaesthetic maintenance	Postoperative analgesia	Primary outcome
			PECS block	Control			
Al Ja'bari et al., 2019 [21]	Intervention (20) Control (22)	Unilateral radical mastectomy with or without axillary lymph node dissection	PECS 2, 30 ml; Ropivacaine 0.5%	No block	Propofol	Paracetamol, ibuprofen, iv PCA of morphine	Opioid consumption at 24 postoperative hours
Bashandy et al., 2015 [22]	Intervention (60) Control (60)	Unilateral radical mastectomy	PECS 2, 30 ml; Bupivacaine 0.5%,	No block	Volatile agent	Paracetamol, ketoprofen, iv PCA of morphine	Pain score at 24 postoperative hours
Cros et al., 2018 [23]	Intervention (62) Control (65)	Unilateral breast cancer surgery	PECS I, 0.4 ml.kg^{-1}; Bupivacaine 0.25% + Epinephrine 5 μg.ml^{-1}	Sham injection	Volatile agent	Paracetamol, naproxen, iv morphine	Pain score in postanaesthetic care unit
Hassn et al., 2016 [24]	Intervention (30) Control (30)	Unilateral radical mastectomy	PECS 2, 30 ml; Bupivacaine 0.5% + Dexmedetomidine 1 μg.kg^{-1}	Sham injection	Volatile agent	Ketorolac, iv morphine	Not specified
Kamiya et al., 2018 [25]	Intervention (29) Control (30)	Unilateral breast tumour resection	PECS 2, 30 ml; Levobupivacaine 0.25%	Sham injection	Propofol	Paracetamol, diclofenac, pentazocine, loxoprofen	Pain score at 6 postoperative hours
Kim et al., 2018 [26]	Intervention (40) Control (38)	Unilateral breast tumour resection	PECS 2, 30 ml; Ropivacaine 0.25%	No block	Volatile agent	Ketorolac, meperidine, tramadol	Opioid consumption at 24 postoperative hours
Kumar et al., 2018 [27]	Intervention (25) Control (25)	Unilateral radical mastectomy	PECS 2, 30 ml; Bupivacaine 0.25%	No block	Volatile agent	Paracetamol, iv tramadol	Pain score at 1 postoperative hour
Matsumoto et al., 2018 [28]	Intervention (25) Control (24)	Unilateral radical mastectomy with axillary lymph node dissection and breast reconstruction	PECS 1 and serratus plane, 30 ml; Ropivacaine 0.375%	No block	Volatile agent	Not specified	Not specified
Mazzinari et al., 2019 [29]	Intervention (28) Control (30)	Unilateral breast tumour resection	Serratus plane, 30 ml; Levobupivacaine 0.25%	No block	Propofol	Paracetamol, dexketoprofen, iv PCA of morphine	Opioid consumption at 24 postoperative hours
Neethu et al., 2018 [30]	Intervention (30) Control (30)	Unilateral radical mastectomy with axillary lymph node dissection	PECS 2, 30 ml; Ropivacaine 0.25%	No block	Volatile agent	Paracetamol, iv PCA of fentanyl	Opioid consumption at 24 postoperative hours
O'Scanaill et al., 2018 [31]	Intervention (15) Control (15)	Unilateral breast cancer surgery	PECS 2, 30 ml; Levobupivacaine 0.25%	No block	Volatile agent	Paracetamol, ibuprofen, oxycodone, local anaesthetic infusion via a wound catheter	Dynamic pain score versus time curve
Sala-Blanch et al., 2018 [32]	Intervention (15) Control (15)	Retropectoral breast augmentation	PECS 2 and serratus plane, 40 ml; Bupivacaine 0.25% + Epinephrine 5 μg.ml^{-1}	Sham injection	Volatile agent	Paracetamol, metamizol	Proportion of patients requiring rescue analgesia in the postoperative period
Senapathi et al., 2019 [36]	Intervention (25) Control (25)	Unilateral modified radical mastectomy	PECS 2, 30 ml; Bupivacaine 0.25%	Sham injection	Volatile agent	iv ketorolac, iv PCA morphine	Intraoperative opioid consumption
Versyck et al., 2017 [33]	Intervention (45) Control (40)	Unilateral quadrantectomy or radical mastectomy with axillary lymph node dissection	PECS 2, 30 ml; Levobupivacaine 0.25%	Sham injection	Volatile agent	Paracetamol, iv tramadol, iv piritramide	Not specified
Wang et al., 2018 [34]	Intervention (30) Control (30)	Unilateral radical mastectomy with axillary lymph node dissection and breast reconstruction	PECS 2, 30 ml; Ropivacaine 0.5%	No block	Volatile agent	iv morphine	Opioid consumption at 24 postoperative hours
Yao et al., 2019 [35]	Intervention (34) Control (34)	Unilateral partial or radical mastectomy with axillary lymph node dissection or biopsy	Serratus plane, 25 ml; Ropivacaine 0.5%	Sham injection	Volatile agent	Flurbiprofen, iv PCA of sufentanil	Quality of recovery assessed with QoR-40

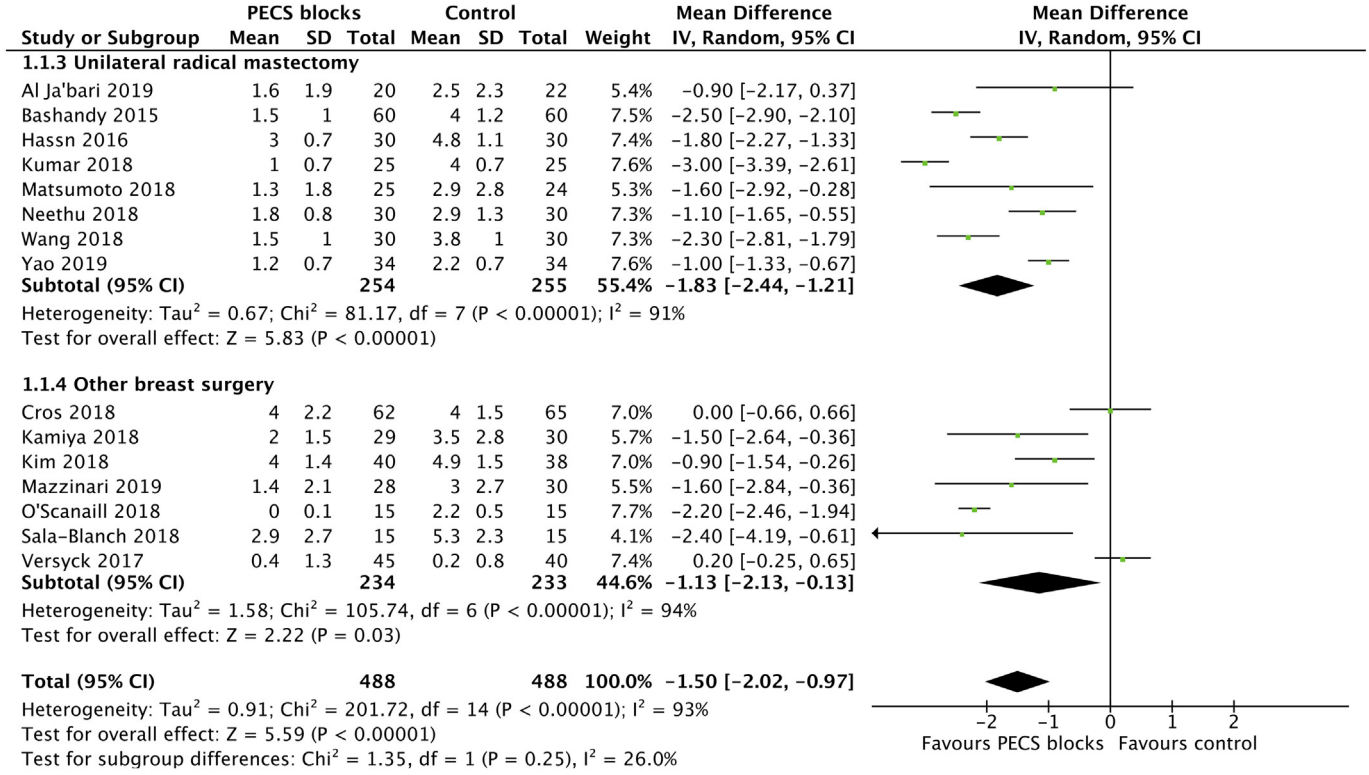

Fig. 2. Rest pain score at 2 postoperative hours according to the type of breast surgery (radical mastectomy vs other breast surgeries).

The trial sequential analysis indicated that firm evidence was reached regarding the contribution of PECS block to decrease pain score at 2 postoperative hours (Fig. 3). Regarding the risk of publication bias for the primary outcome, Duval and Tweedie's trim and fill test calculated the combined studies point estimate to be −0.96 (95%CI: −1.01, −0.82) with a random effects model. Using trim and fill, these values were unchanged, suggesting that no studies are missing. The funnel plot is presenting in Supplementary Fig. 2. According to the GRADE system, the quality of evidence for the primary outcome was high (Table 3).

All secondary acute pain-related outcomes were also significantly improved in the PECS blocks group (Table 2). PONV was significantly reduced in the PECS group with a rate (95%CI) of 18.7% (14.4%, 23.5%), compared with 30.8% (25.7%, 36.3%) in the control group ($p = 0.01$). The subgroup analysis according to the administration of intraoperative PONV prophylaxis or not, did not result in subgroup difference ($p = 0.54$), with a risk ratio (95%CI) of 0.65 (0.38, 1.11), $p = 0.11$, $I^2 = 0\%$ and 0.49 (0.23, 1.01), $p = 0.05$, $I^2 = 71\%$, respectively. Reported by two trials [24,34], hospital length of stay was reduced in the PECS block group, with a mean difference (95%CI) of 1.6 days (−1.6, −1.5); $I^2 = 0\%$; $p < 0.001$. Two trials [21,24] reported the rates of chronic pain at six postoperative months, which were 20% and 35% in the PECS blocks and control groups, respectively, with a risk ratio of 0.6 (95%CI: 0.3, 1.1), $I^2 = 0\%$, $p = 0.08$. Finally, two trials sought the number of block-related infections [21,28] and reported none.

4. Discussion

This systematic review and meta-analysis with trial sequential analysis investigated whether PECS blocks provide postoperative analgesia when compared with no regional anaesthesia in patients having breast surgery. Based on 16 randomized controlled trials, including a total of 1026 patients, we demonstrated that there is moderate-to-high evidence that PECS blocks reduce rest and dynamic pain scores, and morphine equivalent consumption at 2, 12 and 24 postoperative hours, along with the rate of PONV at 24 postoperative hours. The PECS block was equally effective for both unilateral radical mastectomy and other types of breast surgery. In the subgroup of patients having radical mastectomy, the analgesic efficacy was more pronounced when there was no axillary node dissection. This is not surprising, as the thoracodorsal and intercostobrachial nerves are not reliably covered by a PECS block [37]. Of note, the type of PECS block (PECS 2 block or other PECS blocks) did not impact on the postoperative analgesia. Unsurprisingly, there was no difference whether anaesthesia was maintained with volatile agents or propofol, even if it has been shown that propofol might have some analgesic properties [18]. We have also demonstrated that the PECS blocks reduce the overall rate of PONV within 24 postoperative hours with a risk ratio of 1.6 (30.8%/18.7%), a risk difference of 12.1% (30.8%–18.7%) and a number needed to treat of 8 (1/0.121), independently of the routine administration of an intra-operative prophylaxis or not. Finally, and based on what most authors reported, we recommend performing a PECS2 block after the induction of general anaesthesia but before surgery, and injecting a total volume of 30 ml of long-acting local anaesthetics.

Noteworthy, the analgesic benefit following mastectomy in particular was relevant, with a mean difference in pain scores in the immediate postoperative period of 1.4 or 2.2 with or without the prescription of multimodal analgesic treatment, respectively. In addition, the mean difference of 5 to 10 mg iv morphine consumption at 24 postoperative hours represents a 10 to 20 mg oxycodone-reduction. We expect that some physicians and patients could interpret these differences as modest, particularly given that the minimum clinically important reductions in these two outcomes for breast surgery have yet to be demonstrated. That being said, these analgesic benefits are also associated with a reduction in opioid-related side-effects such as PONV. In context of the current opioid epidemic [15], along with the probable safety of the procedure, we believe that the PECS block should be considered as a first-line regional anaesthetic technique within a multimodal analgesic regimen for breast surgery since the balance of risk to benefit favours this block. In particular, this technique is likely to be

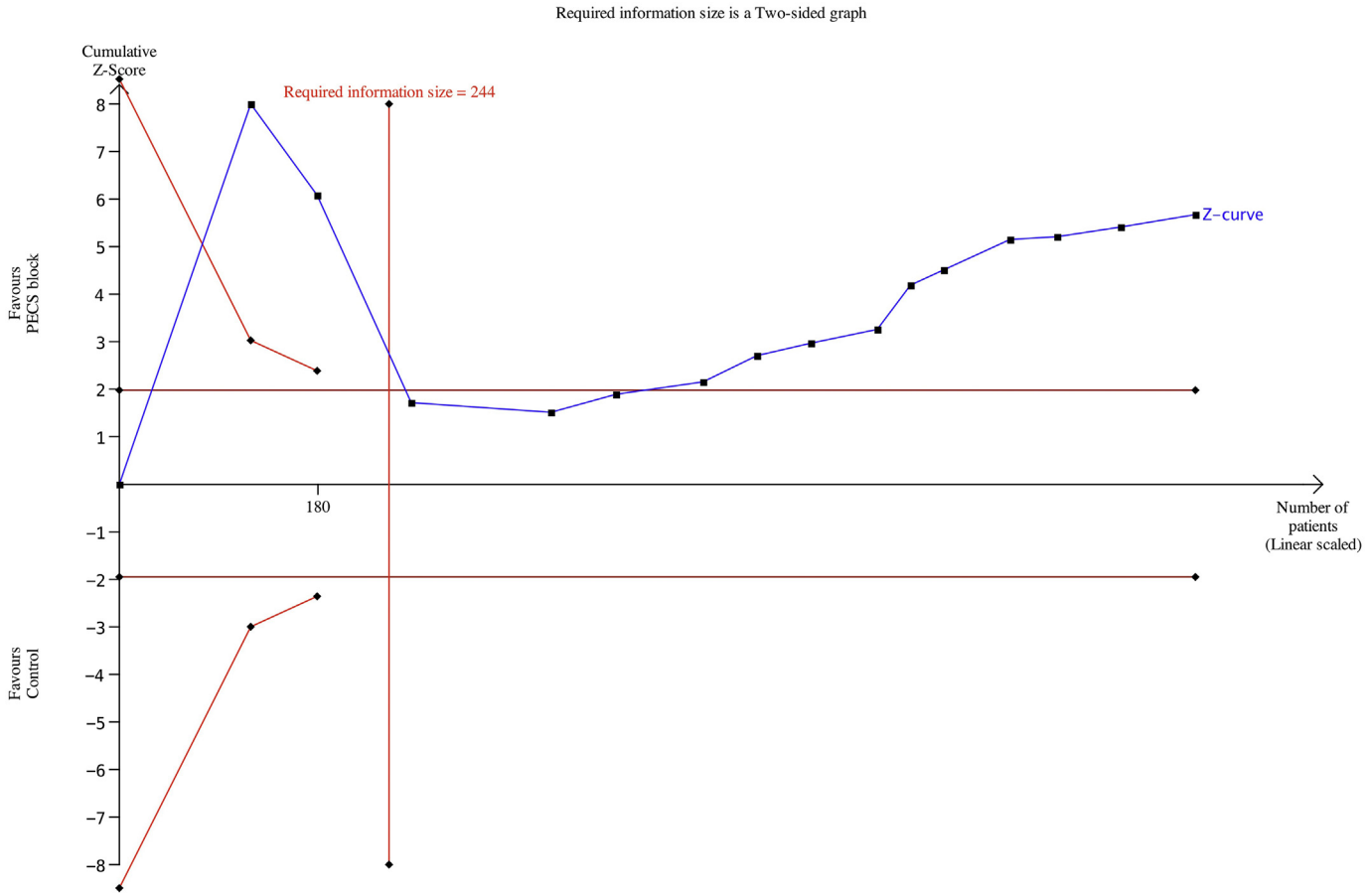

Fig. 3. Trial sequential analysis of rest pain scores at 2 postoperative hours. The cumulative Z-curve (blue) crosses the monitoring boundary curve (red) before reaching the required information size. The data is suggestive of superior pain reduction at 2 postoperative hours with PECS blocks. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

beneficial in patients with predictors of poor postoperative pain control [38], patients undergoing procedures that are likely to be more painful, or as a rescue in the low-risk patient who develops moderate-to-severe postoperative pain. Despite limited data, our subgroup analyses highlighted the benefit of a perioperative multimodal analgesic strategy, which might be sufficient in patients receiving breast-conserving surgery or who are at low risk of poor postoperative pain control. Finally, it is worth mentioning that we did not find any trial examining the analgesic efficacy of the PECS blocks in comparison to surgical infiltration, which represents an important avenue for further investigation.

Unfortunately, we were unable to correlate any association between effective analgesia and rates of chronic postoperative pain, which ranged from 20 to 57%, in the two articles included in this meta-analysis that specifically sought this outcome [21,24] and in others exploring specifically this topic [39,40]. Although this was not the primary outcome in this study, a posthoc analysis demonstrates that 138 patients in each group should be included in order to find a statistically significant difference with alpha and beta values of 0.05 and 0.2, respectively. Of note, Andreae and Andreae concluded in a systematic review that the paravertebral block prevents the development of chronic postoperative pain prevent after breast cancer surgery. However, this statement lacks robustness as only two trials were included in the analysis and one of them suffered from performance and attrition biases [41]. The hypothesis that regional anaesthesia reduces chronic pain after breast surgery is a field of research that requires further exploration.

The reduction of length of stay with a mean difference of 1.6 days in the PECS group is difficult to interpret for three reasons. First, only two trials reported this outcome [24,34]. Secondly, the mean lengths of stay were 3.5 [24] days and 14.5 [34] days in patients who did not receive the block. This is not in keeping with standard clinical practice where breast surgery is often performed on an ambulatory basis [37]. Finally, hospital length of stay is influenced by multiple factors and not by the quality of analgesia alone.

With almost doubling the number of articles included, a focus on PECS blocks versus control and not on different comparators, inclusion of all approaches and not only PECS 2, robustness of the results confirmed by a trial sequential analysis, an assessment of the quality of evidence and the role of PECS blocks in the setting of multimodal analgesia, we believe this study provides significant benefit to the literature, over and above previously published meta-analyses [5,6].

This study has limitations. Despite our attempt to group trials according to the type of surgery, medication used for anaesthetic maintenance, regional technique or prescription of a multimodal analgesic treatment, the coefficient of heterogeneity remained high, reflecting the heterogeneity in surgical and anaesthetic practices in the different centers. The level to which this heterogeneity affects the generalisability of our conclusion is uncertain, however, the consistent effect across all subgroups considered suggests a reliable clinical impact. We did not specify subgroup analyses on PROSPERO registration, and findings from the subgroup analyses should thus be considered with caution. In addition, we were unable to draw any robust conclusion regarding the impact of PECS blocks on hospital resources-related outcomes. We suggest that this represents an opportune area for additional trials with consistent methodology to explore these economic outcomes. Finally, we pooled results of different approaches to the PECS block, which might have contributed to the high heterogeneity

Table 2
Secondary pain-related outcomes and side-effects.

Outcome	Number of trials	References	Total number of patients or number of events/total number of patients		Mean difference (95% confidence interval) or relative risk (95% confidence interval)	I^2 (%)	p value
			PECS block	No block			
Rest pain scores at 12 postoperative hours	11	Bashandy 2015 [22], Hassn 2016 [24], Kamiya 2018 [25], Kim 2018 [26], Kumar 2018 [27], Mazzinari 2019 [29], Neethu 2018 [30], O'Scanaill 2018 [31], Senapathi 2019 [36], Wang 2018 [34], Yao 2019 [35]	346	347	−1.1 (−1.6 to −0.6)	94	< 0.001
Rest pain scores at 24 postoperative hours	15	Al Ja'bari 2019 [21], Bashandy 2015 [22], Cros 2018 [23], Hassn 2016 [24], Kamiya 2018 [25], Kim 2018 [26], Kumar 2018 [27], Matsumoto 2018 [28], Mazzinari 2019 [29], Neethu 2018 [30], O'Scanaill 2018 [31], Sala-Blanch 2018 [32], Senapathi 2019 [36], Wang 2018 [34], Yao 2019 [35]	468	473	−0.9 (−1.3 to −0.4)	95	< 0.001
Dynamic pain scores at 2 postoperative hours	5	Cros 2018 [23], Kumar 2018 [27], Mazzinari 2019 [29], Neethu 2018 [30], O'Scanaill 2018 [31], Sala-Blanch 2018 [32]	175	180	−1.7 (−2.7 to −0.7)	90	< 0.001
Dynamic pain scores at 12 postoperative hours	4	Kumar 2018 [27], Mazzinari 2019 [29], Neethu 2018 [30], O'Scanaill 2018 [31]	98	100	−1.8 (−3.2 to −0.4)	91	0.01
Dynamic pain scores at 24 postoperative hours	5	Kumar 2018 [27], Mazzinari 2019 [29], Neethu 2018 [30], O'Scanaill 2018 [31], Sala-Blanch 2018 [32]	113	115	−1.5 (−2.1 to −0.8)	56	< 0.001
Iv morphine equivalent consumption at 2 postoperative hours (mg)	5	Al Ja'bari 2019 [21], Bashandy 2015 [22], Cros 2018 [23], Matsumoto 2018 [28], Versyck 2017 [33]	212	211	−2.2 (−3.2 to −1.2)	11	< 0.001
Iv morphine equivalent consumption at 12 postoperative hours (mg)	2	Bashandy 2015 [22], Versyck 2017 [33]	105	100	−6.6 (−8.2 to −5.0)	0	< 0.001
Iv morphine equivalent consumption at 24 postoperative hours (mg)	15	Al Ja'bari 2019 [21], Bashandy 2015 [22], Cros 2018 [23], Hassn 2016 [24], Kim 2018 [26], Kumar 2018 [27], Matsumoto 2018 [28], Mazzinari 2019 [29], Neethu 2018 [30], O'Scanaill 2018 [31], Sala-Blanch 2018 [32], Senapathi 2019 [36], Versyck 2017 [33], Wang 2018 [34], Yao 2019 [35]	483	483	−7.2 (−9.7 to −4.6)	99	< 0.001
Time to first analgesic request (min)	4	Bashandy 2015 [22], Hassn 2016 [24], Kumar 2018 [27], Neethu 2018 [30]	145	145	301 (106–497)	100	< 0.001
Rate of postoperative nausea and vomiting within 24 postoperative hours (relative risk)	10	Al Ja'bari 2019 [21], Cros 2018 [23], Hassn 2016 [24], Kamiya 2018 [25], Kumar 2018 [27], Matsumoto 2018 [28], Neethu 2018 [30], O'Scanaill 2018 [31], Wang 2018 [34], Yao 2019 [35]	56/300	94/305	0.55 (0.34–0.88)	55	0.01

Table 3
Quality of evidence assessment for each outcome sought. PONV, postoperative nausea and vomiting.

Quality assessment								Summary of findings
Outcome	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Total number of participants	Conclusion	Quality of evidence (GRADE)
Rest pain score at 2 postoperative hours (analogue scale, 0–10)	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	976	Reduced pain score in PECS block groups	High quality (⊕⊕⊕⊕)[e]
Rest pain score at 12 postoperative hours (analogue scale, 0–10)	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	643	Reduced pain score in PECS block groups	High quality (⊕⊕⊕⊕)[e]
Rest pain score at 24 postoperative hours (analogue scale, 0–10)	No major limitations[a]	No serious inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	891	Reduced pain score in PECS block groups	High quality (⊕⊕⊕⊕)
Dynamic pain score at 2 postoperative hours (analogue scale, 0–10)	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	355	Reduced pain score in PECS block groups	High quality (⊕⊕⊕⊕)[e]
Dynamic pain score at12 postoperative hours (analogue scale, 0–10)	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	198	Reduced pain score in PECS block groups	High quality (⊕⊕⊕⊕)[e]
Dynamic pain score at 24 postoperative hours (analogue scale, 0–10)	No major limitations[a]	No serious inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	227	Reduced pain score in PECS block groups	High quality (⊕⊕⊕⊕)
Intravenous morphine equivalent consumption at 2 postoperative hours	No major limitations[a]	No inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	423	Reduced consumption in PECS block group	High quality (⊕⊕⊕⊕)
Intravenous morphine equivalent consumption at 12 postoperative hours	Two studies sought this outcome	No inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	205	Reduced consumption in PECS block group	Moderate quality (⊕⊕⊕O)[f]
Intravenous morphine equivalent consumption at 24 postoperative hours	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	916	Reduced consumption in PECS block group	High quality (⊕⊕⊕⊕)[e]
Time to first analgesic request	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	290	Increased time to first analgesic request in PECS block group	High quality (⊕⊕⊕⊕)[e]
Rates of PONV within the first 24 postoperative hours	No major limitations[a]	Moderate inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	605	Less PONV in PECS block group	High quality (⊕⊕⊕⊕)[e]
Length of stay	Two studies sought this outcome	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	120	Equivalent length of stay in both groups	Low quality (⊕⊕O O)[f]
Chronic pain at 6 postoperative months	Two studies sought this outcome	No inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	108	Equivalent rate in both groups	Low quality (⊕⊕O O)[f]

[a] As only a limited number of studies suffered from a high-risk of bias, we estimate that this does not represent a major limitation.
[b] I^2 above 50% or not applicable, as only one trial reported this outcome.
[c] Consistent definition of the reported outcome.
[d] No serious imprecision as the clinical decision would not be modified whether the upper of lower boundary limit of the confidence interval represented the truth.
[e] Although there was a concern about inconsistency, we did not rate down the quality of evidence because not every criterion appeared to justify rating down by one level. Moreover, there was consistent evidence from randomized controlled trials, with no plausible confounders.
[f] We rated down for limitations, as two trials reported this outcome.

reported. However, this simply reinforces the relevance of fascial plane blocks in the management of these patients.

In conclusion, there is moderate-to-high evidence that PECS blocks provide modest short-term postoperative analgesia after breast surgery when compared with no regional technique. This could provide the most benefit to those at high-risk of moderate-to-severe postoperative pain.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2020.109744.

Declaration of competing interest

EA has received grants from the Swiss Academy for Anaesthesia Research (SACAR), Lausanne, Switzerland (no grant numbers attributed) and from B. Braun Medical AG, Sempach, Switzerland (no grant numbers attributed) and from the Swiss National Science Foundation to support his clinical research. EA has also received an honorarium from B. Braun Melsungen AG, Melsungen, Germany. No interest declared by the other authors.

Acknowledgment

We are grateful to Mrs. Cécile Jaques (Medical Library, Research and Education Department, Lausanne University Hospital, Switzerland) for the assistance in the literature search.

Disclosure of funding

This work was supported by departmental funding (Department of Anaesthesia, Lausanne University Hospital, Lausanne, Switzerland).

Author's individual contribution to the manuscript

Sina Grape: This author searched the literature, assessed the articles, extracted and analysed the data.

Eric Jaunin: This author assessed the articles and extracted the data.

Kariem El-Boghdadly: This author analysed the data and wrote the manuscript.

Vincent Chan: This author analysed the data and wrote the manuscript.

Eric Albrecht: This author designed the study, searched the literature, assessed the articles, extracted and analysed the date and wrote the primary manuscript.

References

[1] Fecho K, Miller NR, Merritt SA, Klauber-Demore N, Hultman CS, Blau WS. Acute and persistent postoperative pain after breast surgery. Pain Med 2009;10:708–15. https://doi.org/10.1111/j.1526-4637.2009.00611.x.

[2] Blanco R. The 'pecs block': a novel technique for providing analgesia after breast surgery. Anaesthesia 2011;66:847–8. https://doi.org/10.1111/j.1365-2044.2011.06838.x.

[3] Blanco R, Fajardo M, Parras Maldonado T. Ultrasound description of Pecs II (modified Pecs I): a novel approach to breast surgery. Rev Esp Anestesiol Reanim 2012;59:470–5. https://doi.org/10.1016/j.redar.2012.07.003.

[4] Blanco R, Parras T, McDonnell JG, Prats-Galino A. Serratus plane block: a novel ultrasound-guided thoracic wall nerve block. Anaesthesia 2013;68:1107–13. https://doi.org/10.1111/anae.12344.

[5] Versyck B, van Geffen GJ, Chin KJ. Analgesic efficacy of the Pecs II block: a systematic review and meta-analysis. Anaesthesia 2019;74:663–73. https://doi.org/10.1111/anae.14607.

[6] Hussain N, Brull R, McCartney CJ, et al. Pectoralis-II myofascial block and analgesia in breast cancer surgery. Anesthesiology 2019;131:630–48. https://doi.org/10.1097/ALN.0000000000002822.

[7] Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777–84. https://doi.org/10.7326/M14-2385.

[8] Albrecht E, Kern C, Kirkham KR. A systematic review and meta-analysis of perineural dexamethasone for peripheral nerve blocks. Anaesthesia 2015;70:71–83. https://doi.org/10.1111/anae.12823.

[9] Kirkham KR, Grape S, Martin R, Albrecht E. Analgesic efficacy of local infiltration analgesia vs. femoral nerve block after anterior cruciate ligament reconstruction: a systematic review and meta-analysis. Anaesthesia 2017;72:1542–53. https://doi.org/10.1111/anae.14032.

[10] Kirkham KR, Jacot-Guillarmod A, Albrecht E. Optimal dose of perineural dexamethasone to prolong analgesia after brachial plexus blockade: a systematic review and meta-analysis. Anesth Analg 2018;126:270–9. https://doi.org/10.1213/ANE.0000000000002488.

[11] Baeriswyl M, Kirkham KR, Jacot-Guillarmod A, Albrecht E. Efficacy of perineural vs systemic dexamethasone to prolong analgesia after peripheral nerve block: a systematic review and meta-analysis. Br J Anaesth 2017;119:183–91. https://doi.org/10.1093/bja/aex191.

[12] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928. https://doi.org/10.1136/bmj.d5928.

[13] Collaboration TC: Cochrane handbook for systematic reviews of interventions version 5.1.0 Available from http://ims.cochrane.org/revman, Accessed date: 1 June 2019.

[14] Baeriswyl M, Kirkham KR, Kern C, et al. The analgesic efficacy of ultrasound-guided transversus abdominis plane block in adult patients: a meta-analysis. Anesth Analg 2015;121:1640–54. https://doi.org/10.1213/ANE.0000000000000967.

[15] Frauenknecht J, Kirkham KR, Jacot-Guillarmod A, Albrecht E. Analgesic impact of intra-operative opioids vs. opioid-free anaesthesia: a systematic review and meta-analysis. Anaesthesia 2019;74:651–62. https://doi.org/10.1111/anae.14582.

[16] Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401–6. https://doi.org/10.1016/j.jclinepi.2010.07.015.

[17] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.

[18] Scott HB, Choi SW, Wong GT, Irwin MG. The effect of remifentanil on propofol requirements to achieve loss of response to command vs. loss of response to pain. Anaesthesia 2017;72:479–87. https://doi.org/10.1111/anae.13781.

[19] Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63.

[20] Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. BMC Med Res Methodol 2009;9:86. https://doi.org/10.1186/1471-2288-9-86.

[21] Al Ja'bari A, Robertson M, El-Boghdadly K, Albrecht E. A randomised controlled trial of the pectoral nerves-2 (PECS-2) block for radical mastectomy. Anaesthesia 2019;47:1277–81. https://doi.org/10.1111/anae.14769.

[22] Bashandy GM, Abbas DN. Pectoral nerves I and II blocks in multimodal analgesia for breast cancer surgery: a randomized clinical trial. Reg Anesth Pain Med 2015;40:68–74. https://doi.org/10.1097/AAP.0000000000000163.

[23] Cros J, Sengès P, Kaprelian S, et al. Pectoral I block does not improve postoperative analgesia after breast cancer surgery: a randomized, double-blind, dual-centered controlled trial. Reg Anesth Pain Med 2018;43:596–604. https://doi.org/10.1097/AAP.0000000000000779.

[24] Hassn A, Zanfaly H, Biomy T. Pre-emptive analgesia of ultrasound-guided pectoral nerve block II with dexmedetomidine–bupivacaine for controlling chronic pain after modified radical mastectomy. Res Opin Anesth Int Care 2016;3:6–12. https://doi.org/10.4103/2356-9115.184078.

[25] Kamiya Y, Hasegawa M, Yoshida T, Takamatsu M, Koyama Y. Impact of pectoral nerve block on postoperative pain and quality of recovery in patients undergoing breast cancer surgery: a randomised controlled trial. Eur J Anaesthesiol 2018;35:215–23. https://doi.org/10.1097/EJA.0000000000000762.

[26] Kim DH, Kim S, Kim CS, et al. Efficacy of pectoral nerve block type II for breast-conserving surgery and sentinel lymph node biopsy: a prospective randomized controlled study. Pain Res Manag 2018;2018:4315931. https://doi.org/10.1155/2018/4315931.

[27] Kumar S, Goel D, Kumar SS, et al. A randomised controlled study of the post-operative analgesic efficacy of ultrasound-guided pectoral nerve block in the first 24 h after modified radical mastectomy. Ind J Anaesth 2018;62:436–42. https://doi.org/10.4103/ija.IJA_523_17.

[28] Matsumoto M, Flores EM, Kimachi PP, et al. Benefits in radical mastectomy protocol: a randomized trial evaluating the use of regional anesthesia. Sci Rep 2018;8:7815. https://doi.org/10.1038/s41598-018-26273-z.

[29] Mazzinari G, Rovira L, Casasempere A, et al. Interfascial block at the serratus muscle plane versus conventional analgesia in breast surgery: a randomized controlled trial. Reg Anesth Pain Med 2019;44:52–8. https://doi.org/10.1136/rapm-2018-000004.

[30] Neethu M, Pandey RK, Sharma A, et al. Pectoral nerve blocks to improve analgesia after breast cancer surgery: a prospective, randomized and controlled trial. J Clin Anesth 2018;45:12–7. https://doi.org/10.1016/j.jclinane.2017.11.027.

[31] O'Scanaill P, Keane S, Wall V, Flood G, Buggy DJ. Single-shot pectoral plane (PECs I and PECs II) blocks versus continuous local anaesthetic infusion analgesia or both after non-ambulatory breast-cancer surgery: a prospective, randomised, double-blind trial. Br J Anaesth 2018;120:846–53. https://doi.org/10.1016/j.bja.2017.11.112.

[32] Sala-Blanch X, Sánchez CAP, López-Pantaleon LA, Cubero M. Analgesic efficacy of modified pectoral block plus serratus plane block in breast augmentation surgery: a randomised, controlled, triple-blind clinical trial. Rev Esp Anestesiol Reanim 2019;66:62–71. https://doi.org/10.1016/j.redar.2018.08.001.

[33] Versyck B, van Geffen GJ, Van Houwe P. Prospective double blind randomized placebo-controlled clinical trial of the pectoral nerves (Pecs) block type II. J Clin Anesth 2017;40:46–50. https://doi.org/10.1016/j.jclinane.2017.03.054.

[34] Wang K, Zhang X, Zhang T, et al. The efficacy of ultrasound-guided type II pectoral

nerve blocks in perioperative pain management for immediate reconstruction after modified radical mastectomy: a prospective, randomized study. Clin J Pain 2018;34:231–6. https://doi.org/10.1097/AJP.0000000000000529.

[35] Yao Y, Li J, Hu H, Xu T, Chen Y. Ultrasound-guided serratus plane block enhances pain relief and quality of recovery after breast cancer surgery: a randomised controlled trial. Eur J Anaesthesiol 2019;36:436–41. https://doi.org/10.1097/EJA.0000000000001004.

[36] Senapathi TGA, Widnyana IMG, Aribawa IGNM, et al. Combined ultrasound-guided Pecs II block and general anesthesia are effective for reducing pain from modified radical mastectomy. J Pain Res 2019;12:1353–8. https://doi.org/10.2147/JPR.S197669.

[37] Pawa A, Wight J, Onwochei DN, et al. Combined thoracic paravertebral and pectoral nerve blocks for breast surgery under sedation: a prospective observational case series. Anaesthesia 2018;73:438–43. https://doi.org/10.1111/anae.14213.

[38] Yang MMH, Hartley RL, Leung AA, et al. Preoperative predictors of poor acute postoperative pain control: a systematic review and meta-analysis. BMJ Open 2019;9:e025091https://doi.org/10.1136/bmjopen-2018-025091.

[39] Macrae WA. Chronic post-surgical pain: 10 years on. Br J Anaesth 2008;101:77–86. https://doi.org/10.1093/bja/aen099.

[40] Habib AS, Kertai MD, Cooter M, Greenup RA, Hwang S. Risk factors for severe acute pain and persistent pain after surgery for breast cancer: a prospective observational study. Reg Anesth Pain Med 2019;44:192–9. https://doi.org/10.1136/rapm-2018-000040.

[41] Andreae MH, Andreae DA. Regional anaesthesia to prevent chronic pain after surgery: a Cochrane systematic review and meta-analysis. Br J Anaesth 2013;111:711–20. https://doi.org/10.1093/bja/aet213.