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Analgesic efficacy of PECS vs paravertebral blocks after radical mastectomy: A systematic review, meta-analysis and trial sequential analysis

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ABSTRACT

Study objective: Due to conflicting results published in the literature regarding the analgesic superiority between the paravertebral block and the PECS block, the study objective is to determine which one should be the first line analgesic treatment after radical mastectomy.
Design: Systematic review, meta-analysis and trial sequential analysis.
Setting: Operating room, postoperative recovery area and ward, up to 24 postoperative hours.
Patients: Patients scheduled for radical mastectomy under general anaesthesia.
Interventions: We searched five electronic databases for randomized controlled trials comparing any PECS block with a paravertebral block.
Measurements: The primary outcome was rest pain score (0 − 10) at 2 postoperative hours, analyzed according to the combination with axillary dissection or not, to account for heterogeneity. Secondary outcomes included rest pain scores, cumulative intravenous morphine equivalents consumption and rate of postoperative nausea and vomiting at 24 postoperative hours.
Main results: Eight trials including 388 patients were identified. Rest pain scores at 2 postoperative hours were decreased in the PECS block group, with a mean difference (95%CI) of −0.4 (−0.7 to −0.1), I^2 = 68%, p = 0.01, and a significant subgroup difference observed between radical mastectomy with (mean difference [95%CI]: 0.0 [−0.2 to 0.2], I^2 = 0%, p = 1.00), or without axillary dissection (mean difference [95%CI]: −0.7 [−1.1 to −0.4], I^2 = 40%, p < 0.001; p for subgroup difference < 0.001). All secondary pain-related outcomes were similar between groups. The overall quality of evidence was low.
Conclusions: There is low quality evidence that a PECS block provides marginal postoperative analgesic benefit after radical mastectomy at 2 postoperative hours only, when compared with a paravertebral block, and not beyond.
Clinical trial number: PROSPERO – registration number: CRD42019131555.

1. Introduction

Patients having radical mastectomy suffer from moderate-to-severe postoperative pain [1]. The thoracic paravertebral block has long been seen as the regional anaesthetic technique of choice in the setting of radical mastectomy [2]. However, a recent developed fascial plane technique to block the pectoral nerves, the pectoral nerves (PECS) block, has purported safety benefits and is easier to perform than the paravertebral block. The PECS 1 approach 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 [3]. 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 thoracic intercostal nerves and the long thoracic nerve [4]. Finally, the serratus plane block involves a 40 ml-injection of local anaesthetic

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above or below the serratus anterior muscle at the 5th rib and blocks the thoracodorsal nerve [5].

There is conflicting literature reporting the analgesic superiority of one of this technique over the other. Recently, two meta-analysis attempted to resolve this uncertainty and concluded that both methods were equivalent [6,7]. However, these meta-analyses included only five articles regarding the comparison of PECS blocks and paravertebral block groups, did not assess the quality of evidence, and did not perform a trial sequential analysis to establish whether firm evidence was reached; therefore a type II error could not be excluded. Moreover, one of these two meta-analyses did not register prior to publication and therefore is prone to reporting bias [7]. We believe these issues do not allow physicians to rely on robust evidence to inform their clinical practice.

The literature has benefited from several randomized controlled trials published in the interim. In order to build a robust evidence-base, we undertook a systematic review, meta-analysis and trial sequential analysis to determine the comparative analgesic efficacy and clinical effectiveness between PECS or paravertebral blocks for patients undergoing radical mastectomy surgery. The results of this study should definitively recommend the first line regional anaesthetic treatment in this clinical setting.

2. Methods

2.1. Literature search and inclusion criteria

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [8] and was registered with PROSPERO (registration number: CRD42019131555). Our search strategy employed the following electronic databases up to February 1, 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*, Lumpectom*, Mammoplast*, Tumorectom*, Quadrantectom*, Augmentation*, Implantation*, Reconstruction*, PEC*, Pector*, and Interfascial*. No language restrictions or limits on subject age groups were placed on the search, and we included only randomized controlled trials. In addition, the authors scrutinised 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 addressed female adults undergoing radical mastectomy. Initially, we intended to include patients undergoing any oncological breast surgery, but our results demonstrated that the population of interest was only patients who received radical mastectomy with or without axillary clearance. We therefore focused on this population.

2.3. Intervention and comparator

Trials comparing any PECS block with paravertebral block were included. PECS block was defined as PECS 1, PECS 2, serratus plane blocks in any combination or in isolation.

2.4. Outcomes

Defined outcomes were extracted from each article following the routine approach previously described in meta-analyses on acute postoperative pain [9–12]. Our primary outcome was rest pain scores at 2 postoperative hours. We chose this time interval for our primary outcome as this outcome is frequently reported in the literature and as the block effect usually wears off after 12 to 18 h, negating any comparison after that time period. Secondary pain-related outcomes were rest pain at 12 and 24 postoperative hours; dynamic pain scores at 2, 12 and 24 postoperative hours; intravenous (iv) morphine equivalent consumption intraoperatively and at 24 postoperative hours; time to first analgesic request; and rates of postoperative nausea and vomiting at 24 postoperative hours. Complications were also monitored such as postoperative haematoma, pneumothorax and local anaesthetic systemic toxicity. We also sought to capture chronic pain at 3 and 6 postoperative months.

2.5. Trial characteristics

Extracted trial characteristics included whether radical mastectomy was associated with axillary clearance or not and details of the regional anaesthetic technique used, including the volume and type of local anaesthetic injected, any additives, and the perioperative analgesic regimen.

2.6. Evaluation of methodologic quality

For each randomized trial, the methodologic quality was evaluated using the Cochrane Collaboration's Risk of Bias Tool [13]. Briefly, this tool consists of assessing risks of selection, performance, detection, attrition, reporting, and sponsor biases among others.

2.7. Data extraction

Two authors (SG and EA) independently extracted data and disagreements were resolved through discussion with a third author (KE). The texts, 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, the corresponding author was contacted up to two times by email with a request for access to the relevant data or to the author's complete dataset. In the event that a corresponding author failed 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 the standard deviation as the interquartile range divided by 1.35 or the range divided by 4 [14]. All opioids were converted to equianalgesic iv morphine does (iv morphine 10 mg = iv hydromorphone 1.5 mg = oral morphine 30 mg = oral oxycodone 20 mg = oral hydromorphone 7.5 mg = iv tramadol 100 mg = iv pethidine 75 mg) [15,16]. When authors reported pain scores employing a verbal, visual or numeric rating scales, results were transposed to a 0–10 analogue scale to permit statistical evaluation. In addition, the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group system was applied to each pain-related outcome to evaluate the quality of evidence [17].

2.8. Statistical analysis

We used RevMan version 5.3.5 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration 2014) for all meta-analyses conducted. The tool determines the weighted standardised mean difference for ordinal data. For continuous data it 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%), or high (> 75%) levels [18]. Using a conservative approach, a random effects model was employed throughout. Subgroup analyses were conducted for our primary outcome according to the type of surgery (radical mastectomy with or without axillary dissection), as an attempt to account for sources of heterogeneity. The risk of publication bias associated with the primary outcome was estimated by creating a funnel plot of the standard error of the mean differences in resting pain scores on postoperative day 1 as a function of the mean pain score difference at rest on postoperative day 1 and confirmed with Duval and Tweedie's trim and fill test [19]. The Comprehensive Meta-analysis Version 2 software (Biostat, Englewood, NJ) was employed to conduct this assessment. Finally, we performed a trial sequential analysis on the primary outcome in order to evaluate whether firm evidence was reached for rest pain score at 2 postoperative hours (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 determined to be significant.

3. Results

The literature search identified 613 trials, of which 8 met our inclusion criteria, representing 388 patients (Supplementary Fig. 1) [21–28]. The Cochrane Collaboration Risk of Bias tool (Fig. 1) revealed that all included articles had at least one high risk of bias. Six authors were contacted [21,23,24,26–28] and only one supplied the data [24].

Trials characteristics are displayed in Table 1. Three trials recruited patients in whom the surgery combined the radical mastectomy with axillary dissection [23,24,27]. In six trials [21,22,24–26,28], the blocks were performed before the induction of general anaesthesia, and among these, five assessed whether the block was effective or not prior to surgery [21,24–26,28]. Six studies performed a PECS 2 block with one third of the local anaesthetic volume injected between the pectoralis major and minor muscles and two third of the volume, below the pectoralis minor muscle [21,22,25–28]; the two remaining studies performed a serratus plane block [23,24]. All studies performed a paravertebral block under ultrasound guidance, except 2 that used anatomic landmarks [21,28]. The paravertebral block was mainly performed following a single-injection at the T4 level [21–23,27,28], while 1 study reported a single-injection at the T3 level [25], and 2, multiple injections at T2 and T4 levels [26], or at T2, T4 and T6 levels [24].

All blocks were performed with long-acting local anaesthetics, but of note, in a majority of trials, patients who received a PECS 2 block received in average 30 to 50% more volume of local anaesthetics than patients with a paravertebral block [21,22,24,26,28]; only three studies administered an equivalent volume in both groups [23,25,27]. All studies reported maintaining anaesthesia with volatile agents. No studies reported local anaesthetic infiltration performed by surgeons at the end of the procedure.

Rest pain score at 2 postoperative hours was significantly reduced in the PECS block group (mean difference [95%CI]: −0.40 [−0.71, −0.08], I^2 = 68%, p = 0.01), with a significant subgroup difference observed between radical mastectomy with (mean difference [95%CI]: 0.0 [−0.23, 0.23], I^2 = 0%, p = 1.00), or without axillary dissection (mean difference [95%CI]: −0.74 [−1.09, −0.38], I^2 = 40%, p < 0.001; p for subgroup difference < 0.001) (Fig. 2). This difference was primarily driven by studies including patients who had mastectomy surgery without axillary node clearance. The trial sequential analysis indicated that firm evidence was reached regarding the analgesic superiority of PECS block over paravertebral 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 −0.44 (95%CI: −0.76, −0.12), with a random effects model. Using trim and fill, these values are −0.50 (95%CI: −0.81, −0.20), suggesting that one study at least is missing. According to the GRADE system, the quality evidence for our primary outcome was low.

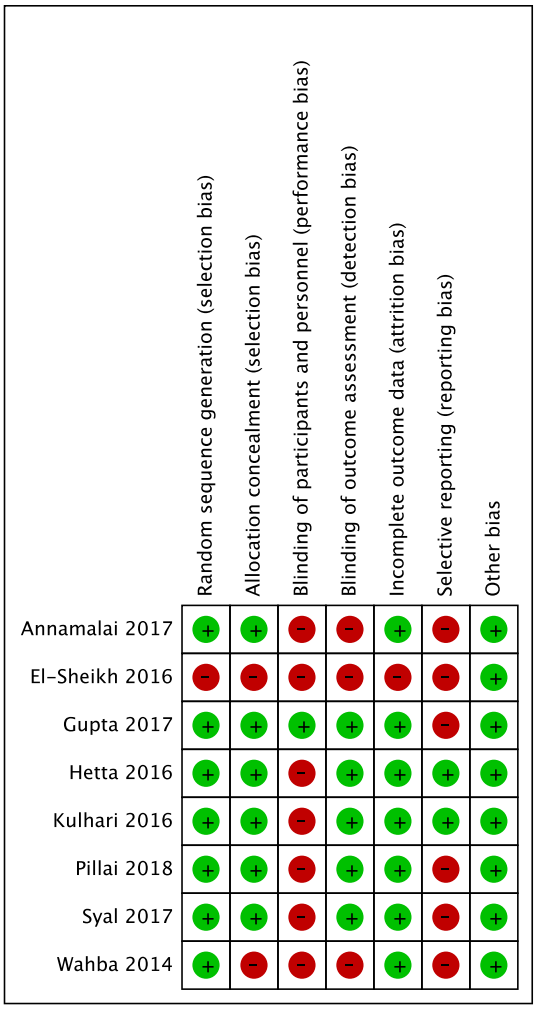

Fig. 1. Cochrane collaboration risk of bias summary: evaluation of bias risk items for each included study. Green circle, low risk of bias; yellow circle, unclear risk of bias; red circle, high risk of bias. (For interpretation of the references to color in this figure legend, the reader is referred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

All secondary pain-related outcomes were similar between groups (Table 2). Two trials sought data on postoperative haematoma formation [26,27], and in the 79 patients included there were no reports of this complication. In the five trials reporting pneumothorax [22,25–28], two patients out of 110 (1.8%) suffered from a pneumothorax after a paravertebral block performed under ultrasound guidance and none in the PECS group, with a risk ratio (95%CI) of 0.20 (0.01–3.92), I^2 = not applicable, p = 0.29. Four trials aimed to capture any local anaesthetic systemic toxicity [25–28] and none was reported out of 179 patients monitored. Finally, no trials investigated the rate of chronic pain at 3 or 6 postoperative months. Table 3 summarises the GRADE recommendation for each outcome.

4. Discussion

This systematic review and meta-analysis with a trial sequential analysis investigated whether a PECS block provided superior analgesia after radical mastectomy, when compared with a paravertebral block. Based on 8 randomized controlled trials, including a total of 388 patients, we demonstrated that there is low evidence that PECS blocks

Table 1
Characteristics of included trials. I.v., intravenous; PCA, patient-controlled analgesia; PECS, pecs blocks; PVB, paravertebral block.

Reference	Group (n)	Surgery	Block performed (technique, volume)		Local anaesthetic	Postoperative analgesia	Primary outcome
			PECS	PVB			
Annamalai et al. [21]	PECS (30) PVB (30)	Unilateral radical mastectomy	PECS 2, 30 ml	Anatomic landmark, Single injection (T4), 15–20 ml	Bupivacaine 0.25%	Not specified	Time to first analgesic request
El-Sheikh et al. [22]	PECS (20) PVB (19)	Unilateral radical mastectomy	PECS 2, 30 ml	Ultrasound-guided, Single injection (T4), 10–20 ml	Not specified	I.v. morphine	Not specified
Gupta et al. [23]	PECS (25) PVB (25)	Unilateral radical mastectomy with axillary dissection	Serratus plane, 20 ml	Ultrasound-guided, Single injection (T4), 20 ml	Bupivacaine 0.5%	I.v. paracetamol, i.v. PCA of morphine	Duration of analgesia
Hetta et al. [24]	PECS (30) PVB (30)	Unilateral radical mastectomy with axillary dissection	Serratus plane, 30 ml	Ultrasound-guided, Multiple injections (T2, T4, T6), 15 ml	Bupivacaine 0.25%	I.v. PCA of morphine	Opioid consumption at 24 postoperative hours
Kulhari et al. [25]	PECS (20) PVB (20)	Unilateral radical mastectomy	PECS 2, 25 ml	Ultrasound-guided, Single injection (T3), 25 ml	Ropivacaine 0.5%	I.v. PCA of morphine	Opioid consumption at 24 postoperative hours
Pillai et al. [26]	PECS (19) PVB (20)	Unilateral radical mastectomy	PECS 2, 30 ml	Ultrasound-guided, Multiple injections (T2, T4), 20 ml	Ropivacaine 0.5%	I.v. paracetamol, i.v. PCA of morphine	Opioid consumption at 24 postoperative hours
Syal et al. [27]	PECS (20) PVB (20)	Unilateral radical mastectomy with axillary dissection	PECS 2, 20 ml	Ultrasound-guided, Single injection (T4), 20 ml	Bupivacaine 0.5% + epinephrine 0.2 $\mu g.ml^{-1}$	I.v. diclofenac, i.v. fentanyl	Postoperative pain scores (time interval not specified)
Wahba et al. [28]	PECS (30) PVB (30)	Unilateral radical mastectomy	PECS 2, 30 ml	Anatomic landmark, Single injection (T4), 15–20 ml	Levobupivacaine 0.25%	I.v. PCA of morphine	Opioid consumption at 24 postoperative hours

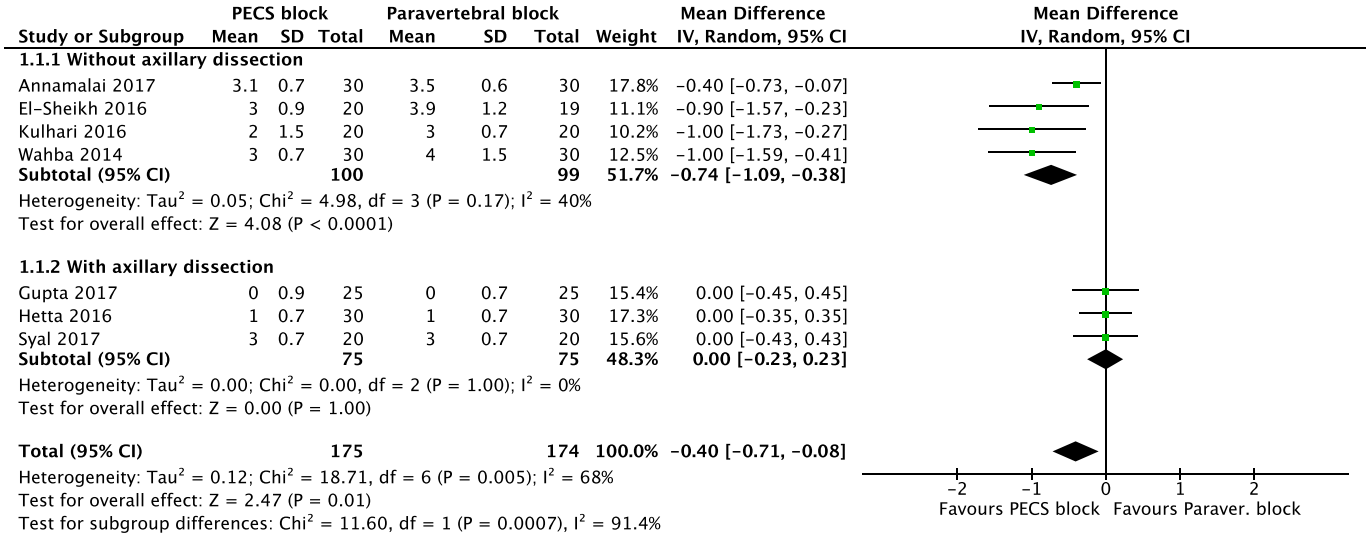

Fig. 2. Forest plot of the primary outcome of rest pain scores at 2 postoperative hours based on surgery without (upper) or with (lower) axillary dissection.

reduce rest pain score at 2 postoperative hours, especially when radical mastectomy is not combined with an axillary dissection. However, the marginal mean difference of 0.4 out of 10 is likely not a clinically important difference [29], especially when all the secondary pain-related outcomes are similar between groups. Notwithstanding, an incidence of pneumothorax in the thoracic paravertebral block group of 1.8% compared to 0% in the PECS group, while not being statistically significant, is highly relevant when determining the regional anaesthetic technique of choice. Interestingly, this incidence of pneumothorax following thoracic paravertebral block is higher than that previously reported [30] and might be related to the anatomical location of where the paravertebral block is performed; one could postulate that the risk is higher if a higher thoracic level is selected for blockade. Consequently, even if our data do not support to recommend one of

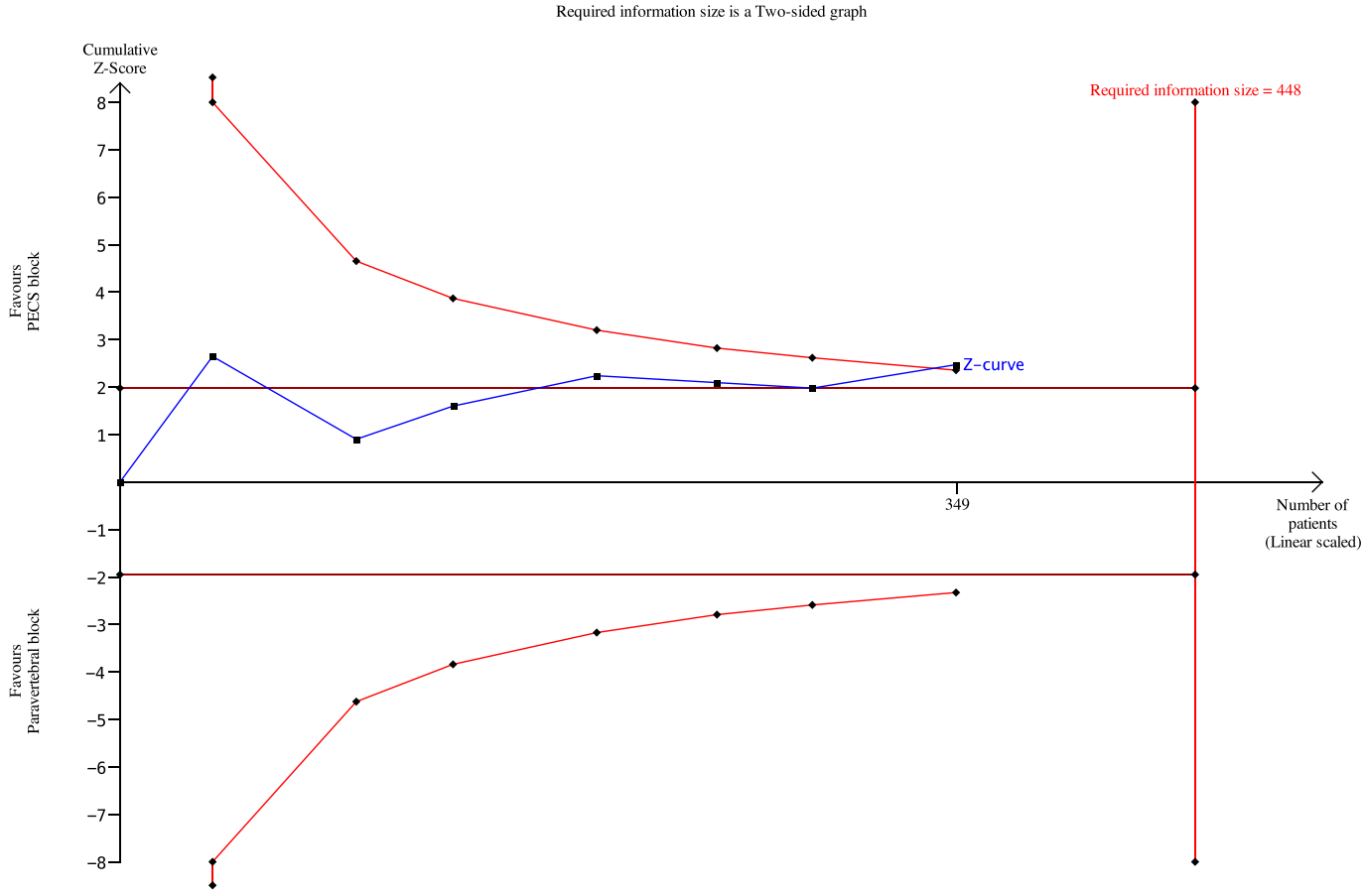

Fig. 3. Trial sequential analysis for rest pain scores at 2 postoperative hours. The cumulative Z-curve (blue) crosses the monitoring boundary curve (red) before reaching the required information size indicating that firm evidence is established regarding superiority of PECS block over paravertebral block in reducing rest pain score at 2 postoperative hours. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Secondary pain-related outcomes.

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	Paravertebral block			
Rest pain score at 12 postoperative hours	5	Gupta [23], Hetta [24], Kulhari [25], Syal [27], Wahba 2014 [28]	125	125	−0.2 (−1.5–1.0)	97	0.72
Rest pain score at 24 postoperative hours	6	El-Sheikh [22], Gupta [23], Hetta [24], Kulhari [25], Syal [27], Wahba [28]	145	144	0.1 (−0.4–0.5)	89	0.74
Dynamic pain score at 2 postoperative hours	2	Hetta [24], Wahba [28]	60	60	−1.0 (−3.0–1.0)	98	0.32
Dynamic pain score at 12 postoperative hours	2	Hetta [24], Wahba [28]	60	60	0.5 (−0.5–1.5)	82	0.32
Dynamic pain score at 24 postoperative hours	2	Hetta [24], Wahba [28]	60	60	1.0 (−1.0–3.0)	97	0.32
Intravenous morphine equivalent consumption intraoperatively (mg)	3	Gupta 2017 [23], Hetta [24], Wahba [28]	85	85	−0.5 (−2.1–1.2)	90	0.58
Intravenous morphine equivalent consumption at 24 postoperative hours (mg)	6	El-Sheikh [22], Gupta [23], Hetta [24], Kulhari [25], Pillai [26], Wahba [28]	144	144	0.5 (−1.8–2.7)	96	0.68
Time to first analgesic request (min)	7	El-Sheikh [22], Gupta [23], Hetta [24], Kulhari [25], Pillai [26], Syal [27], Wahba [28]	164	164	−51.3 (−151.0–48.4)	98	0.31
Rate of postoperative nausea and vomiting within 24 postoperative hours	5	Annamalai [21], El-Sheikh [22], Gupta [23], Kulhari [25], Wahba [28]	26/125	34/124	0.82 (0.55–1.20)	0	0.30

these two regional procedures as a first line treatment, the ease of the PECS block technique [31] compared to the perceived difficulty in performance and reported discomfort with the paravertebral block when the local anaesthetics depresses the pleura [32], along with a possibly reduced incidence of pneumothorax might make the PECS block a more appealing approach in the setting of radical mastectomy.

Interestingly, the subgroup analysis between radical mastectomy combined or not with axillary dissection explains the initial elevated coefficient of heterogeneity, as I^2 values for both subgroups are low. The short-term analgesic benefits of PECS blocks compared to paravertebral blocks are most pronounced in patients who have not had axillary clearance. This might be explained by the fact that axillary dissection would likely require coverage of the intercostobrachial nerve (T1–T2), whose blockade with both paravertebral and PECS blocks are unreliable.

In all included trials, authors investigated the analgesic efficacy of the block rather than anaesthetic efficacy. Therefore, patients all received general anaesthesia and systemic opioid analgesia. But in the light of the recent opioid epidemic, it is worth mentioning that the combination of both techniques with minimal sedation was sufficient to perform radical mastectomy with axillary dissection without requiring general anaesthesia [33].

While our data reports similar modest findings to that described by previous authors [6,7], we included almost three times more randomized controlled trials and patients. We have also used trial sequential analysis to demonstrate that firm evidence has been reached for our primary outcome and excluded a type II error. Based on this robust methodology, we believe that our results require widespread dissemination and will help physicians in their decision-making process.

One of the limitations of this meta-analysis is the difference of local anaesthetic volume injected between groups in more than half of the studies. However, we do not believe that it impacted our pain-related outcomes, as a significant difference appeared at a short time interval after surgery and one would expect that the increased volume would prolong the time to first analgesic request. A further limitation was that the subgroup analysis was not an a priori hypothesis and therefore the superiority of PECS block over PVB when radical mastectomy is not combined with an axillary dissection, should be interpreted with caution. Due to absence of patients monitoring several months after surgery among included trials, we were unable to determine whether PECS block reduces persistent postoperative pain, as it has been demonstrated with paravertebral block [34]. We suggest this topic to be a field of further scientific exploration. As no trials compared both techniques in breast-conserving surgery, we focused on mastectomy surgery, contrary to what we planned to do initially. However, this reduced the heterogeneity of our results. Finally, patient-centred outcome measures, including quality of recovery and satisfaction, have not been assessed in any of the included studies, representing a further critical avenue for further investigation.

In conclusion, there is low evidence that PECS blocks provide marginal postoperative analgesia after radical mastectomy at 2 postoperative hours only, when compared with a paravertebral block, and not beyond. The clinical significance of this finding is probably not meaningful. However, the ease in performing the PECS block, the absence of discomfort of the procedure, along with a possibly reduced incidence of pneumothorax, might make the PECS block a more appealing approach in the setting of radical mastectomy.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2020.109745.

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Table 3
Quality assessment of outcomes reported, with overall quality of evidence reported according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria.

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)	High risk of biases[a]	Inconsistency explained[b]	No serious indirectness[c]	No imprecision[d]	Publication bias detected	349	Reduced pain score in PECS blocks groups	Low quality (⊕⊕OO)[e]
Rest pain score at 12 postoperative hours (analogue scale, 0–10)	High risk of biases[a]	Inconsistency explained[b]	No serious indirectness[c]	Slight imprecision[d]	Publication bias detected	250	Similar pain score in both groups	Low quality (⊕⊕OO)[e]
Rest pain score at 24 postoperative hours (analogue scale, 0–10)	High risk of biases[a]	Inconsistency explained[b]	No serious indirectness[c]	Slight imprecision[d]	Publication bias detected	289	Similar pain score in both groups	Low quality (⊕⊕OO)[e]
Dynamic pain score at 2 postoperative hours (analogue scale, 0–10)	High risk of biases[a]	Inconsistency explained[b]	No serious indirectness[c]	Slight imprecision[d]	Publication bias detected	120	Similar pain score in both groups	Low quality (⊕⊕OO)[e]
Dynamic pain score at12 postoperative hours (analogue scale, 0–10)	High risk of biases[a]	Inconsistency explained[b]	No serious indirectness[c]	Slight imprecision[d]	Publication bias detected	120	Similar pain score in both groups	Low quality (⊕⊕OO)[e]
Dynamic pain score at 24 postoperative hours (analogue scale, 0–10)	High risk of biases[a]	Inconsistency explained[b]	No serious indirectness[c]	Slight imprecision[d]	Publication bias detected	120	Similar pain score in both groups	Low quality (⊕⊕OO)[e]
Intravenous morphine equivalent consumption intraoperatively	High risk of biases[a]	Inconsistency explained[b]	No serious indirectness[c]	Slight imprecision[d]	Publication bias detected	170	Similar consumption in both groups	Low quality (⊕⊕OO)[e]
Intravenous morphine equivalent consumption at 24 postoperative hours	High risk of biases[a]	Inconsistency explained[b]	No serious indirectness[c]	Slight imprecision[d]	Publication bias detected	288	Similar consumption in both groups	Low quality (⊕⊕OO)[e]
Time to first analgesic request	High risk of biases[a]	Inconsistency explained[b]	No serious indirectness[c]	Slight imprecision[d]	Publication bias detected	328	Similar rate in both groups	Low quality (⊕⊕OO)[e]
Rate of postoperative nausea and vomiting within 24 postoperative hours	High risk of biases[a]	Inconsistency explained[b]	No serious indirectness[c]	No imprecision[d]	Publication bias detected	249	Similar rate in both groups	Low quality (⊕⊕OO)[e]

[a] All articles had at least one item quoted as high risk of bias.
[b] Elevated I^2 explained with subgroup analysis.
[c] Consistent definition of the reported outcome.
[d] The clinical decision would not be modified whether the upper of lower boundary limit of the confidence interval represented the truth.
[e] There was an initial concern with inconsistency, which was addressed by subgroup analysis. Because of Limitations and Publication bias, we down-rated the quality of evidence by two levels.

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Author's contribution

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

Kariem El-Boghdadly: This author assessed the articles, extracted the data, and wrote the manuscript.

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

Declaration of competing interest

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