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Original Article

Pectoral Nerve (PECs) block for postoperative analgesia-a systematic review and meta-analysis with trial sequential analysis

Zhaosheng Jin[1], Ru Li[1], Tong J Gan[1], Yaohua He[2], Jun Lin[1]

[1]*Department of Anesthesiology, Stony Brook University Health Science Center, Stony Brook, NY 11794-8480, USA;* [2]*Taiho Oncology, Inc., Princeton, NJ 08540, USA*

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Abstract: Background and objective: Pectoral Nerve (PECs) block is a fascial plane block first described by Blanco et al. for postoperative analgesia in breast surgery. The procedure is now widely used, and several small clinical trials have been published and reported favorably on the analgesic efficacy of PECs block. In this systematic review and meta-analysis, we will summarize the current evidence on the efficacy of PECs block. Methods: We identified and analyzed 19 randomized control trials from PubMed, Central, EMBASE, CINAHL, Web of Science citation index, US clinical trials register and Google Scholar. The primary outcome was 24-hour opioid requirement, and secondary outcomes included pain scores, postoperative nausea and vomiting and other complications. Results: Compared to systemic analgesia, PECs block was associated with reduced 24 hours opioid requirement [mean difference (MD) = -10.66 mg], lower pain score [9-12 hours postoperatively: MD = -1.18; 24 hours postoperatively: MD = -0.79] and less frequent PONV [risk ratio (RR) = 0.37, numbers needed to treat (NNT) = 5]. While the failure rate of PECs block was not well defined, several studies reported significant intraoperative opioid requirement despite PECs block. Lastly, trial sequential analysis indicated that no more clinical trials are needed to demonstrate the opioid sparing effect of PECs block. Conclusion: When compared to general anesthesia with systemic opioids, PECs block was associated with significantly better perioperative pain control. There are currently insufficient data on the complication and failure rate of PECs block in clinical practice.

Keywords: Truncal blocks, pain outcome measurement, postoperative pain, acute pain

Introduction

It is estimated that 394,000 breast cancer related surgeries as well as 497,000 cosmetic surgeries are carried out in the US every year [1, 2]. Breast procedures can be associated with significant postoperative pain, delayed ambulation and increased risk of complications. Systemic opioid is the primary analgesic option after surgery. However opioid administration is associated with adverse effects such as nausea, vomiting, respiratory complications, hyperalgesia and immunosuppression [3, 4]. Over the last few decades, the opioid based postoperative analgesia is increasingly replaced by regional anesthesia techniques such as thoracic epidural anesthesia and paravertebral nerve block (PVB) [5]. Although there is a risk of block related complications and toxicity with regional anesthesia [6], they provide high quality postoperative analgesia and reduce long-term complications such as persistent postoperative pain [7, 8].

The 'PECs' block is a novel regional anesthesia technique first described by Blanco in 2011, and involve ultrasound-guided local anesthetic infiltration of the tissue plane between the pectoralis major and minor muscles with the aim of anesthetizing the pectoral nerves [9]. The technique was subsequently modified with an additional injection to block the upper intercostal nerves which supply the chest and axilla, and named the PECs II block [10]. This is typically done with the patient in the supine position, under ultrasound guidance, with a recommended local anesthetic dose of 0.4 $ml.kg^{-1}$ 0.25% levobupivacaine [9, 10]. As suggested by Bl-

anco, this is a fairly simple technique to learn, provides good analgesia, and avoids the risk of complications associated with PVB and thoracic epidural such as sympathetic blockade, risk of dura puncture and unintentional bilateral block [9, 11, 12].

In the past few years, several small-scale single center studies of PECs block have been published. We therefore conduct this systematic review and meta-analysis to summarize the finding from the published clinical trials to date and use the aggregated data to compare the immediate postoperative outcomes of PECs block to general anesthesia with postoperative systemic opioids. Our primary hypothesis is that PECs block is associated with reduced postoperative pain and opioid requirement compared to systemic analgesia alone.

Methods

Study objectives

Our primary aim is to compare the postoperative pain control in patients who had breast surgery with PECs block to those who had general anesthesia only with postoperative systemic analgesia. The primary outcome of our study is the 24-hour opioid requirement in the two cohorts.

Secondary outcomes included pain numeric rating scale (NRS) score at the following time points: In Post-anesthesia care unit (PACU) or within 1 hour postoperatively, 4-6, 9-12 and 24 hours postoperatively. We also included intraoperative opioid dose, time to first rescue analgesia, and the incidence of postoperative nausea and vomiting (PONV) as well as incidence of any other significant complications. While we also compiled patient satisfaction as a parameter, the heterogeneous nature of the assessment methods means we were unlikely to have meaningful comparison between the studies, we therefore decided only to include the descriptive findings.

Search strategy

This study conformed to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) statement (Supplementary Table 1) [13]. We used search terms 'PECs block OR pectoral block OR pectoralis block' in PubMed, Central, EMBASE, CINAHL, Google Scholar, Web of Science citation index, US clinical trials register, and we hand searched the major regional anesthesia conference abstracts for the last 3 years. We did not conduct a preliminary literature search. All searches were conducted independently by two authors and discrepancies were discussed after the search process. The last search was carried out on July 18th, 2019.

Study selection criteria

Studies were initially filtered based on title and abstract using the following criteria:

Patients: Adult (>18 years old) patients undergoing breast surgeries, studies with non- breast relate surgeries were noted but excluded from the meta-analysis. Intervention: General anesthesia with single injection PECs I or PECs II block. Control: General anesthesia without PECs block. We excluded studies where PECs blocks were conducted on all participants (i.e. no valid control group), studies on subjects who has not had surgery under general anesthesia, studies where patient received more than one regional anesthesia. Outcomes: Opioid requirement, pain score, risk of PONV, time to rescue analgesia as described in the study objective section. Studies: Only competed randomized control trials were selected for inclusion. Conference abstracts more than 3 years old were excluded. At the time of the literature search we did not impose any date or language restriction on published journal articles.

Data extraction

Data extraction was conducted using standardized pro-forma and checked by a second author. Extracted data included bibliographical information (author, year, PubMed ID or article URL), study design (description of control and intervention, number of participants), pain related outcomes (NRS score and opioid requirement at the time points outlined above, time to first rescue analgesia), other outcome measures (incidence of PONV, other complications, length of stay in PACU and length of stay in the hospital). All opioid doses were converted to morphine equivalent dose according to the standard conversion [14]. Wherever the data is incomplete, we collected the data according to the following protocol: When NRS was reported as non-parametric data (with median and inter-

quartile range), we estimated the mean and standard deviation assuming normal distribution using methods described by Cochrane [15], if the standard deviation (SD) is still not available we substituted the SD with the pooled SD of the other studies within the same comparison by: $\sum \frac{\sqrt{N \times SD^2}}{N}$. When study results are only displayed as graphical form, two authors independently extracted the data using WebPlot Digitizer as previously described [16, 17].

Risk of bias assessment was done by two authors independently but at the same time, any disagreements were discussed with and resolved by a third author. We assessed each included study according to the Cochrane Collaboration tool for assessing risk of bias [18]. Studies were assessed on randomization, allocation concealment, participants and personnel blinding, observer blinding, incomplete data and selective reporting; each category of the study was assigned 'low risk', 'high risk' or 'unclear risk'.

Statistical analyses

We conducted meta-analysis for outcomes reported in more than one study, if only one study is available, the results were reported descriptively. The data is analyzed using Review Manager V5.3. (Cochrane Collaboration, Copenhagen). As the effect size for the outcomes are of clinical relevance, for continuous variables, we calculated mean differences (MD) by inverse-variance method. For dichotomous variables, we calculated the risk ratios (RRs) by Mantel-Haenszel method, we also calculated the numbers needed to treat (NNT) to quantify the clinical significance of the effect. Due to the inherent heterogeneous nature of block performance by different practitioner, random effect model was used in the analysis. For outcomes that contained more than 5 studies, publication bias was assessed using Egger's regression using methods described by Suurmond et al. [19]. For outcome measures with positive findings, we also calculated the Fail-safe number using Rosenthal's methods using the Comprehensive Meta-Analysis V3 [20]. For all outcomes, the statistical significance was set to $P<0.05$. We used GRADEpro Guideline Development Tool (GRADEpro GDT, McMaster University, 2015) to assess the quality of the meta-analysis findings.

In addition, we also conducted a trial sequential analysis (TSA) of the included studies using our primary outcome. TSA is a form of sequential hypothesis testing which analyze the available data (in this case RCT findings) in chronological order. In meta-analyses, TSA can be used to assess the likely influence of future trials on the pooled findings and estimate the point at which further studies are not likely to change the pooled findings [21]. For the statistical analysis, we used the TSA Viewer version 0.9 β (Copenhagen Trial unit, Copenhagen). We determined that for moderate quality clinical evidence, α is set to 5% significance level and statistical power set at 80%; for strong clinical evidence, α is set to 1% significance level and statistical power set at 90%.

Results

Description of included studies

Following the search criteria, we screened a total of 1,409 clinical studies in addition to conference abstracts from 14 recent conferences and identified 19 studies for inclusion (**Figure 1**). The risk of bias assessments were shown in **Figure 2**, and the characteristics of all the included studies were described in **Table 1** [22-40]. The most common source of bias identified was blinding of the patients and personnel, as not all studies used sham block as part of the protocol, and some regional anesthesia techniques (epidural anesthesia and paravertebral block) were generally done with the patient awake in sitting position.

In addition, we noted one study by Kumar et al. [41] investigated the benefit of PECs block for sternotomy for cardiac surgery, and an unpublished clinical trial which investigated the benefit of PECs block for shoulder surgery [42]. These were not included in the meta-analysis.

PECs block analgesic efficacy

There were 16 studies, which reported the 24-hour opioid requirements, and pooled results reported significantly lower opioid requirement in the PECs cohort. There was however significant heterogeneity [MD = -10.7 mg (-13.5 to -7.8), I^2 = 98%, Egger's regression $P<0.001$, **Figure 3**]. Due to the high heterogeneity, we conducted post hoc subgroup analyses, dividing the studies according PECs I compared to

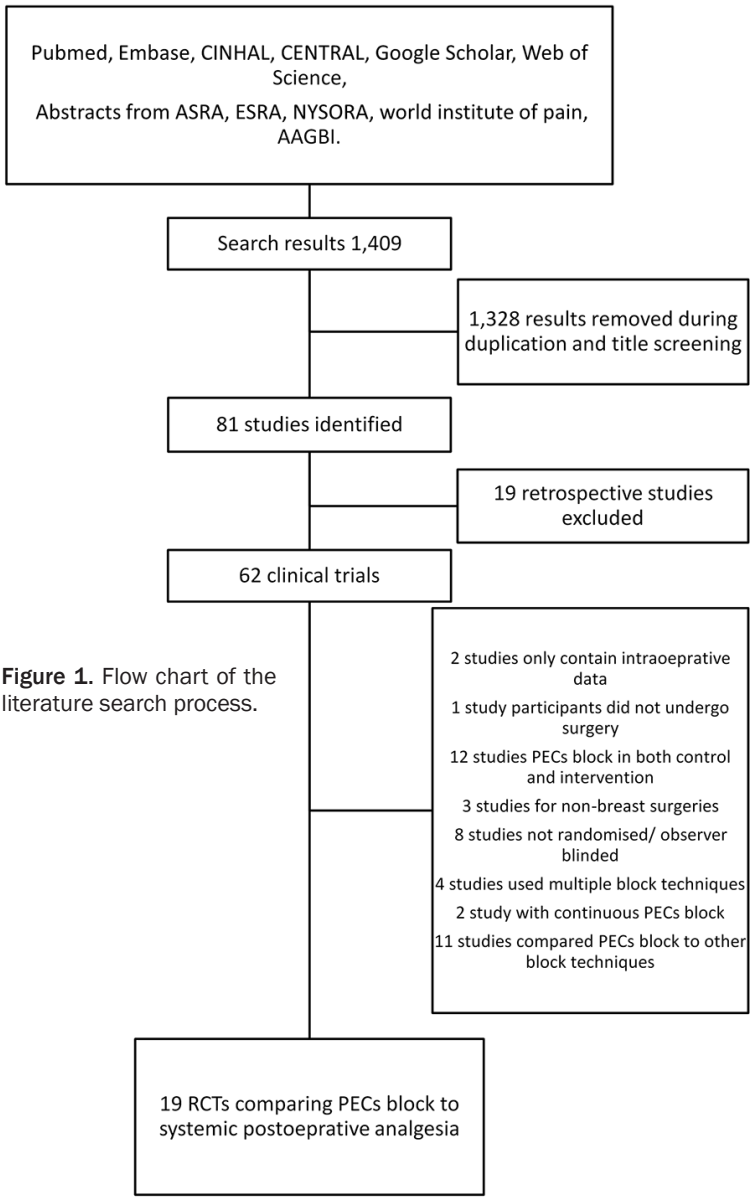

Figure 1. Flow chart of the literature search process.

PECs II block; the dose of local anesthetic administered; as well as the surgery types (Supplementary Figures 1, 2, 3). However, none of the models considerably reduced the heterogeneity. The quality of evidence is low due to heterogeneity and publication bias.

There were 13 studies which reported NRS score in PACU; 13, 10 and 15 studies reported NRS score at 4-6 hours, 9-12 hours, and 24 hours respectively [23-25, 27, 29, 31, 32, 34, 35, 37-40]. Meta-analysis demonstrated a statistically significant mean difference in pain score at all time points, however the effect size diminished over time. [PACU: MD = -1.93 (favoring PECs block, -1.01 to -2.85), I^2 = 98%; 4-6 Hours: MD = -1.17 (-0.48 to -1.87), I^2 = 97%; 9-12 Hours: MD = -1.18 (-0.45 to -1.92), I^2 = 97%; 24 hours: MD = -0.79 (-0.37 to -1.22), I^2 = 97%, **Figure 4**, Supplementary Figures 4, 5, 6]. There was considerable heterogeneity and Egger's regression for publication bias was positive at PACU, 4-6 hours and 9-12 hours.

Meta-analysis reported significantly longer time to rescue opioid in the PECs cohort [MD = 280 min (127 to 443) (favors PECs) I^2 = 100%, Egger's regression P<0.001, Supplementary Figure 7], Most notably, Kumar et al. [32] reported considerable longer time to rescue analgesia in the PECs cohort than any other study (18.8 hours), whether this is due to long block duration or different threshold for rescue analgesia administration is not clear.

Nine studies compared the incidence of postoperative nausea and vomiting. Meta-analysis demonstrated significantly lower rate of PONV in the PECs group [RR = 0.37 (0.17-0.83), I^2 = 82%, NNT = 5, **Figure 5**]. Egger's regression was significant. Eight studies reported monitoring of other complications. The aggregated complications included 5 cases of paranesthesia in the PECs cohort (from 452 cases), no other complications were reported in the systemic analgesia cohort.

Two studies reported findings on patient satisfaction. Neethu et al. reported on patient satisfaction and found significantly better satisfaction in the PECs cohort compared to the systemic analgesia cohort [35]; while Al Ja'bari et al. [22] reported no significant difference.

PECs block failure rate

In addition, we also conducted a post hoc analysis on the rate of PECs block failure. We identi-

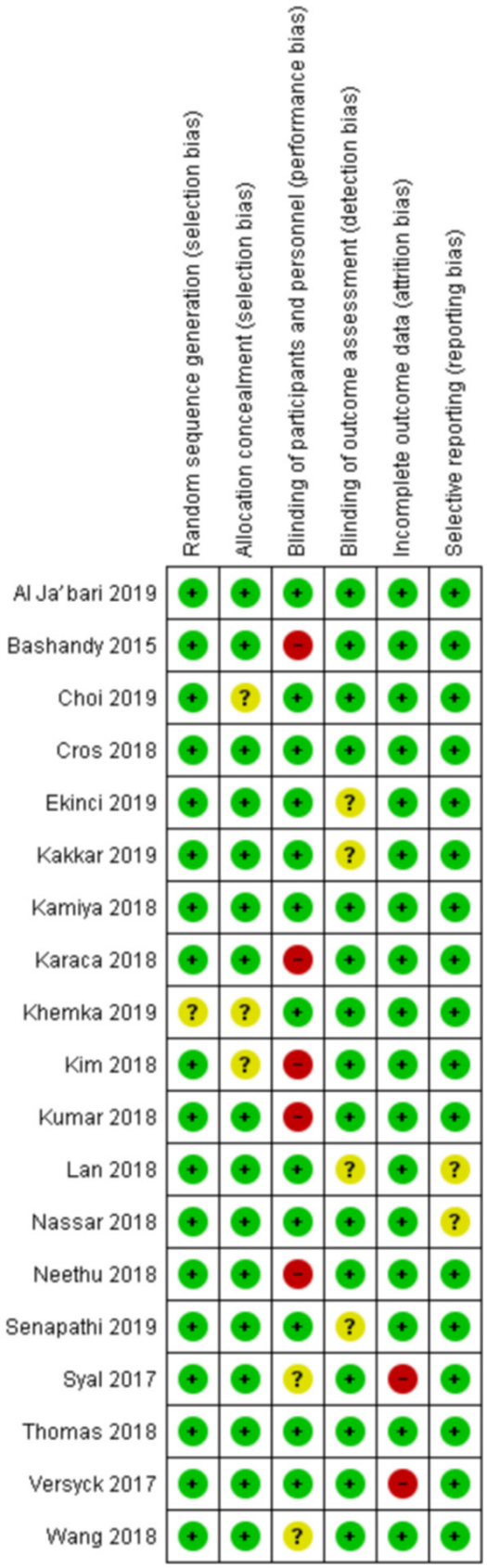

Figure 2. Risk of bias assessment according to Cochrane Collaboration tool for assessing risk of bias [18].

fied several studies which reported very high intraoperative opioid requirements in the PECs cohort [22, 25, 31, 40]. This may be down to variation in institutional practice and could also suggest high prevalence of unreported block failure.

Trial sequential analysis

We found that the cumulative Z score crossed the monitoring boundaries of both moderate and strong evidence models, which indicates statistically significant benefit of the cumulative study results. For moderate evidence, information size required for moderate evidence is 293, and 528 for strong evidence; in comparison, the included studies contained a total of 1,116 participants (**Figure 6**).

Discussion

Our meta-analysis demonstrated that compared to general anesthetic and systemic analgesia, PECs block is associated with significantly better postoperative pain relief and less opioid use. PECs block is also associated with significantly less frequent PONV. The TSA also suggests that the currently available evidence has already exceeded the amount required for conclusive evidence.

Hussain et al. published a similar meta-analysis in 2019, which was limited to PECs II block in mastectomy patients, and identified eight studies comparing PECs block to no block [43]. The authors also conducted various subgroup analyses and reported that the extent of opioid sparing was not associated with the surgical invasiveness and local anesthetic dosage. In addition to the above, we also found no difference between PECs I and PECs II block in terms of analgesic efficacy, further head to head comparisons are needed in this area.

Implications for clinical practice

Compared to systemic analgesia only, PECs block required significantly less opioid over the first postoperative day and this is associated with lower incidence of PONV, a common opioid related adverse effect. While good analgesia is

Table 1. Characteristics of included studies

	Methods	Participants	Interventions	Outcomes	Note
Al Ja'bari 2019 [22]	RCT, patient, observer blinded	42 female adults for radical mastectomy	PEC 2 block after GA vs systemic analgesia	Opioid requirement, complications	
Bashandy 2015 [23]	RCT, Observer blinded	120 female adults for breast cancer surgery	PEC 2 before GA vs systemic analgesia	Pain, opioid use, Length of stay in PACU and hospital, PONV	
Choi 2019 [24]	RCT, patient, and observer blinded	39 female adults for breast cancer surgery	PEC 2 block after GA vs systemic analgesia	Intraoperative hemodynamics, pain score, rescue analgesia requirement	Registered on ClinicalTrials.gov, NCT03210220
Cros 2018 [25]	RCT, patient, practitioner and observer blinded	128 female adults for breast cancer surgery	PEC 1 with Bupivacaine vs Saline after GA	Pain-intraoperative to 7 days post op	
Ekinci 2019 [26]	RCT, patient blind	90 female adults for breast augmentation surgery	PEC 1 block 30 ml after GA vs systemic analgesia	Pain, opioid requirement, complications	
Kamiya 2018 [27]	RCT, patient, practitioner and observer blinded	59 female adults for breast cancer surgery	PEC 2 with Bupivacaine vs saline after GA	pain, PONV	
Kakkar 2019 [28]	RCT, patient blind	60 female adults undergoing modified radical mastectomy	PEC 1 and 2 block after GA vs systemic analgesia	Pain, opioid requirement and time to rescue analgesia	
Karaca 2018 [29]	Randomized control trial, observer + patient blinded	54 female adults for breast augmentation	PEC 2 block after GA vs systemic analgesia	Opioid requirement; pain at rest + movement, LOS PACU + hospital, first opioid time, PONV, other complications	Registered in the Australian New Zealand Clinical Trials Registry (No: ACTRN 12617000687392)
Khemka 2019 [30]	RCT, patient blind	100 female adults for breast cancer surgery with axillary dissection	PEC 1 and 2 block after GA vs systemic analgesia	Pain, opioid requirement, PONV, shoulder mobility	Registered with the Clinical Trials Registry of India, CTRI/2017/10/010131
Kim 2018 [31]	RCT, only observer blinded	78 female adults for breast cancer surgery	PEC 2 block after GA vs systemic analgesia	Pain, analgesia related complication, opioid and NSAIDs consumption	Registered on Clinical Research Information Service KCT0002509
Kumar 2018 [32]	RCT, observer blinded only	50 female adults for breast cancer surgery	PEC 2 before GA VS systemic analgesia	Pain at rest and on abduction, opioid requirement, PONV	
Lan 2018 [33]	RCT, patient blind	65 female adults for modified radical mastectomy	PEC 2 block after GA vs systemic analgesia	Pain, opioid requirement	
Nassar 2018 [34]	RCT, patient, personnel and observer blinded	20 female adults for breast augmentation	PEC 2 with bupivacaine vs saline	pain score	
Neethu 2018 [35]	RCT, patient and observer blinded	60 female adults for breast cancer surgery	PEC 2 after GA vs systemic analgesia	Pain, opioid requirement, side effects	Registered with the Clinical Trials Registry of India CTRI/2015/12/006457
Senapathi 2019 [36]	RCT, patient blinded	50 adult females for modified radical mastectomy	PEC 2 block after GA vs systemic analgesia	Pain, opioid requirement	
Syal 2017 [37]	RCT	65 f female adults for breast cancer surgery	PEC 2 vs paravertebral block post-op vs systemic analgesia	Pain score, opioid requirement, time to rescue analgesia	
Thomas 2018 [38]	RCT	60 adult female patients for mastectomy	PEC 2 with Bupivacaine vs saline	Pain severity, opioid requirement	
Versyck 2017 [39]	RCT	140 female adults for breast cancer surgery	PEC 2 with Bupivacaine vs saline	opioid use	Registered on ClinicalTrials.gov, NCT02544282
Wang 2018 [40]	RCT, patient and observer blinded	64 adult female undergoing mastectomy with immediate reconstruction	PEC 2 under GA vs systemic analgesia	Pain score, opioid requirement, Length of stay	Registered on Chinese Clinical Trial Register, ChiCTR-IOR-17010540

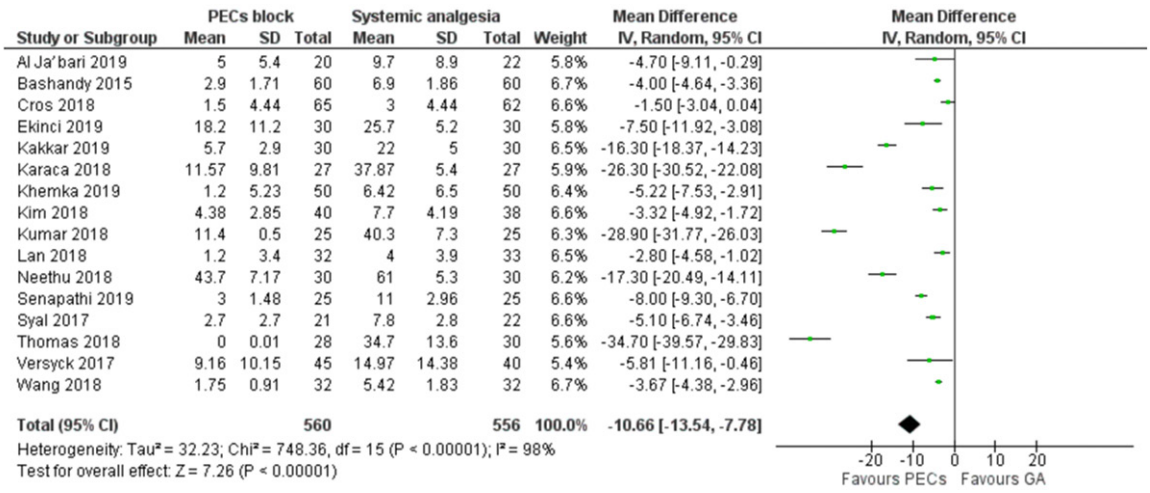

Figure 3. Forest plot comparing the 24-hour opioid requirement of PECs and systemic analgesia cohort.

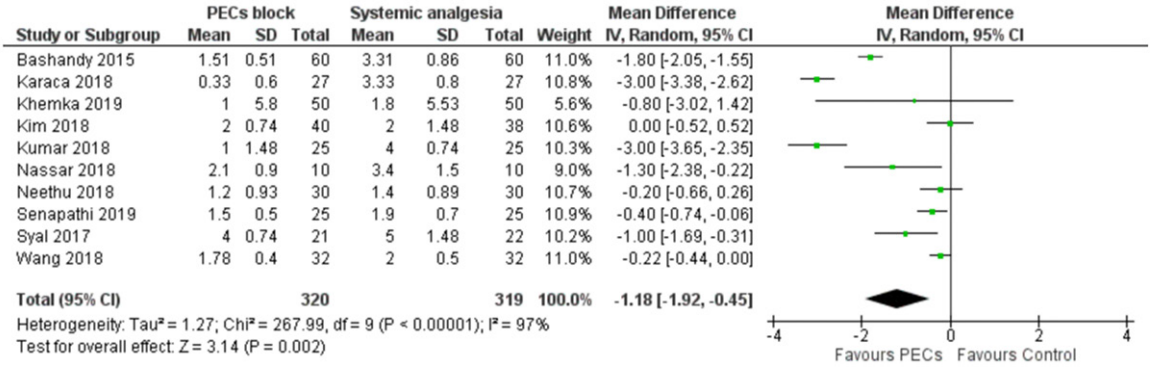

Figure 4. Forest plot comparing the Numerical Rating Scale score at 9-12 hours postoperatively, between the PECs and systemic analgesia cohort. +: pooled standard deviation was used.

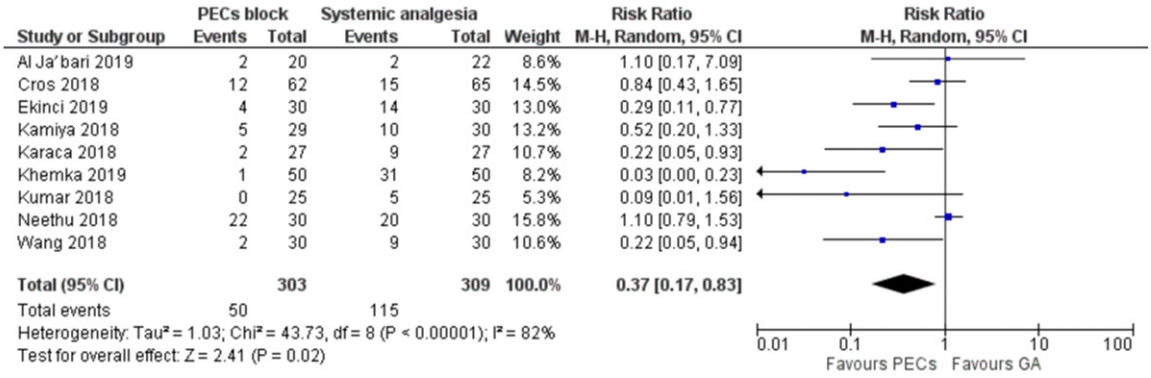

Figure 5. Forest plot comparing the incidence of PONV of PECs and systemic analgesia cohort.

vital for postoperative recovery, excessive postoperative opioid administration have been linked to increased complication rate and health care cost [44-46]. Due to the small size of the studies and the short follow-up window (up to 24 hours), it is not possible to directly link the opioid sparing effect of PECs block to reduced postoperative complications in our analysis. Larger scale studies are needed to fully assess the effect of regional anesthesia on postoperative outcomes as well as the cost effectiveness.

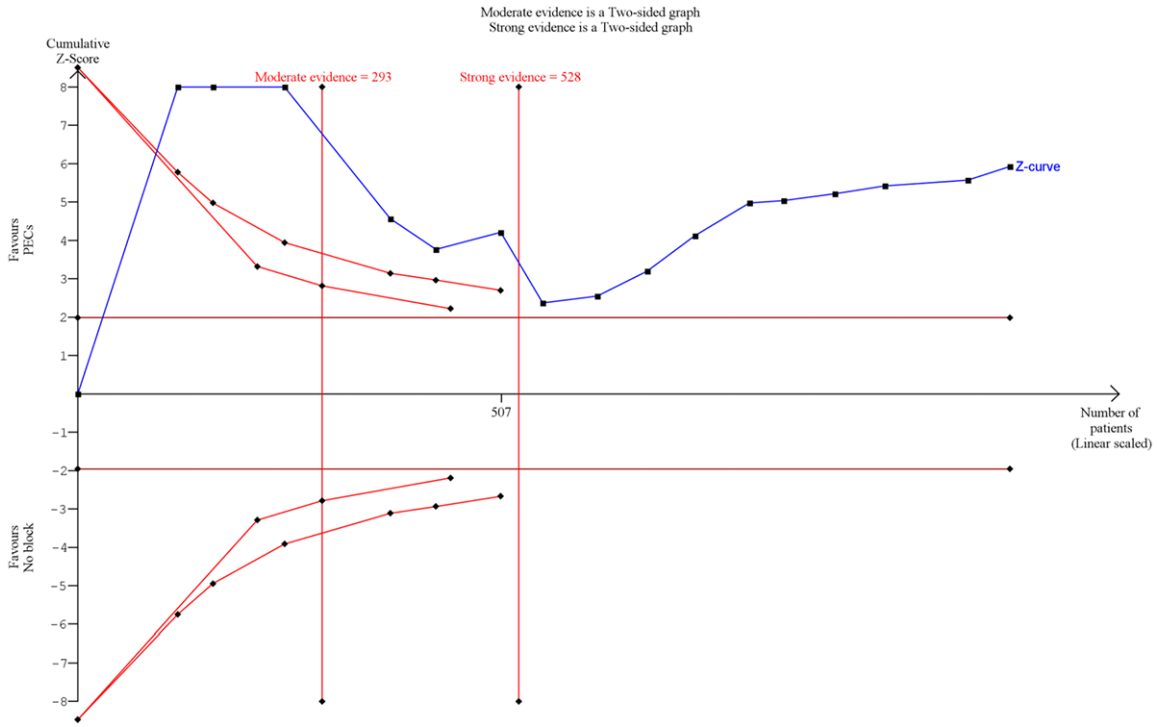

Figure 6. Trial sequential analysis of opioid requirement in PECs block vs systemic analgesia cohorts. Y axis (Z-score) represents the normalized effect size, with positive Z-score represents superiority of PECs block and negative Z-score represents superiority of no block. The blue line represents the cumulative Z-score of the clinical trials added in chronological order. The maroon lines represent the conventional model boundary of P<0.05; the red curves represent the moderate and strong evidence monitoring boundaries. Information size required is displayed as red vertical lines.

The results of our meta-analysis also suggest that despite requiring less opioid, patients in the PECs cohort still reported less postoperative pain than the systemic analgesia only. This is not surprising as most literatures support the superior analgesic effects of regional anesthesia compared to opioids [8]. However, the inter-study difference could indicate that the extent of the therapeutic benefit differs considerably between practitioners, so depending on availability of skilled practitioner it may not be possible to achieve the pooled effect size reported here.

Implications for research

The trial sequential analysis indicates the currently available RCTs are sufficient in demonstrating the opioid sparing effect of PECs block, and further RCTs on the same topic are not likely to alter the conclusion. Instead, we would recommend that future studies should be powered to rarer outcomes, such as block and opioid related complications, as well as longer term outcomes.

In addition, a multi-center clinical trial with standardized skilled practitioner at each site would be needed in order to conduct a large trial while accounting for any possible practitioner skill related confounding.

As Kumar et al. mentioned, PECs block may potentially be beneficial for non-breast surgeries [41]. Patients who undergo cardiothoracic surgeries with subsequent intensive care unit admission are at a significant risk of developing pain related complications. Regional anesthesia is increasingly being adopted by intensive care physicians for postoperative pain management [47, 48]. PECs block could be carried out in intensive care units for cardiothoracic surgery patients. This would require further study.

Lastly, the analgesic efficacy of PECs block compared to other thoracic wall regional anesthesia techniques (such as paravertebral block and serratus plane block) are not well studied. Most notably, thoracic paravertebral block was once seen as the 'gold standard' regional anesthesia technique for breast surgery. However,

some have argue that PECs block may have some advantages in terms of safety [11] and may be technically less challenging to administer [49, 50]. The analgesic efficacy of the different techniques remains to be studied.

Limitations

One major limitation of our meta-analysis is the high degree of heterogeneity of the studies, which may limit the reliability of the findings. Despite controlling for surgery type, block technique, and local anesthetic dosage, there were significant inter-study difference in the reported opioid dosages and pain scores. For example, we observe that in some studies very minimal amount of opioid were given after radical mastectomy without regional anesthesia [23, 31], while other studies reported very high opioid dose despite PECs block [51]. One explanation is that the control cohort may have received local anesthetic infiltration at the wound site which reduces the postoperative pain, this was however not specified in most of the studies. The variation in opioid requirement could also be due to skill difference in block performance between studies. Indeed, the heterogeneity in intraoperative opioid requirement reported in several studies would suggest inconsistent block success rate across the included studies. Despite the high heterogeneity, both the random effect model meta-analysis and the trial sequence analysis would suggest that current literature does still support the analgesic efficacy of PECs block. Lastly, we did not search any non-English databases, this was due to the practical difficulties in constructing stringent search strategy in foreign language as well as accurate appraisal of foreign language articles. While it is possible that this may introduce an element of bias in the study selection, previous study by Moher et al. suggests that this is unlikely to have significant impact on the findings of the meta-analysis [52].

Conclusion

When compared to general anesthesia with systemic opioids, PECs block is associated with significantly better postoperative pain control, this conclusion is not likely to change with further clinical trials. There are however limited data on the risk of both block and opioid related complications, as well as the comparison between PECs block and other regional anesthesia techniques.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jun Lin, Department of Anesthesiology, Stony Brook University Health Science Center, Stony Brook, NY 11794-8480, USA. Tel: 631-444-2975; E-mail: jun.lin@stonybrookmedicine.edu

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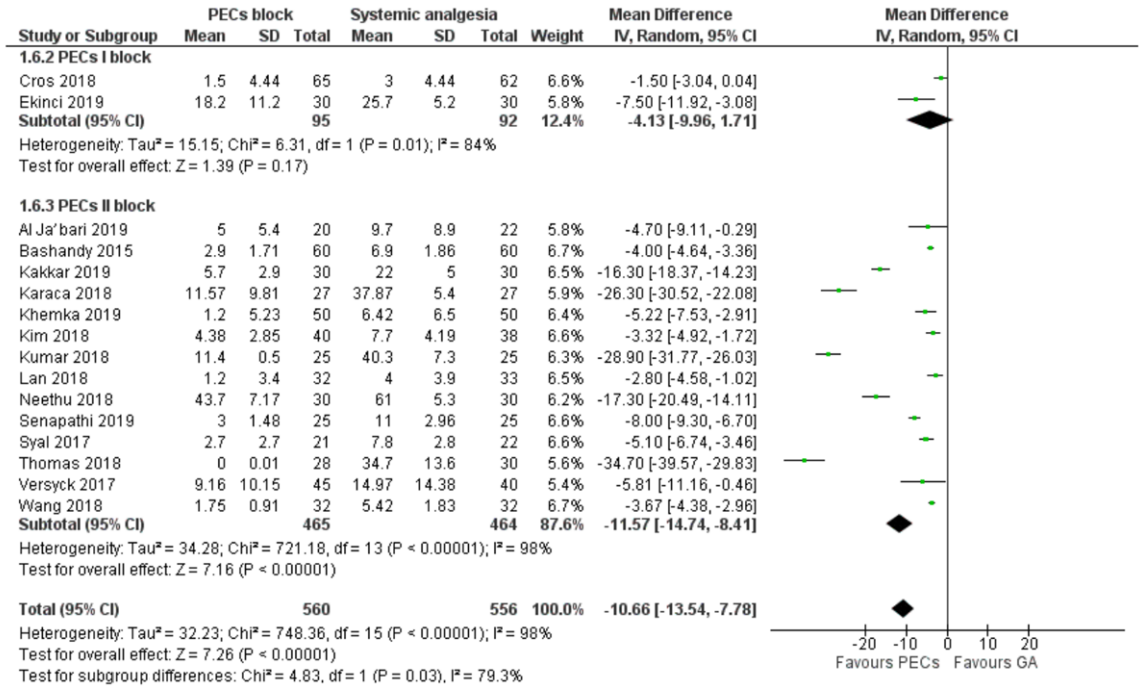
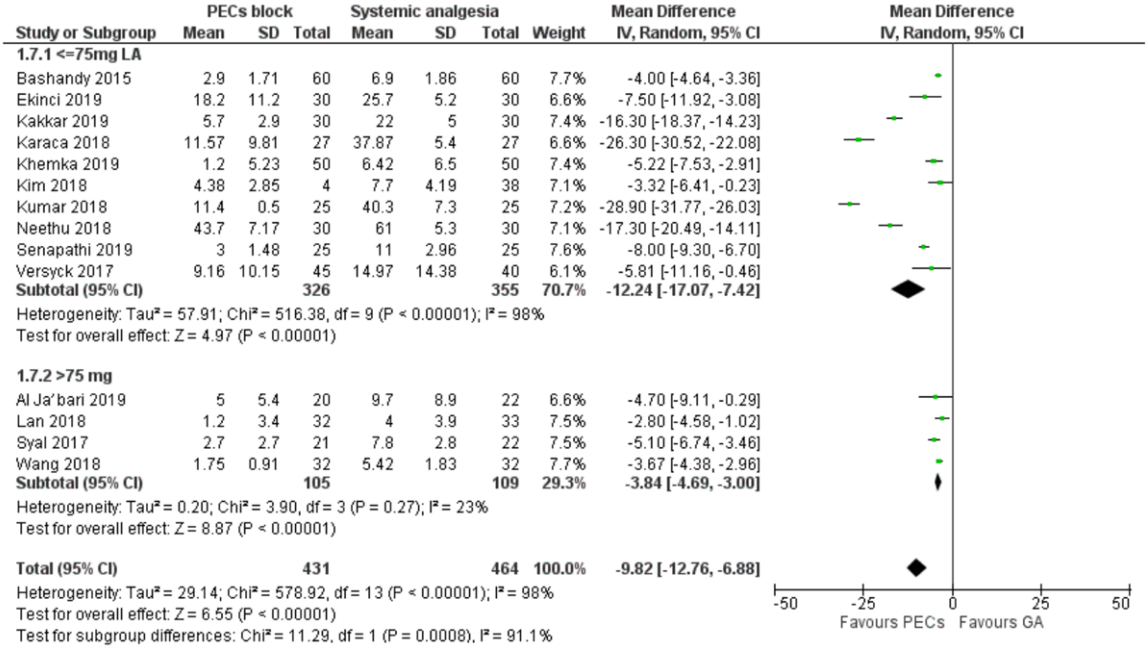
Supplementary Table 1. PRISMA Statement

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7 and **Figure 2**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8 and **Figure 1**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**Table 1**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8 and **Figure 2**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**Figures 3-5**, Supplementary Figures

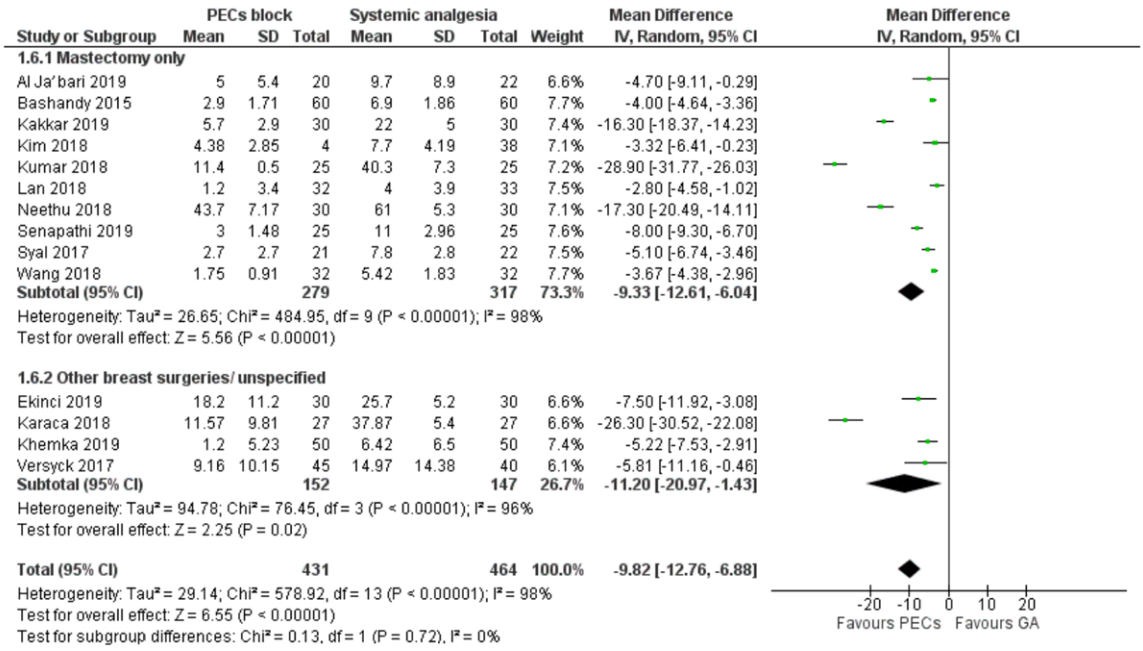
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-10, **Table 1**, **Figures 3**-**5**, Supplementary Figures
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**Figure 2**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**Table 1**, Supplementary Figure.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13



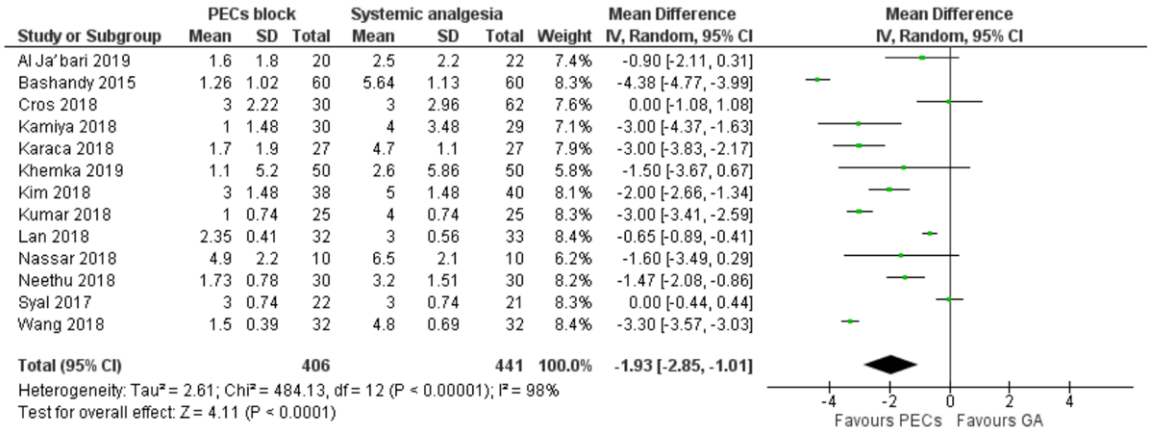
Supplementary Figure 1. Subgroup analysis of 24-hour opioid requirement of PECs I studies compared to PECs II studies.



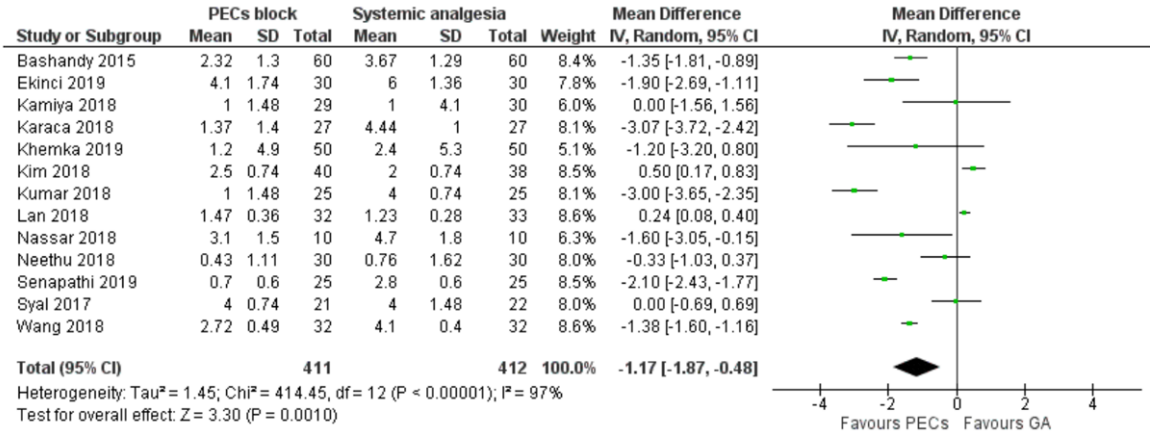
Supplementary Figure 2. Subgroup analysis of 24-hour opioid requirement according to the dose of local anesthetics used for the PECs block, studies was divided at the 75 mg threshold.



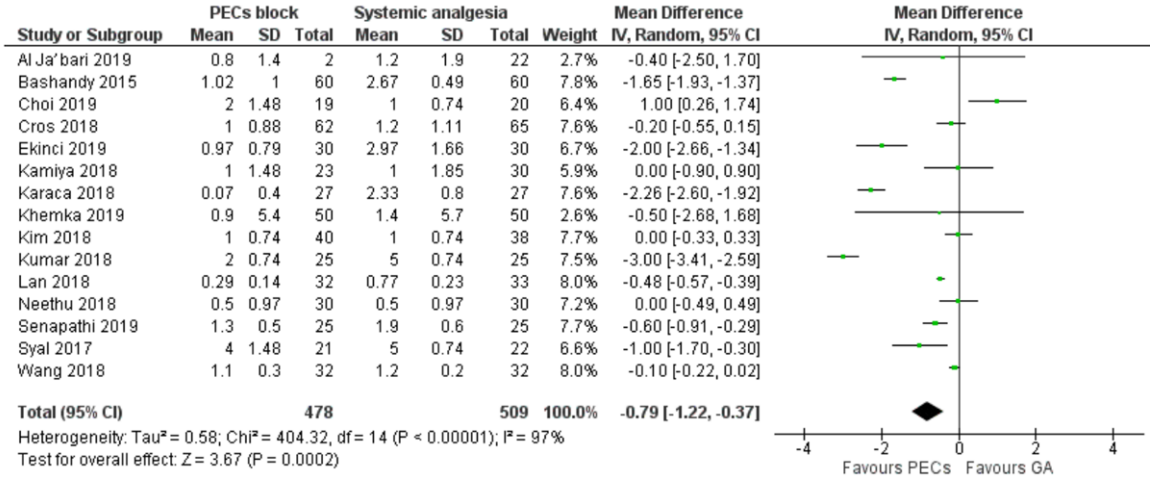
Supplementary Figure 3. Subgroup analysis of 24-hour opioid requirement according to the surgeries included, studies with only modified radical mastectomy were group separately to those which included all breast cancer surgery.



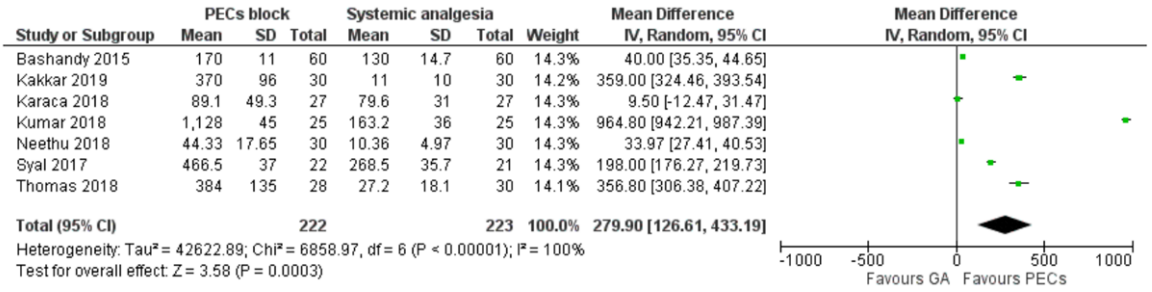
Supplementary Figure 4. Forest plot comparing the Numerical rating scale (NRS) of PECs and systemic analgesia cohorts in PACU.



Supplementary Figure 5. Forest plot comparing the Numerical rating scale (NRS) of PECs and systemic analgesia cohorts 4-6 hours postoperatively.



Supplementary Figure 6. Forest plot comparing the Numerical rating scale (NRS) of PECs and systemic analgesia cohorts 24 hours postoperatively.



Supplementary Figure 7. Forest plot comparing the time to rescue analgesia (min) in the PECs and systemic analgesia cohort.