Analgaesic efficacy of single-injection serratus anterior plane block for breast surgery: A systematic review, meta-analysis and trial sequential analysis of randomised controlled trials

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ABSTRACT

There is conflicting evidence regarding the analgaesic efficacy of single-shot serratus anterior plane block (SAP) for breast surgery. This meta-analysis aimed to evaluate the analgaesic efficacy of SAP compared with non-block care (NBC) and other regional blocks, i.e. paravertebral block (PVB) and modified pectoral nerve block (PECS block) for breast surgery. PubMed, Embase, Scopus, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov were searched. We included randomized controlled trials reporting the use of the SAP block in adult breast surgery. The primary outcome was postoperative oral morphine equivalent (OME) consumption for up to 24 hours. Random-effects models were used to pool results and mean difference (MD), and odds ratio (OR) was calculated for continuous and dichotomous outcomes, respectively. GRADE guidelines were used to evaluate the strength of evidence, and trial sequential analysis (TSA) was performed to provide certainty to the conclusion. Twenty-four trials enrolling 1789 patients were included. Moderate strength evidence suggested that SAP provided a significant reduction in 24-hour OME compared with NBC [MD – 24.9 mg (95% CI – 41.54, –8.25; $P < 0.001$, $I^2 = 99.68\%$)]. TSA ruled out the possibility of false-positive results. Subgroup analysis for the SAP demonstrated that the superficial plane approach was more effective in reducing opioid consumption than the deep approach. The odds of developing PONV were significantly lower in SAP compared to NBC. Compared with PVB and PECS, SAP block was not statistically different for 24-hour OME and time to first rescue analgaesia. Single-shot SAP reduced opioid consumption, prolonged analgaesia duration, lowered pain scores, and decreased the incidence of PONV compared to NBC. There was no statistically significant difference in the studied endpoints between SAP, PVB, and PECS blocks.

Key words: Analgesia, breast surgery, meta-analysis, opioid consumption breast surgery, regional breast surgery, serratus anterior plane, systematic review

INTRODUCTION

Poor postoperative pain management after breast surgery increases recovery time, length of hospital stay and overall healthcare cost.[1] Effective multimodal analgesia is the cornerstone of postoperative pain management.[2] Several regional blocks are utilized for postoperative analgesia, including thoracic epidurals, paravertebral blocks (PVB), pectoral nerve (PECS) blocks and serratus anterior plane (SAP)

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blocks.[3] Although PVB and PECS blocks have an established role in postoperative pain management, PVBs can be technically challenging to perform and include life-threatening complications such as pneumothorax and unintentional subarachnoid injection. High-volume injections in the PECS block can complicate the identification of surgical planes.

The SAP block is a simpler and less invasive alternative. It involves depositing local anaesthetic (LA), either superficial or deep, to the serratus anterior muscle (SAM), with resultant blockade of the third through sixth intercostal nerves, long thoracic nerve and thoracodorsal nerve.[4] The randomized controlled trials (RCTs) conducted to evaluate the role of SAP in breast surgery have revealed conflicting evidence. Previous meta-analyses evaluating the role of SAP block have been limited by pooling of trials involving different surgical procedures (including breast and thoracic surgery trials) and pooling of SAP with other blocks.[5,6]

Hence, we performed this meta-analysis and collated the existing data from prospectively published RCTs evaluating the analgesic efficacy of SAP block compared to NBC or other blocks. The primary outcome of this meta-analysis was analgaesic consumption during the first 24 hours. We also investigated the pain scores at various time intervals, time to first rescue analgaesia, intraoperative opioid supplementation, rescue analgaesic requirement, opioid-related adverse effects, patient satisfaction and block-related complications as secondary outcomes.

METHODS

The study protocol was registered with the International Prospective Register of Systematic Reviews (registration number: PROSPERO CRD42021257535) and can be assessed on the PROSPERO website. Our findings are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.[7]

RCTs reporting postoperative analgaesia outcomes after SAP block compared with other active blocks or NBC in patients undergoing breast surgery were sought. We conducted the search according to PICOTS criteria[8]:

Population: Adult females >18 years undergoing breast surgery with or without axillary interventions were eligible for inclusion.

Intervention: Patients receiving SAP (superficial injection) when the local anaesthetic was deposited between the plane of the latissimus dorsi and serratus anterior muscle or (deep injection) when the deposition was between the serratus anterior muscle and fourth or fifth rib. Trials were excluded if SAP was performed with other blocks or a catheter was placed for continuous infusion. Studies were also excluded if different types or doses of local anaesthetics were used or if multiple techniques of SAP were evaluated without active or inactive comparators. Trials evaluating the role of local anaesthetic adjuncts only without a control treatment arm were also not included. Treatment arms were grouped together as active if more than one arm compared different active agents, and a non-active comparator was present in the trial.

Comparators: NBC (placebo or sham block, surgical site infiltration, or no block) or another active block (PVB, PECS, ESP block).

Outcomes: The primary outcome was the cumulative OME in the postoperative period up to 24 hours. Morphine-related adverse effects include nausea, vomiting, pruritus, urinary retention and respiratory depression. Prolonged use also increases the risk of developing opioid dependence.[9] Accordingly, we chose to study OME reduction as our primary outcome since minimizing opioid consumption is vital for early ambulation, rehabilitation and discharge.

Secondary outcomes were pain scores at rest and on movement at various time intervals (PACU admission, 2, 6, 12 and 24 hours), time to first rescue analgesic, intraoperative opioid supplementation, rescue analgesic requirement, opioid-related adverse effects, patient satisfaction and block-related complications.

Timing: 24-hour postoperative period.

Setting: Inpatient ward.

Two independent reviewers (JKM and NPS) undertook a comprehensive literature search in *PubMed*, EMBASE, SCOPUS and the Cochrane Central Registers of Controlled Trials (CENTRAL) and was last updated in January 2022. The following search terms were used: 'serratus anterior block' OR 'serratus anterior plane block' OR 'SAP block' AND 'breast surgery' OR 'modified radical mastectomy' AND 'postoperative pain'. The detailed search strategy is provided

in the Supplementary Appendix. No language restriction was placed on the publication of included manuscripts. Non-English studies were translated using an online translator (https://www.enago.com/translation/). Additionally, reference lists of relevant publications and identified trials were hand searched, and those meeting the below-mentioned criteria were included in this analysis. Zotero version 5.0 (Corporation for Digital Scholarship) was used to catalogue references

The abstracts were assessed and screened for full-text eligibility. Any disagreements between authors regarding a trial's eligibility were resolved by consensus or by harmonization by another author.

The following data were extracted: study design, year and country of publication, sample size, type of breast surgery performed, intervention and comparator groups, the timing of performance of block, dose and volume of local anaesthetic used and postoperative analgesia scores. We also extracted data at all reported times for postoperative pain scores, time to first analgesic request (minutes), postoperative analgesic consumption at various intervals, functional assessments, any block-related complication and opioid-related side effects (i.e. postoperative nausea and vomiting (PONV), respiratory depression, sedation or pruritus). The principal investigators of included trials were contacted using electronic mail for additional information, where required.

Outcome data were extracted as mean and standard deviation (SD) for continuous variables and as proportions for dichotomous outcomes. Data provided as the median and interquartile range (IQR) were converted to mean and SD using Hozo's formula.[10] Perioperative opioid usage was converted to intravenous fentanyl equivalents (IFE) for intraoperative consumption and OME for postoperative consumption.[11] Pain scores reported as Visual or Numeric Rating Scales were rescaled to a standardized 0–10 cm for quantitative evaluations.[12] Patient satisfaction scores were converted to a Visual Analog Scale (VAS) equivalent score (0 equals least satisfied and 10 equals most satisfied).[12] For calculation of the area under the curve, pain scores were collected at 1 and 4 hours, and if these were not available, data for pain scores at 2 hours and 6 hours, respectively, were used. We used 'graphreader.com' to extract numbers from graphs (https://www grap hreader.com).

Risk of bias assessment of individual trials

The risk of bias (ROB) was assessed based on the criteria recommended by the Cochrane Collaboration (ROB2).[13] This tool evaluates the ROB according to five domains: bias arising from the randomization process, bias due to deviation from intended interventions, bias due to missing data outcomes, bias in the measurement of outcomes and bias in the selection of reported results. Two independent reviewers (NPS and JKM) answered 'Yes', 'Probably yes', 'No', 'Probably no' or 'No information' to denote whether adequate precautions were taken into consideration to protect against each potential source of bias. The overall ROB was expressed as low risk, some concerns or high risk.

Strength of evidence across trials

The overall methodologic quality of evidence across pooled outcomes was also assessed using the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) guidelines.[14] Evidence for pooled outcomes was classified based on predefined criteria: study quality, consistency, directness, precision and publication bias. The level of bias across these criteria was used to classify the overall pooled outcome as follows: (1) high quality: further research will very unlikely change the confidence in the estimate of effect; (2) moderate quality: further research will very likely have an important impact on the confidence of the estimate of effect and may change the estimate; (3) low quality: further research very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate; or (4) very low quality: there is uncertainty surrounding the estimate.

Data synthesis and analysis of outcome

In anticipation of heterogeneity among the included studies, continuous data were pooled using the inverse variance method with random-effects modelling, whereas Mantel–Haenszel (MH) with random-effects modelling was used for the dichotomous data.[15] The statistical analysis of the pooled data was performed using Comprehensive Meta-Analysis-Version 3 (Biostat Inc, USA). All reported P values were two-sided, and a $P < 0.05$ was considered statistically significant. The MD and 95% confidence interval (CI) were calculated for continuous outcomes and the MH odds ratio (OR) with 95% CI for dichotomous outcomes. Forest plots were constructed to exhibit and evaluate treatment effects. An outcome reported by three or more trials and involving more than 100 patients was synthesized for analysis, while

qualitative reporting was done for the other outcomes. The potential small-study effect was quantified by visual inspection of the Doi plot and was further evaluated using the Luis Furuya Kanamori asymmetry (LFK index). In the case of a symmetric shape, no publication bias is indicated and an asymmetric shape shows publication bias. An LFK index within −1 and +1 indicates no publication bias, an LFK of −1 to −2 or +1 to +2 minor asymmetry and an LFK of +2 major asymmetry.

An I^2 statistic was calculated to evaluate inconsistency for all outcomes. The inconsistency in the pooled estimate of effect was considered significant if the I^2 value was greater than 50%.[16] Additional meta-regression analyses utilizing mixed-effects modelling were conducted to examine whether the results were influenced by prespecified predictors of treatment effect in case of significant inconsistency for OME. The mixed-effects modelling used here is without assuming a common among-study variance component across the study groups. We reported R^2 values (coefficient of determination) to quantify the extent to which each covariate explains data variability. The covariate explains all the variability if the value of $R^2 = 1$, whereas an $R^2 = 0$ means that none of the variability is explained by the covariate. If fewer than two trials were available for a specific covariate, sensitivity analysis was done through the sequential exclusion of studies with the prespecified covariates.

The following covariates were considered for our meta-regression analysis: time of block (before/after induction of GA or after completion of the surgery), surgical extent (a procedure done with or without axillary dissection), laterality of surgery (bilateral or unilateral surgery), choice of anaesthetic maintenance (intravenous versus volatile agent), short-acting versus intermediate/long-acting local anaesthetics, the addition of adjuvants that can prolong analgaesic or block duration (*e.g.* epinephrine, dexamethasone, and dexmedetomidine), postoperative analgaesic regimen (with or without multimodal analgaesia) and publication type of the trial (PubMed indexed or not). We performed subgroup analyses for covariates, where the R^2 value was >25%. Sensitivity analysis was also performed for the primary outcome after excluding the trials with a high risk of bias. The single-study effect on the primary outcome was extrapolated by removing each trial at a time.

'Trial sequential analysis' (TSA) using the TSA Module version 0.9.5.10 (Copenhagen trial unit, Denmark) was performed to determine whether the cumulative sample size was appropriately powered to obtain the pooled effect values and avoid a random error. Both conventional (with an alpha of 5%) and alpha O'Brien boundaries (for random-effects modelling with an alpha of 5%, beta of 20%) were created for the need for OME consumption. The heterogeneity correction in the TSA was set to variance-based, and the random-effects model was used. For the TSA modelling, the requisite 'information size' (IS) was considered for the primary outcome using two approaches. (classical boundary and O'Brien–Fleming alpha spending boundary). The cumulative, sequential Z-score curve was constructed by calculating Z statistics from each trial. Once the cumulative Z curve crosses the TSA monitoring boundary, a firm conclusion can be drawn that there is a significant difference before achieving the IS.

RESULTS

The literature search revealed 629 trials. Figure 1 shows the study inclusion/elimination process. Twenty-four trials enrolling 1789 patients were included in this systematic review.[17-40]

The characteristics of included trials are shown in Table 1. Of the 1789 patients enrolled across 24 RCTs, 852 received SAP, 401 received other blocks (PVB in 191, PEC block in 160, and ESP block in 50), and 534 patients were included in the NBC group (sham block in 90, placebo block in 147, no block in 276 and surgical site infiltration in 23). Six of the included trials were three-armed, whereas the rest were two-armed. As reporting of individual values for each group was done separately in three-armed trials, we could pool the results as two separate comparisons labelled as (1) and (2). Fifteen comparisons could be drawn for SAP versus NBC, seven for SAP versus PVB, five for SAP versus PECS block and two for SAP versus ESP block.

SAP was performed preoperatively in 14 studies, intraoperatively (after the induction of general anaesthesia) in eight and postoperatively in two trials. All but one trial explicitly described the plane of the block. Fifteen trial authors deposited the local anaesthetic below the serratus anterior muscle (deep plane), and seven performed the block superficial to serratus anterior muscle (superficial plane). In all but one trial, the SAP was performed with long-acting local anaesthetics. Participants received ropivacaine and bupivacaine in ten trials each, levobupivacaine in three and articaine (short-acting) in one trial.

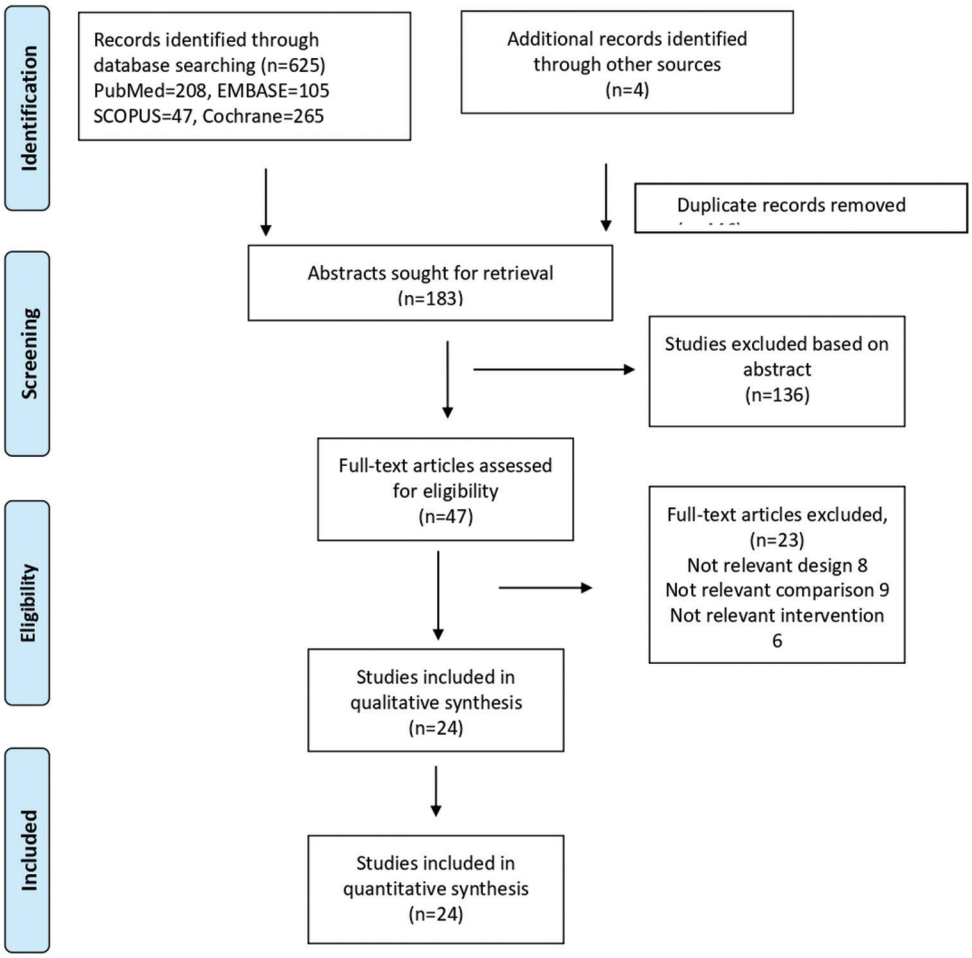

Figure 1: PRISMA flow diagram of included randomized controlled trials

Epinephrine was used as an adjuvant in four trials, and dexmedetomidine and fentanyl were used together in one trial. Anaesthesia was maintained intraoperatively with an intravenous agent (propofol) in five studies, while the rest of the trials utilized volatile agents.

Two trial authors recruited patients for breast surgery without detailing the specific procedures. One trial enrolled patient undergoing non-reconstructive surgery and another enrolled patient undergoing breast reduction surgery. The remaining twenty studies evaluated the role of SAP in oncological breast surgeries, twelve of which included trials recruiting patients undergoing modified radical mastectomy. Five trials included patients undergoing mastectomy with sentinel lymph node dissection. Eleven studies administered intraoperative PONV prophylaxis. Multimodal analgaesia regimens were utilized in 15 trials, with opioid-based patient-controlled analgaesia regimens in 10 trials. Eighteen trials reported cumulative 24-hour opioid consumption. Time to first rescue analgaesia was evaluated in 14 trials. Analgaesic consumption and postoperative pain were reported beyond 24 hours in three trials, whereas the incidence of chronic postsurgical pain was assessed in two trials. Block-related complications were recorded in 15 trials. According to the prespecified analysis protocol, results are presented stratifying according to SAP versus either NBC or other active blocks. An overall summary of findings is presented in Table 2.

The risk of bias assessment for each individual study is presented in supplementary figure 1. Overall, 16 of the 24 RCTs were deemed to be at low risk of bias, three had some concerns, and five were at high risk of bias. Of the included trials, three did not provide sufficient information about random sequence generation or allocation concealment (unclear risk of detection and selection bias), and eight did not provide adequate information regarding the selection of the reported result (unclear risk of reporting bias). Furthermore, three trials did not explicitly state whether outcome assessors were blinded (unclear risk of outcome measurement).

Table 1: Characteristics of included trials

Author year (Country)	Timing of intervention	Anaesthesia maintenance	Type of surgery	Location of SAP block (*n*)	Comparator (*n*)	Local anaesthetic dose (SAP)	Background analgaesic modality
Abdallah *et al*. 2021[17] (Canada)	Before induction	Propofol	Mastectomy ± SLND	Deep (20)	Sham block (20)	0.5% Ropivacaine 20 ml (100 mg)	CAO
Ahiskalioglu *et al*. 2020[18] (Turkey)	Before induction	Volatile agent	Breast reduction surgery (bilateral)	Superficial (20)	Sham block (20)	0.25% Bupivacaine 30 ml (75 mg)	Fentanyl PCA Pethidine IV PRN
Amin *et al*. 2019[19] (Egypt)	Postoperative	Volatile agent	Mastectomy	Deep (30)	Paravertebral block (30)	0.25% Bupivacaine 0.4 ml/kg	CAO
Arora *et al*. 2016[20] (India)	Before induction	Volatile agent	Modified radical mastectomy	Deep (20)	Paravertebral block (30)	0.25% Ropivacaine 0.4 ml/kg	Diclofenac IV PRN Tramadol IV PRN
Aslan *et al*. 2020[21] (Turkey)	After induction	Volatile agent	Modified radical mastectomy	Superficial (20)	No block (20)	0.25% Bupivacaine 40 ml (100 mg)	Morphine PCA Paracetamol IV PRN
Bakeer *et al*. 2020[22] (Egypt)	Before induction	Volatile agent	Modified radical mastectomy	Deep (58)	Modified pectoral block (57) No block (58)	0.25% Bupivacaine 30 ml (75 mg) Nothing	Paracetamol 1 g IV 8-hourly Ketorolac 30 mg IV PRN CAO
Bhan *et al*. 2020[23] (India)	Before induction	Volatile agent	Modified radical mastectomy	Deep (50)	No block (50)	0.375% Ropivacaine 0.4 ml/kg	Diclofenac IV PRN
Eldemrdash *et al*. 2019[24] (Egypt)	After induction	Volatile agent	Modified radical mastectomy	Deep (25)	Paravertebral block (25) Erector spinae block (25)	2% Artecaine 20 ml (400 mg)	Morphine PCA Paracetamol 1 g IV 8-hourly
Elsabeeny *et al*. 2020[25] (Egypt)	After induction	Volatile agent	Modified radical mastectomy	Deep (25)	Erector spinae block (25) No block (25)	0.25% Bupivacaine 25 ml (62.5 mg)	Paracetamol 1 g IV 8-hourly Ketorolac 30 mg IV PRN CAO
Fujii *et al*. 2019[26] (Japan)	After induction	Propofol	Mastectomy	Superficial (40)	Modified pectoral block (40)	0.5% Ropivacaine 30 ml (150 mg)	Morphine PCA
Gabriel *et al*. 2021[27] (USA)	Before induction	Volatile agent	Breast surgery (unilateral or bilateral)	Deep (49)	Paravertebral block (51)	0.5% Ropivacaine 16/20 ml (80/100 mg)	CAO
Gad *et al*. 2019[28] (Egypt)	After induction	Volatile agent	Breast cancer surgery	Superficial (100)	Sham block (100)	0.25% Levobupivacaine 0.5 ml/kg and with Dexmedetomidine	Ketorolac 30 mg IV PRN
Gupta *et al*. 2017[29] (India)	After induction	Volatile agent	Modified radical mastectomy	Superficial (25)	Paravertebral block (25)	0.5% Bupivacaine 20 ml (100 mg)	Morphine PCA
Herrero *et al*. 2016[30] (Spain)	Before induction	Propofol	Breast cancer surgery	Deep (35)	Paravertebral block (35)	0.25% Bupivacaine 20 ml (50 mg)	CAO
Jain *et al*. 2020[31] (India)	Before induction	Volatile agent	Mastectomy ± ALND	Deep (15)	Paravertebral block (15) Modified pectoral block (15)	0.375% Ropivacaine 30 ml (112.5 mg)	Fentanyl PCA
Kaur *et al*. 2020[32] (India)	After induction	Volatile agent	Modified radical mastectomy	Deep (18)	Modified pectoral block (18) No block (19)	0.2% Ropivacaine 0.4 ml/kg	Paracetamol 1 g IV 6-hourly Diclofenac 75 mg 8-hourly Tramadol IV PRN

Contd...

Table 1: Contd...

Author year (Country)	Timing of intervention	Anaesthesia maintenance	Type of surgery	Location of SAP block (*n*)	Comparator (*n*)	Local anaesthetic dose (SAP)	Background analgaesic modality
Mazzinari *et al*. 2019[33] (Spain)	Before induction	Propofol	Mastectomy + ALND + reconstruction	Deep (28)	No block (30)	0.25% Levobupivacaine 30 ml (75 mg)	Paracetamol 1 g IV 6-hourly Dexketoprofen 50 mg 8-hourly Morphine PCA
Qian *et al*. 2021[34] (China)	Before induction	Volatile agent	Modified radical mastectomy	Deep (90)	Placebo block (89)	0.5% Ropivacaine 30 ml (150 mg)	Parecoxib 40 mg IV 12-hourly Morphine PCA
Rahimzadeh *et al*. 2018[35] (Iran)	Postoperative	Not mentioned	Modified radical mastectomy	Not reported	No block (30)	0.2% Bupivacaine 0.3 ml/kg	Fentanyl PCA Paracetamol IV PRN
Razek *et al*. 2018[36] (Egypt)	Before induction	Volatile agent	Non-constructive breast surgery	Deep (30)	Modified pectoral block (30)	0.25% Levobupivacaine 40 ml (100 mg)	Ketorolac 30 mg IV 8-hourly Fentanyl IV PRN
Shokri *et al*. 2017[37] (Egypt)	Postoperative	Volatile agent	Breast surgery	Deep (23)	Surgical site infiltration (23)	0.25% Bupivacaine 0.4 ml/kg	Pethidine IV PRN
Tang *et al*. 2021[38] (China)	After induction	Propofol	Modified radical mastectomy	Superficial (43)	No block (44)	0.5% Ropivacaine 20 ml (100 mg)	Sufentanil IV PRN
Yao *et al*. 2019[39] (China)	Before induction	Volatile agent	Breast cancer surgery + LND	Superficial (34)	Placebo block (34)	0.5% Ropivacaine 25 ml (125 mg)	Sufentanil IV PCA Flurbiprofen 50 mg IV 12-hourly
Yayik *et al*. 2019[40] (Turkey)	Before induction	Volatile agent	Modified radical mastectomy	Superficial (24)	Placebo block (24)	0.25% Bupivacaine 30 ml (75 mg)	Dexketoprofen 50 mg 12-hourly Fentanyl PCA

CAO, clinician-administered opioid; IV, intravenous; PCA, patient-controlled analgaesia; PRN, on demand; ALND, axillary lymph node dissection

Results for SAP block versus NBC stratum

Cumulative 24-h postoperative OME consumption

Eleven studies (882 patients; SAP: 465, NBC: 417) that reported postoperative cumulative 24-hour OME provided sufficient reporting for statistical pooling [Figure 2a]. Overall, SAP significantly reduced the OME by a mean difference of −24.9 mg (95% CI −41.54 to −8.25, $P < 0.001$, $I^2 = 99.68\%$) compared with NBC. The overall strength of evidence was moderate [Table 2]. The Supplementary Figure 2 shows the effect of removing a single study at a time, and none of the included trials had a clear outlier; thus, we did not perform an outlier analysis.

Trial sequential analysis (TSA)

To construct the alpha-spending boundary, we used trials with a low risk of bias, an alpha error of less than 5%, and a power of 80% [Figure 2b]. As our information size (882) was more than the required sample size of 850 (alpha boundary) and 795 (conventional boundary), the likelihood of false-positive results is ruled out. This finding also highlights that additional trials on this topic are unlikely to alter the results. The cumulative Z score crossed the trial sequential monitoring boundary for the benefit of SAP block for breast surgery compared to the NBC group.

The small-study effect was visualized in a Doi plot, indicating a symmetric shape for the pooled OME consumption in 24 hours [Supplementary Figure 3]. The LFK index was 0.78, also indicating no publication bias.

Meta-regression performed to explore the sources of inconsistency using predefined covariates suggested that cumulative 24-h OME consumption did not correlate with the invasiveness of surgery (with or without axillary dissection; $R^2 = 0.00$), bilateral or unilateral surgery; $R^2 = 0.02$, postoperative analgesic strategy (with or without multimodal analgesia; $R^2 = 0.00$) and publication indexing status (PubMed indexed or not; $R^2 = 0.00$). Deposition of local anaesthetic (superficial or deep to serratus anterior muscle; $R^2 = 0.33$), anaesthetic used for maintenance (propofol vs volatile agent; $R^2 = 0.29$), the volume of local anaesthetic (<30 or ≥30 ml); $R^2 = 0.17$) and addition of adjuvants ($R^2 = 0.13$) had bearing on the outcome and thus were the covariates that contributed towards heterogeneity across groups.

Table 2: Summary of findings table. Population: Patients undergoing breast surgery. Intervention: Serratus anterior plane (SAP) block. Comparator: Non-block care, paravertebral block, modified pectoral block

Outcomes	Anticipated absolute effect with SAP block Mean (SD)	Effect with comparator Mean (SD)	Mean difference or Odds Ratio [95% Confidence Interval]	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
Oral morphine equivalents in 24 hours (mg)	35.1 (14.14)	60 (12)	-24.9 (-41.50 to -8.25)	882 (11)	⊕⊕⊕◯[a] MODERATE	High inconsistency; I^2=99.7% and *P*<0.001
Intraoperative fentanyl equivalents (mcg)	74.19 (10.77)	106.32 (7.44)	-32.13 (-45.43 to -18.82)	592 (6)	⊕⊕◯◯[a b] LOW	High inconsistency; I^2 =94% with non-overlapping confidence intervals and *P*<0.001
Rescue analgaesia usage (*n*)	428.63 per 1000	537.03 per 1000	0.20 (0.13 to 0.33)	431 (7)	⊕⊕⊕◯[b] MODERATE	Low inconsistency; and *P*<0.001.
Postoperative nausea and vomiting (n)	190.45 per 1000	264.51 per 1000	0.28 (0.13 to 0.62)	816 (10)	⊕⊕⊕◯[a b] MODERATE	Moderate inconsistency; I^2 64% and *P* < 0.001
Versus paravertebral block						
Oral morphine equivalents in 24 hours (mg)	41.62 (10.51)	42.54 (14.43)	1.92 (-5.47 to 9.31)	330 (6)	⊕⊕◯◯[a c] LOW	High inconsistency; I^2=96% and *P* < 0.61.
Time to first rescue analgaesia (minutes)	313.79 (85.99)	363.76 (93.69)	46.17 (-60.43 to 152.76)	230 (5)	⊕⊕◯◯[a b] LOW	High inconsistency; I^2=97% and *P* < 0.38.
Intraoperative fentanyl equivalents (mcg)	86.47 (12.64)	93.37 (13.72)	-3.05 (-12.94 to 6.85)	180 (3)	⊕⊕◯◯[a b c] LOW	High inconsistency; I^2=82% with non-overlapping confidence intervals; and *P* < 0.55.
Postoperative nausea and vomiting (n)	189.75 of 1000	150.60 of 1000	1.26 (0.48 to 3.29)	330 (6)	⊕⊕⊕◯[b] MODERATE	Moderate inconsistency; I^2 =49% and *P* < 0.64.
Versus modified pectoral block						
Oral morphine equivalents in 24 hours (mg)	70.24 (34.28)	69.03 (30.91)	1.21 (-6.27 to 8.70)	225 (3)	⊕⊕◯◯[a b] LOW	High inconsistency; I^2=86% with non-overlapping confidence intervals; and *P* < 0.75.
Time to first rescue analgaesia (minutes)	288.96 (89.76)	240.40 (58.2)	48.56 (-55.92 to 153.03)	205 (3)	⊕⊕◯◯[a c] LOW	High inconsistency; I^2 = 96% and *P* < 0.36.
Intraoperative fentanyl equivalents (mcg)	63.0 (19.99)	59.50 (15.6)	1.13 (0.28 to 4.54)	211 (3)	⊕⊕◯◯[a b] LOW	High inconsistency; I^2=86% and *P* < 0.66.
Postoperative nausea and vomiting (n)	90 of 1000	45.45 of 1000	1.98 (0.6 to 6.49)	181 (3)	⊕⊕⊕◯[b] MODERATE	Low inconsistency; I^2=0% and *P* < 0.26.

SD, standard deviation. GRADE (Grading of Recommendations Assessment, Development and Evaluation) . [a]imprecision; [b]indirectness; [c]inconsistency Working Group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect may differ substantially from the effect's estimate

Meta-regression was not performed on the type of local anaesthetic used as none of the studies used a short-acting formulation. Additionally, the direction and magnitude of the treatment effect did not change after excluding studies having a high risk of bias.

The results were pronounced when superficial [MD -32.01 mg (95% CI -54.45 to -9.56, $P = 0.01$)] and deep approach [MD -18.9 mg (95% CI -46.30 to -8.40, $P = 0.17$)] subgroups were compared [Figure 3a]. Similarly, the results were also accentuated when volatile agents [MD -31.24 mg (95% CI -50.37 to -12.11, $P = 0.0001$)] and propofol [MD -9.5 mg (95% CI -12.43 to -5.56, $P = 0.17$)] subgroups [Figure 3b] were compared.

Time to first rescue analgesic

Time to first analgesic request was reported in nine trials (650 patients; SAP: 350, NBC: 300). This metric was prolonged in patients receiving the SAP by 287.87 min (95% CI 173.99 to 403.62 min, $P < 0.001$; $I^2 = 99.42\%$) compared with NBC [Supplementary Figure 4].

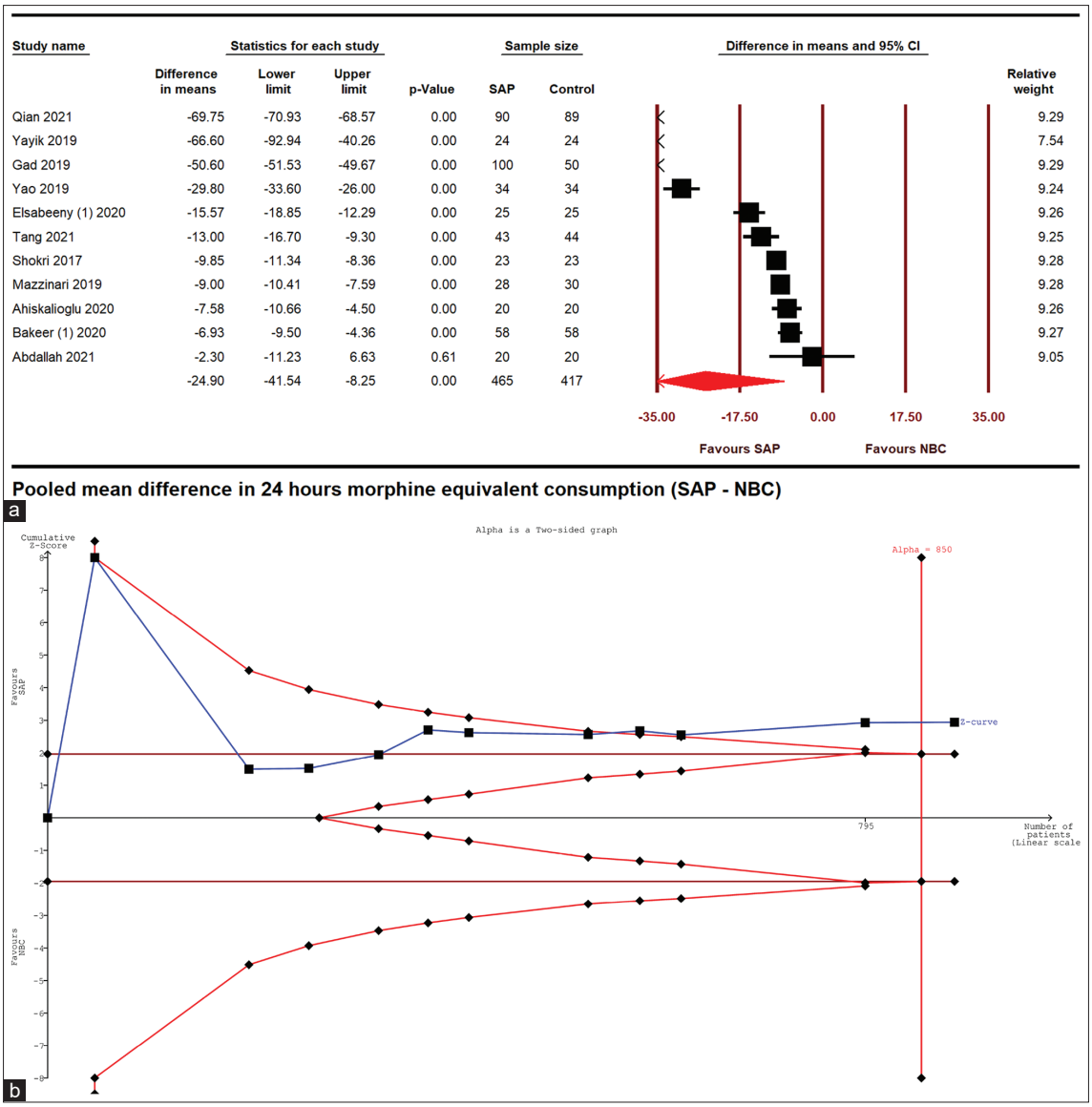

Figure 2: (a) Pooled data evaluating oral morphine equivalent consumption in 24 hours of SAP block versus non-block care. (b) Trial sequential analysis for effect on oral morphine equivalent consumption in 24 hours. The lower half of the graph below the zero-axis represents the area of advantage with the non-block care group and the upper half represents the advantage area with the SAP block group. The accumulating number of participants (and hence the growing 'information size') is shown on the x-axis. The horizontal brown lines represent the conventional thresholds for statistical significance at a constant Z value of 1.96, which corresponds to a *P* value of 0.05. The curved (red) lines at the top and bottom (trial sequential boundaries) represent the sequential analysis thresholds for statistical significance. The blue line is the cumulative Z curve and represents the accumulating amount of information as trials are added, each square denoting an individual trial. The Z values calculated from the accumulating data are plotted and compared with significance thresholds which can then be translated into the trial sequential analysis (TSA)-adjusted confidence intervals. The red diagonal lines inside the horizontal brown lines represent the futility boundaries. The cumulative z-score line (blue) crosses the conventional boundaries (brown lines), indicating the superiority of SAP block over non-block care based upon the conventional model (non-block care). The curved (red) lines at the top and bottom cross the vertical red line shows that we have reached the required information size to detect or reject the anticipated effect with certainty

Difference in Area under the Curve (AUC) for pain severity at rest

The area under the curve (AUC) for pain at rest over the first 24 h was used to estimate the mean difference in AUC for each of the two comparisons of interest. The number of patients included at the initial observation in PACU was 728 (SAP: 363, control: 365), 824 (SAP: 411, control: 413) at 2 and 6 hours, and 861 (SAP: 429, NBC: 432) at 12, and 24-h comparisons [Supplementary Figure 5]. SAP decreased the AUC of the pooled rest pain scores by -1.7 cm·h ($P = 0.021$).

Resting pain scores at individual time points

SAP improved pain control in the PACU on initial observation and at 2, 6, 12 and 24 hours by mean differences of -1.50 (-2.21 to -0.80; $P < 0.001$; $I^2 = 95.6\%$), -0.86 (-1.24

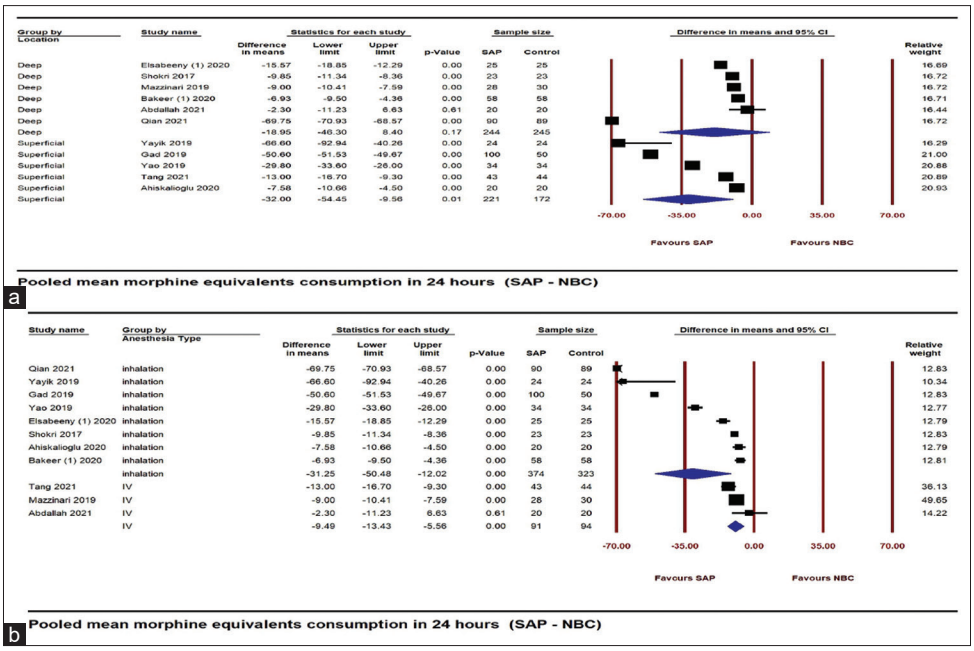

Figure 3: (a) Subgroup analysis for opioid consumption in 24 hours based on the plane (deep versus superficial) of SAP block. (b) Subgroup analysis for opioid consumption in 24 hours based on anaesthetic maintenance (inhalation versus intravenous)

to -0.48, $P < 0.001$, $I^2 = 96.6\%$), -1.62 (-2.40 to -0.84, $P = 0.05$, $I^2 = 99.1\%$) and -0.67 (-1.08 to -0.26, $P < 0.001$, $I^2 = 87.4\%$), respectively. The strength of evidence was low due to inconsistency in the pooled estimates for the individual time points.

Intravenous fentanyl equivalents (IFE)

Six trials (592 patients; SAP: 321, NBC: 271) reported intraoperative fentanyl consumption. Significantly lower fentanyl supplementation was required in patients receiving the SAP compared with NBC -32.13 mcg (95% CI -45.43 to -18.82, $P < 0.001$, $I^2 = 94\%$).

Rescue analgesia usage and patient satisfaction

There was a lower number of patients requiring postoperative analgesics at 0–24 hours of receiving SAP in comparison with the NBC group (OR 0.20; 95% CI 0.13, 0.33, $P < 0.001$, $I^2 = 6\%$). Patient satisfaction scores were reported in five trials, and four of these reported it quantitatively. SAP was associated with better patient satisfaction with MD -2.11 (95% CI -0.78 to -3.44, $P < 0.001$, $I^2 = 99\%$).

Side effects and block-related complications

PONV was the only opioid-related adverse effect that was consistently reported in 10 trials. There was a significant reduction in the incidence of PONV in the SAP group as compared to NBC (OR 0.28; 95% CI 0.13 to 0.62, $P < 0.001$, $I^2 = 64\%$). Block-related complications were explicitly reported in nine trials; no studies reported significant block-related complications (such as pneumothorax, local anaesthetic systemic toxicity or permanent nerve damage) in either of the groups.

Results for SAP block vs paravertebral block (PVB)

Cumulative 24-h OME data were reported and pooled from six studies (330 patients; SAP: 164, paravertebral block: 166). Overall, SAP was not statistically different from the paravertebral block for postoperative cumulative 24-h oral morphine consumption, with a mean difference of 1.92 mg (95% CI −5.47 to 9.31, $P = 0.61$, $I^2 = 96\%$).

There was no statistical difference between the SAP and PVB for time to first rescue analgaesia, intraoperative fentanyl supplementation, and incidence of PONV [Table 2]. Two cases of pneumothorax were reported in the PVB group, whereas no block-related complication was reported in the SAP group.

Results for SAP block vs. modified pectoral block (PECS)

Postoperative cumulative 24-h OME data were reported and pooled from three studies (225 patients; SAP: 113, paravertebral block: 112). No statistically significant difference was found between SAP and PECS for cumulative 24-h oral morphine consumption, with a mean difference of 1.21 mg (95% CI −6.27 to 8.70, $P = 0.75$, $I^2 = 86\%$). Additionally, the SAP block was not statistically different from the PECS block for time to first rescue analgesia, intraoperative fentanyl supplementation and incidence of PONV [Table 2].

Results for SAP block vs erector spinae (ESP) block

Cumulative 24 hours OME and time to first rescue analgesia data were reported in two studies each, and there was no significant difference for both outcomes. Pain scores at rest, reported in two trials, were also not significantly different at various time intervals.

DISCUSSION

This systematic review and meta-analysis with TSA investigated 24 RCTs, including 1789 patients, that compared the analgesic efficacy of SAP to NBC or other active blocks in patients undergoing breast surgery. Compared with NBC, SAP significantly reduced 24 hours OME with an MD of −24.9 mg (95% CI −41.54 to −8.25; $P = 0.003$). The strength of evidence was moderate because of the high statistical inconsistency. The covariates contributing to inconsistency were block plane (33%), anaesthetic maintenance (29%), the volume of LA (17%) and the addition of adjuvants (13%). A greater reduction in 24-hour OME was seen with a superficial plane block and maintenance of anaesthesia with volatile agents. The odds of developing PONV were reduced by 72%, and the odds of needing postoperative analgaesia were decreased by 80%. Additionally, the time to first rescue analgaesia was prolonged by 287.87 minutes. The block appeared safe, with no trial reporting any block-related complications. No statistical differences were observed in 24 hours of OME consumption, time to first rescue analgaesia, need for postoperative analgaesia and incidence of PONV when SAP was compared to other active blocks (PVB, PECS and ESP).

PVB and PECS blocks are attractive techniques for analgaesia following breast surgeries. Although the analgaesic efficacy of PVB versus placebo is well established, PVB carries potential risks to important vital structures, and not all healthcare providers possess the requisite expertise to safely perform this technique. As a deep block, PVB is best avoided in patients with abnormal coagulation, and given the rare risk of pneumothorax, this block may be deferred in patients with pre-existing lung disease. Anterior techniques such as PECS or SAP blocks may improve the patient experience, as these blocks can be performed after induction of general anaesthesia without requiring patient repositioning.[3] PECS block can, however, result in a collection of LA in the axilla and blockade of the long thoracic nerve.[41] For these reasons, the SAP block remains an appealing technique. Ultimately, clinicians should select the technique they are most comfortable performing and most appropriate for their hospital setting.

The minimal clinically important difference (MCID) for analgaesia after breast surgery is defined as 30 mg of oral morphine (or 10 mg intravenous morphine) in the first 24 hours and 1.1 cm or 3.3 cm/h on a 10 cm scale.[42] These cut-offs are derived from chronic breast pain studies unrelated to acute postoperative pain. An intervention is considered clinically meaningful or important if it minimizes opioid consumption, causes fewer associated adverse effects in the short and/or long term and improves functional outcomes.[43] Our results suggest that SAP is not only associated with a modest reduction in OME (25 mg) but also reduces the odds of developing PONV by 72% and modestly reduces resting pain scores (1.7 cm/h) during the first 24 hours. It also prolongs the time to first rescue analgaesia with MD by almost 5 hours, which may, subsequently, lower the incidence of chronic pain.[44] These findings strongly justify performing the SAP block for patients undergoing breast surgery.

Although there are case reports of block-related complications, such as pneumothorax, with deep SAP block, none of the included trials reported these complications.[45] This may be a consequence of under-reporting. However, recognizing that needle advancement during SAP block does not involve proximity to major vital structures, and recognizing that SAP block can be performed in anticoagulated patients, under-reporting is unlikely. The optimal plane of the block (superficial or deep) to establish sufficient and reliable analgaesia for breast surgery has not yet been identified.[46] Our subgroup analysis suggested that the superficial plane approach crosses the MCID limit 24-h OME reduction of 30 mg. The superficial plane block is also easier to learn, can be performed in the supine position without the need for patient repositioning and is associated with negligible risk of inadvertent pneumothorax.

Interestingly, the use of volatile agents for intraoperative maintenance was associated with a better reduction in OME 24 hours compared to intravenous maintenance. The previous meta-analysis on patients undergoing cardiac surgery found no difference in analgaesia-related outcomes with propofol or volatile-based anaesthesia.[47] However, a study conducted on urethane-anesthetized rats inferred that volatile agents at anaesthetic doses suppressed

dorsal horn activity, which would contribute to their analgaesic properties.[48]

Of the 19 RCTs evaluated in a 2019 meta-analysis by Chong *et al*., 13 included breast surgery patients, and six included thoracic surgery patients.[5] The heterogeneous patient population reduces the generalizability of the results to a population of breast surgery patients undergoing SAP block alone. A 2020 meta-analysis and TSA by Grape *et al*. evaluated PECS block in breast surgery patients and included 16 RCTs and 1026 patients.[6] In this study, the SAP block was pooled with PECS 1 and PECS 2 blocks in combination or alone, and the role of the SAP block alone was not clearly established. Hu *et al*. recently published a meta-analysis evaluating the role of SAP in patients undergoing breast surgery; however, SAP block was only compared with NBC.[49] The omission of TSA also increases the risk of misinterpretation of random error. By analysing a greater number of RCTs and focusing on more comparators and technical approaches, this meta-analysis and TSA substantially contribute to the current body of evidence regarding the analgaesic management of patients undergoing breast surgery.

Futures trials should compare SAP block with other active interventions and interrogate their risk–benefit ratio and whether maintenance with volatile or intravenous anaesthetic provides a comparable effect on acute pain control in the postoperative period. The ideal volume of LA should also be determined.

This meta-analysis is strengthened by the inclusive and thorough nature of the systematic review, enhancing its external validity. Most trials (20 of 24) were homogenous concerning investigating oncological breast surgeries associated with moderate-to-severe pain. We chose to perform a random-effects analysis, which is more statistically conservative in settings of high heterogeneity. Furthermore, inconsistency in our primary outcome has been extensively explored by meta-regression and subgroup analysis. Possible additional sources of inconsistency, which we could not evaluate, include dose and concentration of LA and type of NBC (sham block vs. no block vs. systemic opioids vs. local infiltration).

Our review has several limitations. Many included studies were small and did not report important outcomes such as dynamic pain score, quality of recovery, functional outcomes or effect on the incidence of chronic pain. Also, the strength of evidence was low to moderate for various secondary endpoints. We attempted to identify an influencing variable that could alter morphine consumption across groups via meta-regression; however, we could not control for all ecological and patient-related factors. Another limitation is that meta-regression results do not support causal inferences because the included studies are not randomly assigned to covariates. Therefore, the associations observed in the current investigation would need to be assessed in appropriately powered RCTs.

CONCLUSION

Our review provides evidence that single-shot SAP improves patient recovery by reducing opioid consumption, prolonging analgesia duration, lowering pain scores and decreasing the incidence of PONV in comparison to NBC after breast surgery. SAP is also statistically not different from PVB and PECS blocks for the outcomes studied. Future studies should compare its analgesic potential to established regional techniques and elucidate the superior plane for breast surgery.

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Conflicts of interest

There are no conflicts of interest.

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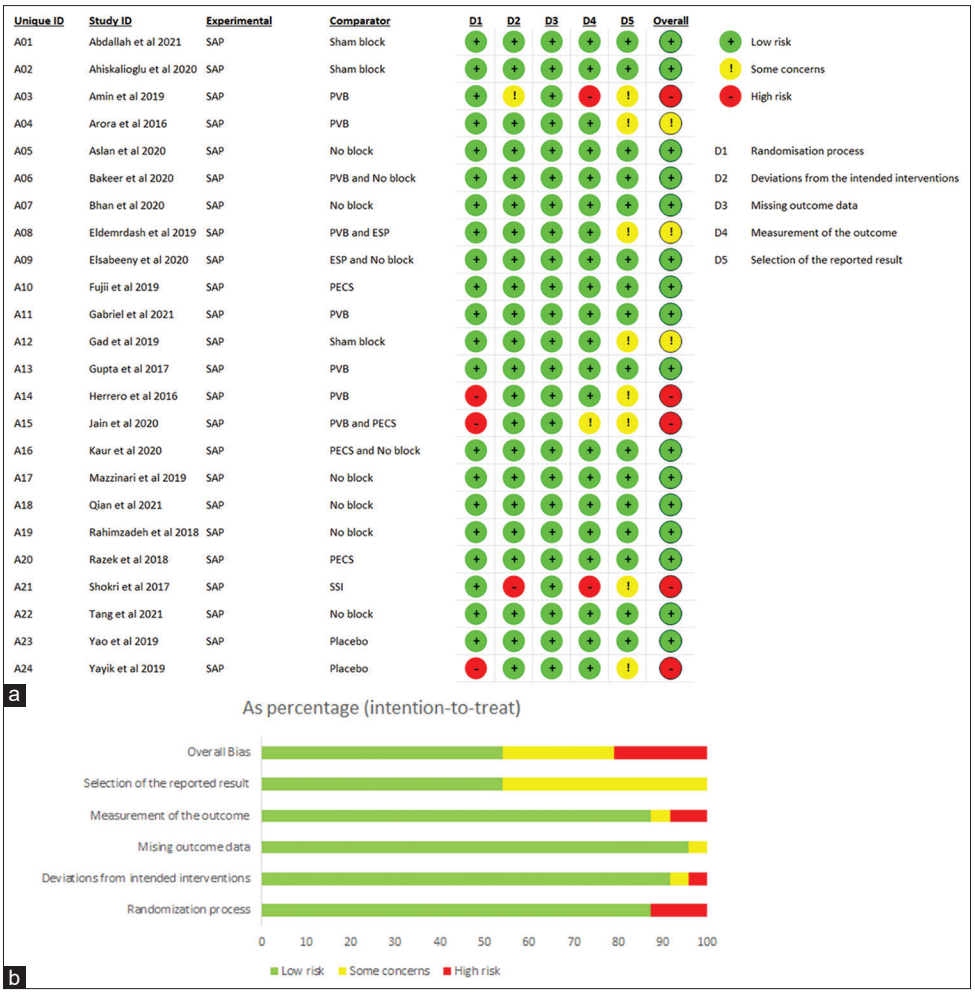
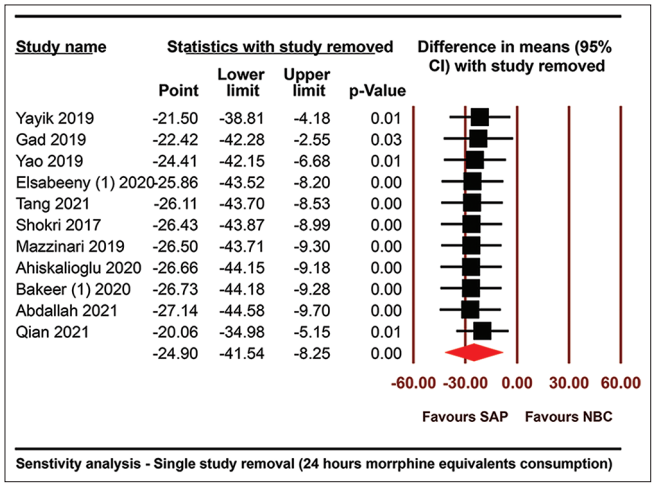
Appendix

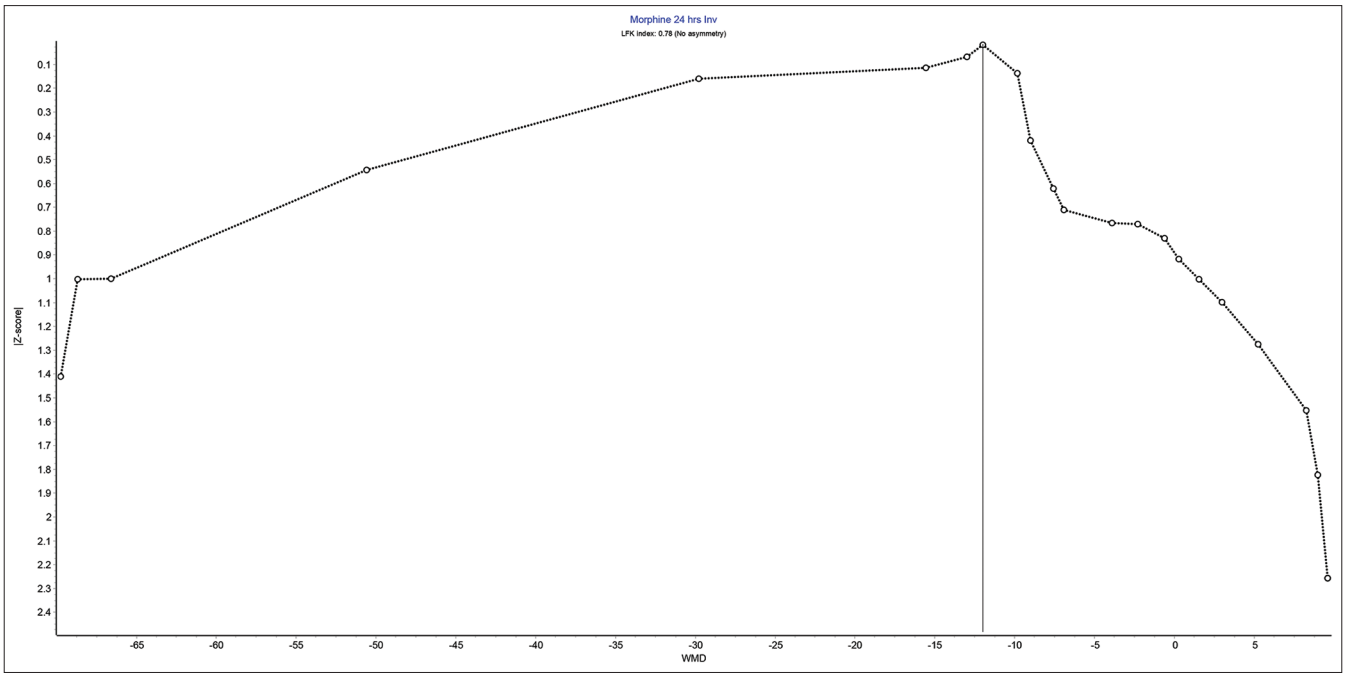
PUBMED	**"**Serratus anterior block" OR "serratus anterior plane block" OR "sap block" AND breast surgery **OR modified radical mastectomy AND postoperative pain**- **208**
EMBASE	'serratus anterior block':ti,ab,kw OR 'serratus anterior plane block':ti,ab,kw OR 'sap block':ti,ab,kw) AND 'breast surgery':ti,ab,kw OR 'modified radical mastectomy':ti,ab,kw) AND 'postoperative pain':ti,ab,kw **105**
SCOPUS	TITLE-ABS -KEY (serratus AND anterior AND block OR "serratus anterior plane block" OR "sap block" AND breast AND surgery) -47
Cochrane	serratus anterior block in Title Abstract Keyword OR serratus anterior plane block in Title Abstract Keyword OR SAP block in Title Abstract Keyword AND breast surgery 265



Supplementary Figure 1: (a) Risk of bias summary of included studies according to Cochrane Collaborationguidelines (b) Overall risk of bias of included trials



Supplementary Figure 2: Sensitivity analysis after removing a single study at a time for oral morphine equivalents in 24 hours for SAP block versus non-block care

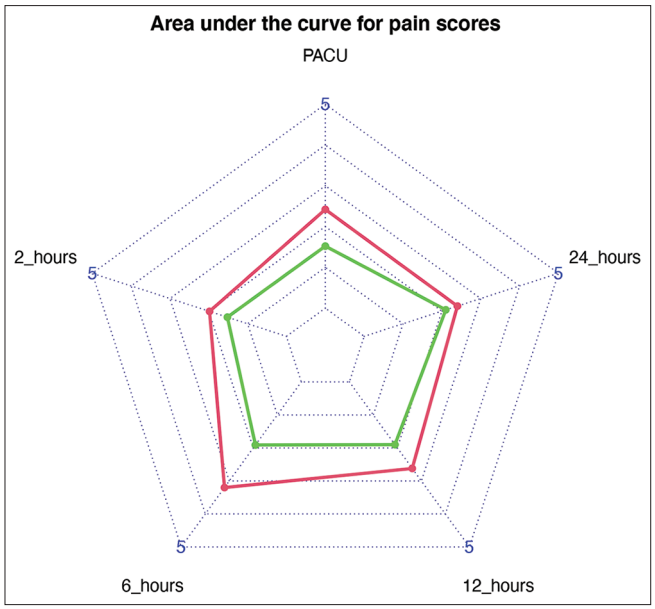


Supplementary Figure 3: Doi plots of publication bias for oral morphine equivalent consumption in 24 hours for SAP block versus non-block care

Study name	Difference in means	Lower limit	Upper limit	p-Value	SAP	Control	Relative weight
Bhan 2020	-14.10	-34.99	6.79	0.19	50	50	11.42
Ahiskalioglu 2020	42.78	4.55	81.01	0.03	20	20	11.31
Yayik 2019	61.70	31.40	92.00	0.00	24	24	11.37
Aslan 2020	252.60	224.86	280.34	0.00	20	20	11.38
Rahimzadeh 2018	306.90	289.11	324.69	0.00	30	30	11.43
Bakeer (1) 2020	320.50	309.97	331.03	0.00	58	58	11.45
Shokri 2017	392.40	363.89	420.91	0.00	23	23	11.38
Gad 2019	508.50	485.92	531.08	0.00	100	50	11.41
Elsabeeny (1) 2020	840.00	663.75	1016.25	0.00	25	25	8.86
	287.87	177.72	398.02	0.00	350	300	

Pooled mean difference in time to first analgesia (SAP - NBC)

Supplementary Figure 4: Pooled data evaluating the effect on time to first rescue analgesia for SAP block versus non-block care



Supplementary Figure 5: Graphical representation (star plot) of the area under the curve of the pooled weighted mean pain scores at rest (five-time points) for each of SAP block and non-block care