Dexmedetomidine as an adjuvant for patients undergoing breast cancer surgery
A meta-analysis
Changjun Liu, BMa, Wei Wang, BMa, Zhengkun Shan, BMb, Huapeng Zhang, MMc, Qiang Yan, BMd,∗,∗

Abstract
Background: The goal of this study was to comprehensively evaluate the analgesic and antiemetic effects of adjuvant dexmedetomidine (DEX) for breast cancer surgery using a meta-analysis.

Methods: Electronic databases were searched to collect the studies that performed randomized controlled trials. The effect size was estimated by odd ratio (OR) or standardized mean difference (SMD). Statistical analysis was performed using the STATA 13.0 software.

Results: Twelve published studies involving 396 DEX treatment patients and 395 patients with control treatment were included. Pooled analysis showed that the use of DEX significantly prolonged the time to first request of analgesia (SMD = 1.67), decreased the postoperative requirement for tramadol (SMD = -0.65) and morphine (total: SMD = -2.23; patient-controlled analgesia: SMD = -1.45) as well as intraoperative requirement for fentanyl (SMD = -1.60), and lower the pain score at 1 (SMD = -0.30), 2 (SMD = -1.45), 4 (SMD = -2.36), 6 (SMD = -0.63), 8 (SMD = -2.47), 12 (SMD = -0.81), 24 (SMD = -1.78), 36 (SMD = -0.92), and 48 (SMD = -0.80) hours postoperatively compared with the control group. Furthermore, the risks to develop postoperative nausea/vomiting (PONV) (OR = 0.38) and vomiting (OR = 0.54) were significantly decreased in the DEX group compared with the control group. The pain relief at early time point (2, 6, 12, 24 hours postoperatively) and the decrease in the incidence of PONV were especially obvious for the general anesthesia subgroup (P < .05) relative to local anesthesia subgroup (P > .05).

Conclusion: DEX may be a favorable anesthetic adjuvant in breast cancer surgery, which could lower postoperative pain and the risk to develop PONV. DEX should be combined especially for the patients undergoing general anesthesia.

Abbreviations: 5-HT = 5-hydroxytryptamine, BC = breast cancer, CI = confidence interval, CRP = C-reactive protein, DBP = diastolic blood pressure, DEX = dexmedetomidine, GA = general anesthesia, HR = heart rate, IL = interleukin, NRS = numerical rating scale, OR = odd ratio, PECs = pectoral nerve block, PONV = postoperative nausea/vomiting, PVB = paravertebral block, RCTs = randomized controlled trials, SBP = systolic blood pressure, SMD = standardized mean difference, VAS = visual analog scale, VNS = verbal numerical score.

Keywords: breast surgery, dexmedetomidine, postoperative nausea/vomiting, postoperative pain

1. Introduction
Breast cancer (BC) is one of the most common malignancies seen in women, accounting for 268,600 new cases and 41,760 deaths in 2019 in the USA.¹ Surgery is the major option for the management of patients with BC, which causes a 40% reduced risk of death compared with women who did not have surgery.² However, it is recorded that patients experience several complications following breast cancer surgery, such as postoperative pain,³ postoperative nausea/vomiting (PONV),⁴,⁵ pneumothorax,⁶ bradycardia,⁷,⁸ respiratory depression,⁹ etc. These complications not only seriously influence the quality of life of patients, but also increase the hospital costs.¹⁰ Hence, it is urgently required to explore effective methods to prevent these complications.

Recently, adding adjuvants to local (LA) or general anesthetic (GA) agents has been suggested as an underlying strategy to improve these side effects. Dexmedetomidine (DEX) is a highly selective agonist which acts by binding with presynaptic alpha 2-adrenergic receptor and then activating the negative feedback loop of the sympathetic nerve response, leading to inhibited norepinephrine release from the sympathetic terminals and decreased reflex activity of the sympathetic nervous.¹¹ These
subsequently depress the transmission of pain sensations and reactions of nausea and vomiting. Thus, DEX may be a potent adjuvant to exert analgesia and antiemetic effects. This hypothesis has been demonstrated in breast cancer surgery by some studies. For example, Mohta et al.\(^{[15]}\) evaluated the analgesic efficacy of DEX adjuvant for paravertebral block (PVB) and found patients receiving DEX had significantly lower pain score at 2, 4, 8, and 24 hours after surgery compared with controls. Mukherjee et al.\(^{[16]}\) observed that the pain score was significantly decreased in the group administered DEX adjuvant for PVB at 1, 2, 4, and 6 hours postoperatively. Shi et al.\(^{[17]}\) identified that patients undergoing GA with DEX showed a lower incidence of vomiting. However, its analgesic and antiemetic effects during breast cancer surgery remain inconclusive because there were contrary conclusions reported by some authors. Kaur et al.\(^{[17]}\) only proved that the addition of DEX in pectoral nerve block (PECS) significantly reduced the pain score at 2 hours postoperatively, but not at other time points. Also, no statistical difference in the postoperative nausea was present between the DEX and the control groups.\(^{[17]}\) Similarly, the results of the study performed by Jin et al.\(^{[18]}\) showed that paravertebral regional anesthesia with DEX did not significantly decrease the pain score and the risk to various adverse events (nausea, vomiting, and pneumothorax) compared with the control groups. Hereby, it is essential to comprehensively assess the effects of DEX for breast surgery by integrating all relevant evidence.

In the present study, we aimed to conduct a meta-analysis to investigate the influence of DEX on the analgesic efficacy and complications during the surgical treatment of breast cancer.

### 2. Materials and methods

This report was conducted according to the guidelines of Preferred Reporting Items for Systematic Review and Meta-analysis. Patient consent and ethical approval were unnecessary since this study is a meta-analysis.

#### 2.1. Search strategy

The electronic databases PubMed, EMBASE, and Cochrane Library were used for searching relevant literature. A search strategy included a combination of the following words: “dexmedetomidine” AND ("breast cancer") AND ("surgery" OR "mastectomy"). The retrieval time was from the inception to November 9, 2019. Furthermore, a manual search for the reference lists of included studies and reviews was also performed to identify potentially eligible trials.

#### 2.2. Study selection criteria

Studies were eligible if they met the following inclusion criteria: randomized controlled trials (RCTs); patients underwent radical surgery due to suffering from breast cancer; studies using DEX as an adjuvant for various anesthesia methods, were considered; studies using all comparators, including placebo and other drugs, were included; availability of full-text publication in English; at least 1 outcome was reported; the treatment outcomes recorded in at least 2 studies; and providing sufficient data for statistical analysis. Studies were excluded if they were: duplicate publications; case report, reviews, animal, or cell studies; observational studies without control; and data unavailable.

#### 2.3. Data extraction and quality assessment

Extracted data included the name of first author, publication year, country, study design, the size of samples, anesthesia technique, analgesic efficacy [time to first request of analgesia, the use dosage of analgetics (tramadol, fentanyl, morphine), pain score (numerical rating scale, NRS; visual analog scale, VAS; or verbal numerical score, VNS); sedation score], influence on the hemodynamic outcomes (heart rate, HR; systolic blood pressure, SBP; diastolic blood pressure, DBP) and adverse effects (PONV, pneumothorax, bradycardia, itching, sedation, hypotension). Some data in the bar or line graph were extracted by using the GetData Graph Digitizer (version 2.25; http://www.getdata-graph-digitizer.com).

The methodological quality of each study was assessed using the Cochrane risk-of-bias tool which included 6 aspects for RCTs: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; adequate assessment of incomplete outcome; selective reporting avoided; and no other bias. Two reviewer authors independently extracted the data and completed the quality assessment. Disagreements were resolved by consensus with a third reviewer.

#### 2.4. Statistical analysis

Statistical analysis was performed using the STATA software (version 13.0; STATA Corporation, College Station, TX). The incidence of adverse events was expressed by odd ratio (OR) and its 95% confidence interval (CI), while all continuous outcomes were expressed by standardized mean difference (SMD) and 95% CI. Cochrane Q and I\(^2\) statistic tests were used for determining the heterogeneity among studies. If the P value was < .1 and I\(^2\) was > 50%, the heterogeneity was considered to be significant and thus, the random-effects model was used to calculate the effect size; otherwise, there was no evidence of significant heterogeneity and then, a fixed-effect model was chosen. Subgroup analysis was performed based on anesthetic technique and ethnicity. Publication bias was measured by Egger linear regression test.\(^{[19]}\) Trim and fill method was utilized to adjust pooled HR if significant publication bias existed (P < .05).\(^{[20]}\) Sensitivity analysis was performed to evaluate the results stability by omitting each study in turn. P < .05 was considered to be statistically significant.

### 3. Results

#### 3.1. Study selection

The study search process is shown in Figure 1. In total, 1072 articles were initially yielded from the online databases. Of them, 610 studies were removed due to duplication. After reviewing the titles and abstracts, 451 articles were further eliminated because they failed to meet the inclusion criteria: animal studies (n = 142), case report (n = 45), irrelevant topic (n = 191), meta-analysis (n = 19), cell studies (n = 8), not cancer-related (n = 28), observational studies without control (n = 1), and no English publications (n = 17). The remaining 14 studies were examined in detail by reading the full text, after which 2 studies were excluded because they did not investigate the effects of DEX. Thus, these 12 studies (DEX treatment group, n = 396; control group, n = 395) were finally included in our meta-analysis.\(^{[6,7,8,15–18,21–24]}\)

#### 3.2. Study characteristics and quality assessment

The characteristics of these studies are summarized in Table 1. All these studies were RCTs and performed in India (n = 6),
Egypt (n=2), Korea (n=1), or China (n=3). Six trials used the DEX for GA, 4 for PVB, and 2 for PECS. The comparator was saline (normal or Ringer) solution in 6 studies and other anesthetic drugs (ropivacaine, bupivacaine, clonidine + ropivacaine, or fentanyl) in 7 studies (Table 1; in which the study of Mohta et al\textsuperscript{[15]} had 2 comparison groups, including normal saline and bupivacaine). All included studies investigated the analgesic efficacy or the influence on other complications, with at least one of the interested outcomes reported.

The risk of bias in the RCTs is present in Table 2. In general, the included trials had a low risk of bias. Only blinding of participants was unclear in 3 trials and blinding of outcomes assessment was not performed in 1 trial.
### Table 1
Characteristics of included studies.

| Study | Year | Country | Number | Age (Mean ± SD) | Used drugs | Anesthesia using dexmedetomidine |
|-------|------|---------|--------|-----------------|------------|----------------------------------|
| Kaur H | 2017 | India   | 30     | 51.6 ± 11.0     | Desmedetomidine + Ropivacaine | Pectoral nerve block |
| Bakr MA | 2018 | Egypt   | 30     | 47.3 ± 9.7      | Desmedetomidine + Bupivacaine | Paravertebral block |
| Mohta M | 2014 | Egypt   | 44     | 52.4 ± 5.6      | Desmedetomidine + Ropivacaine | General anesthesia |
| Shi C  | 2017 | China   | 24     | 43.8 ± 1.8      | Desmedetomidine | General anesthesia |
| Mohamed SA | 2016 | Egypt   | 30     | 45.3 ± 7.4      | Normal saline | General anesthesia |
| Jin LJ | 2017 | China   | 36     | 57.6 ± 10.3     | Desmedetomidine + Bupivacaine | Paravertebral block |
| Mohamed SA | 2018 | Egypt   | 30     | 50.4 ± 6.0      | Bupivacaine | Paravertebral block |
| Bakr MA | 2018 | Egypt   | 15     | 47.9 ± 8.1      | Desmedetomidine | General anesthesia |
| Kaur H | 2017 | India   | 30     | 46.2 ± 10.6     | Ropivacaine | Pectoral nerve block |
| Mohta M | 2018 | Egypt   | 30     | 48.5 ± 13.7     | Bupivacaine | Paravertebral block |
| Mohta M | 2016 | India   | 30     | 49.9 ± 10.6     | Bupivacaine | Paravertebral block |
| Jin LJ | 2017 | China   | 36     | 58.8 ± 11.0     | Bupivacaine | Paravertebral block |
| Fan W | 2017 | China   | 24     | 43.8 ± 1.8      | Desmedetomidine | General anesthesia |
| Shi C | 2017 | China   | 24     | 49.2 ± 8.5      | Desmedetomidine | General anesthesia |
| Goyal S | 2017 | India   | 30     | 40.2 ± 11.5     | Desmedetomidine | General anesthesia |
| Fan W | 2017 | China   | 24     | 43.8 ± 1.8      | Desmedetomidine | General anesthesia |
| Jain G | 2012 | India   | 34     | 50.8 ± 16.4     | Desmedetomidine | General anesthesia |
| Kwak H | 2019 | Korea   | 49     | 48.2 ± 7.1      | Desmedetomidine | General anesthesia |

### Table 2
Bias evaluation of RCTs.

| First author | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Adequate assessment of incomplete outcome | Selective reporting avoidance | No other bias |
|--------------|----------------------------|------------------------|---------------------------------------|--------------------------------|------------------------------------------|-----------------------------|--------------|
| Kaur H       | Yes                        | Yes                    | Yes                                   | Yes                            | Yes                                      | Yes                         | Yes          |
| Bakr MA      | Yes                        | Yes                    | Yes                                   | Yes                            | Yes                                      | Yes                         | Yes          |
| Mohta M      | Yes                        | Yes                    | Yes                                   | Yes                            | Yes                                      | Yes                         | Yes          |
| Jin LJ       | Yes                        | Yes                    | Unclear                               | Unclear                        | Yes                                      | Yes                         | Yes          |
| Mohamed SA   | Yes                        | Yes                    | Yes                                   | Yes                            | Yes                                      | Yes                         | Yes          |
| Mukherjee A  | Yes                        | Yes                    | Yes                                   | Yes                            | Yes                                      | Yes                         | Yes          |
| Das R        | Yes                        | Yes                    | Yes                                   | Yes                            | Yes                                      | Yes                         | Yes          |
| Shi C        | Yes                        | Unclear                | Yes                                   | Yes                            | Yes                                      | Yes                         | Yes          |
| Goyal S      | Yes                        | Yes                    | Yes                                   | Yes                            | Yes                                      | Yes                         | Yes          |
| Fan W        | Yes                        | Yes                    | Unclear                               | Yes                            | Yes                                      | Yes                         | Yes          |
| Jain G       | Yes                        | Yes                    | Yes                                   | Yes                            | Yes                                      | Yes                         | Yes          |
| Kwak H       | Yes                        | Yes                    | Yes                                   | Yes                            | Yes                                      | Yes                         | Yes          |

#### 3.3. Meta-analysis to show the analgesic efficacy of DEX

Analgesic efficacy was first assessed in terms of intraoperative fentanyl requirement (n=6), postoperative tramadol consumption (n=2), total postoperative morphine consumption (n=4), patient-controlled analgesia (PCA) morphine consumption (n=3), and time to first request of analgesia (n=12) (Table 3). Pooled analysis demonstrated that the use of DEX significantly prolonged the time to first request of analgesia (SMD=1.67; 95% CI = 1.02–2.32, P < .001; Fig. 2) and decreased the postoperative requirement for tramadol (SMD = −0.65; 95% CI = −1.04 to −0.30, P < .001) and morphine (total: SMD = −2.23; 95% CI = −2.63 to −1.84, P < .001; PCA: SMD = −1.45; 95% CI = −2.26 to −0.64, P < .001) as well as intraoperative requirement for fentanyl (SMD = −1.60; 95% CI = −2.94 to −0.27, P < .018) compared with the control group (Table 3). The same effect were seen in most of subgroups based on ethnicity (Asian and non-Asian) and anesthetic technique. Only the intraoperative fentanyl requirement in the GA group (P = .305) and time to first request of analgesia in the PECS group (P = .120) were not significantly improved by the use of DEX compared with their controls (Table 3).

VAS, NRS, and VNS score were quantified to further represent the pain effects. They were evaluated at different time points and thus, meta-analysis was performed for them, respectively. The pooled results demonstrated that compared with the control group, the pain score (VAS/NRS/VNS at rest and movement) was significantly reduced in the DEX group at 1 (SMD = −0.30; 95% CI = −0.53 to −0.07, P = .012), 2 (SMD = −1.45; 95% CI = −2.20 to −0.70, P < .001), 4 (SMD = −2.36; 95% CI = −3.30 to −1.42, P < .001), 6 (SMD = −0.63; 95% CI = −1.05 to −0.21, P < .001), 8 (SMD = −2.47; 95% CI = −3.20 to −1.74, P < .001), 12 (SMD = −0.81; 95% CI = −1.35 to −0.28, P < .003), 24 (SMD = −1.78; 95% CI = −2.47 to −1.08, P < .001; Fig. 3), 36 (SMD = −0.92; 95% CI = −1.51 to −0.33, P = .002), and 48 (SMD = −0.80; 95% CI = −1.34 to −0.26, P = .004) hours postoperatively (Table 3). The further stratification of subgroup analysis indicated that the addition of adjuvant DEX may not provide beneficial effects on relieving pain at 1 (P = .553), 2 (P = .276), 6 (P = .519), 12 (P = .065), and 24 (P = .440) hours postoperatively to the LA approach (PECS), but was significantly effective at later time point (36 and 48 hours). The results of GA were similar to the overall results, except for 1 hour.
Table 3

Algesic effect of dexmedetomidine.

| Comparison                                      | Group         | Studies | SMD (95% CI) | P< value | I²   | P< value |
|------------------------------------------------|---------------|---------|--------------|----------|------|----------|
| Intraoperative fentanyl requirement (µg)       | Overall       | 6       | −1.60 (−2.94, −0.27) | .018     | 96.0 | <.001    |
| Anesthetic technique                           | GA            | 2       | −3.15 (−6.17, 2.97)  | .005     | 0.0  | <.369    |
|                                                | PVB           | 3       | −0.75 (−1.08, −0.41) | <.001    | 99.0 | <.001    |
|                                                | PECS          | 1       | —              | —        | —    | —        |
| Ethnicity                                      | Asian         | 6       | −1.60 (−2.94, −0.27) | .018     | 96.0 | <.001    |
|                                                | Non-Asian     | 0       | —              | —        | —    | —        |
| Postoperative tramadol consumption (mg)        | Overall       | 2       | −0.65 (−1.00, −0.30) | <.001    | 0.0  | .916     |
| Total postoperative morphine consumption (mg)  | Overall       | 4       | −2.23 (−2.63, −1.84) | <.001    | 0.0  | .451     |
| Anesthetic technique                           | GA            | 1       | −2.41 (−3.18, −1.63) | <.001    | 13.8 | .281     |
|                                                | PVB           | 2       | −1.94 (−2.56, −1.31) | <.001    | 13.8 | .281     |
|                                                | PECS          | 1       | −2.45 (−3.13, −1.78) | <.001    | —    | —        |
| Ethnicity                                      | Asian         | 4       | −2.23 (−2.63, −1.84) | <.001    | 0.0  | .451     |
|                                                | Non-Asian     | 0       | —              | —        | —    | —        |
| PCA morphine consumption (mg)                  | Overall       | 3       | −1.45 (−2.26, −0.64) | <.001    | 71.8 | .029     |
| Anesthetic technique                           | GA            | 2       | 3.50 (2.91, 4.10)   | <.001    | 0.0  | .447     |
|                                                | PVB           | 7       | 1.25 (0.75, 1.75)   | <.001    | 78.7 | <.001    |
|                                                | PECS          | 2       | 1.60 (−0.42, 3.61)  | .120     | 95.4 | <.001    |
| Ethnicity                                      | Asian         | 9       | 1.16 (0.63, 1.68)   | <.001    | 89.7 | <.001    |
|                                                | Non-Asian     | 2       | 0.43 (0.07, 0.80)   | .019     | 0.0  | .421     |
| Sedation score at 0 h postoperatively          | Overall       | 2       | 2.40 (0.95, 3.86)   | <.001    | 88.8 | .003     |
| Sedation score at 1 h postoperatively          | Overall       | 3       | 1.14 (0.27, 2.01)   | <.001    | 81.0 | .022     |
| Anesthetic technique                           | GA            | 2       | 0.71 (0.22, 2.10)   | .004     | —    | —        |
|                                                | PVB           | 1       | 1.60 (0.22, 2.18)   | <.001    | —    | —        |
| Ethnicity                                      | Asian         | 3       | 1.14 (0.27, 2.01)   | <.001    | 81.0 | .022     |
|                                                | Non-Asian     | 0       | —              | —        | —    | —        |
| Sedation score at 2 h postoperatively          | Overall       | 3       | 2.06 (−0.32, 4.45)  | .965     | 97.6 | <.001    |
| Anesthetic technique                           | GA            | 1       | 0.58 (0.10, 1.06)   | .018     | —    | —        |
|                                                | PECS          | 2       | 2.91 (−3.10, 8.92)  | .342     | 98.8 | <.001    |
| Ethnicity                                      | Asian         | 2       | 0.23 (−0.47, 0.93)  | .516     | 74.7 | .047     |
|                                                | Non-Asian     | 1       | 6.00 (4.80, 7.20)   | <.001    | —    | —        |
| Sedation score at 6 h postoperatively          | Overall       | 3       | 0.67 (0.04, 1.31)   | .038     | 78.0 | .011     |
| Anesthetic technique                           | GA            | 1       | 0.67 (0.18, 1.15)   | .007     | —    | —        |
|                                                | PVB           | 2       | 0.68 (−0.45, 1.81)  | .238     | 89.0 | .003     |
| Ethnicity                                      | Asian         | 2       | 0.39 (−0.15, 0.94)  | .158     | 58.9 | .119     |
|                                                | Non-Asian     | 1       | 1.27 (0.71, 1.82)   | <.001    | —    | —        |
| Sedation score at 12 h postoperatively         | Overall       | 3       | 1.30 (−0.06, 2.65)  | .060     | 91.5 | .001     |
| Anesthetic technique                           | GA            | 1       | 0.62 (0.14, 1.10)   | .012     | —    | —        |
|                                                | PECS          | 2       | 2.00 (1.38, 2.62)   | <.001    | —    | —        |
| Ethnicity                                      | Asian         | 2       | 0.62 (0.14, 1.10)   | .012     | —    | —        |
|                                                | Non-Asian     | 1       | 2.00 (1.38, 2.62)   | .000     | —    | —        |
| Sedation score at 24 h postoperatively         | Overall       | 3       | 0.27 (−0.25, 0.78)  | .306     | 55.2 | .135     |
| Anesthetic technique                           | GA            | 1       | 0.53 (0.05, 1.01)   | .030     | —    | —        |
|                                                | PVB           | 2       | 0.00 (−0.51, 0.51)  | 1.000    | —    | —        |
| Ethnicity                                      | Asian         | 2       | 0.53 (0.05, 1.01)   | .030     | —    | —        |
|                                                | Non-Asian     | 1       | 0.00 (−0.51, 0.51)  | 1.000    | —    | —        |
| Sedation score at 36 h postoperatively         | Overall       | 2       | 0.16 (−0.19, 0.50)  | .379     | 0.0  | .410     |
| Anesthetic technique                           | GA            | 1       | 0.29 (−0.18, 0.77)  | .228     | —    | —        |
|                                                | PVB           | 1       | 0.00 (−0.51, 0.51)  | 1.000    | —    | —        |
| Ethnicity                                      | Asian         | 1       | 0.29 (−0.18, 0.77)  | .228     | —    | —        |
|                                                | Non-Asian     | 1       | 0.00 (−0.51, 0.51)  | 1.000    | —    | —        |
| Pain score at 1 h postoperatively              | Overall       | 4       | −0.30 (−0.53, −0.07) | .012     | 0.0  | .8411    |
| Anesthetic technique                           | GA            | 2       | −0.27 (−0.60, 0.07) | .117     | 0.0  | 97.7     |
|                                                | PVB           | 1       | −0.45 (−0.87, −0.03) | .038     | —    | —        |
|                                                | PECS          | 1       | −0.15 (−0.66, 0.35) | .553     | —    | —        |
| Ethnicity                                      | Asian         | 4       | −0.30 (−0.53, −0.07) | .012     | 0.0  | .8411    |
|                                                | Non-Asian     | 0       | —              | —        | —    | —        |
| Pain score at 2 h postoperatively              | Overall       | 10      | −1.45 (−2.20, −0.70) | <.001    | 90.7 | <.001    |

(continued)
3.4. Meta-analysis to show the effects of DEX on hemodynamic outcomes

Hemodynamic parameters HR, SBP, and DBP were monitored during surgery at 30, 60, and 120 minutes; while only HR was recorded at 0, 2, 6, 12, 24, 36, and 48 hours postoperatively. The pooled analysis showed that intraoperative HR (30 minutes: SMD = -0.97; 95% CI = -1.36 to -0.58, P < .001; 60 minutes: SMD = -0.71; 95% CI = -0.92 to -0.50, P = .001) and DBP (30 minutes: SMD = -1.52; 95% CI = -1.84 to -1.20, P < .001) were significantly lower in the DEX group at the early time point, but restored to no differences at 120 minutes intraoperatively.

Also, the difference in postoperative HR could only achieve statistical significance between 2 groups at 6-hours (SMD = -0.30; 95% CI = -0.58 to -0.02, P = .039), but not the other time points. However, SBP showed a significant reduction at all time points (30 minutes: SMD = -1.50; 95% CI = -1.78 to -1.22, P < .001; 60 minutes: SMD = 1.05; 95% CI = -1.66 to -0.44, P = .001; 120 minutes: SMD = -0.60; 95% CI = -0.95 to -0.25, P = .001) in the DEX group compared with the control group (Table 4). These results were almost not altered by the subgroup analyses based on ethnicity and anesthetic technique except for postoperative HR at 24 hours which was found to be increased in the general anesthesia group (P = .002) (Table 4).
3.5. Meta-analysis to show the effects of DEX on adverse events

In line with the above effects on the SBP, the pooled analysis also showed that the incidence of hypotension was significantly increased in the DEX group compared with the control group (OR = 2.17; 95% CI = 1.06–4.47, P = .035), which was especially significant in the PVB subgroup (P = .037) (Table 5). Furthermore, the risks to develop PONV (OR = 0.38; 95% CI = 0.16–0.93, P = .034) and vomiting (OR = 0.54; 95% CI = 0.30–1.00, P = .048; Fig. 4) were significantly decreased in the DEX group compared with the control group, which was only significant in the GA subgroup (P = .017), but not in the LA subgroups (Table 5). Meta-regression revealed that sedation score was significantly enhanced in the DEX group at 0 (SMD = 2.40; 95% CI = 0.95–3.85, P = .001), 1 (SMD = 1.14; 95% CI = 0.27–2.01, P = .01), and 6 (SMD = 0.67; 95% CI = 0.04–1.31, P = .038; Fig. 5) hours postoperatively than that in the control group. No difference was observed between 2 groups in the later time points (12, 24, and 36 hours). Subgroup analysis also showed there were no differences in the sedation score for each group at 36 hours postoperatively (Table 5). These findings indicated the incidence of over-sedation may be similar between 2 groups at the last follow-up, which was confirmed in our overall study (P = .407; Table 5) and PVB group (P = .240; Table 5). Even, the incidence of over-sedation was reduced in the GA group (OR = 0.23; Table 5). Also, there were no differences in the incidence of other side effects, including nausea, pneumothorax, bradycardia, and itching between the DEX and the control groups (Table 5). In addition, ethnicity stratification analysis revealed the incidence of hypotension was particularly increased in the Asian population (Table 5).

3.6. Publication bias and sensitivity analyses

Publication bias analysis was performed for all significant outcomes with the random-effect model. The Egger test results showed there was no evidence of publication bias for intraoperative fentanyl requirement (P = .133), sedation score at 6 hours (P = .548), pain score at 6 hours (P = .489), 8 hours (P = .051), 12 hours (P = .093), 48 hours postoperatively (P = .059), SBP at 60 minutes intraoperatively (P = .427), HR at 30 minutes intraoperatively (P = .366), and PONV (P = .914). Publication bias was present for time to first request of analgesia (P = .015), total postoperative morphine consumption (P = .032), pain score at 1 (P = .001), 2 (P = .004), 4 (P = .002), 24 (P < .001), and 36 hours postoperatively (P = .001). Thus, trim and fill method was utilized to adjust the pooled HR for them. As a result, the difference was still significant (time to first request of analgesia: SMD = 0.86; 95% CI = 0.16–1.56; total postoperative morphine consumption: SMD = −1.28; 95% CI = −1.83 to −0.73; pain score at 1 hour: SMD = −0.34; 95% CI = −0.55 to −0.13; pain score at 2 hours: SMD = −1.45; 95% CI = −2.22 to −0.70; pain score at 4 hours: SMD = −0.92; 95% CI = −1.51 to −0.33; 95% CI = −2.39 to −0.63; pain score at 24 hours: SMD = −1.78; 95% CI = −2.47 to −1.08; pain score at 36 hours:
SMD = -0.92; 95% CI = -1.51 to -0.33). The sensitivity analyses also indicated the robust stability of the results (Fig. 6).

4. Discussion

In the present study, 12 RCTs were integrated to comprehensively evaluate the analgesic efficacy of DEX and its influence on complications during the surgical treatment of breast cancer. The meta-analysis demonstrated that the use of DEX as an anesthetic adjuvant may significantly decrease the requirement for analgesics (tramadol, morphine, or fentanyl), prolong the time to first request of analgesia, and relieve the postoperative pain. Furthermore, it also lowered the incidence of PONV and vomiting. These findings of analgesic effects seemed to be in line with previous meta-analyses on abdominal surgery,[25,26] while the antiemetic effects were in accordance with the study of total knee or hip arthroplasty.[27]

The analgesic and antiemetic mechanisms of DEX in surgical patients remain unclear other than its roles for reduction of noradrenaline release.[11,28] In this study, we speculated that the analgesic effects of DEX may be associated with its anti-inflammatory roles by decreasing interleukin (IL)-6, tumor necrosis factor-α and C-reactive protein (CRP),[29,30] while the antiemetic effects were in accordance with the study of total knee or hip arthroplasty.[27]

The analgesic and antiemetic mechanisms of DEX in surgical patients remain unclear other than its roles for reduction of noradrenaline release.[11,28] In this study, we speculated that the analgesic effects of DEX may be associated with its anti-inflammatory roles by decreasing interleukin (IL)-6, tumor necrosis factor-α and C-reactive protein (CRP),[29,30] while the antiemetic effects were in accordance with the study of total knee or hip arthroplasty.[27]

The analgesic and antiemetic mechanisms of DEX in surgical patients remain unclear other than its roles for reduction of noradrenaline release.[11,28] In this study, we speculated that the analgesic effects of DEX may be associated with its anti-inflammatory roles by decreasing interleukin (IL)-6, tumor necrosis factor-α and C-reactive protein (CRP),[29,30] while the antiemetic effects were in accordance with the study of total knee or hip arthroplasty.[27]

The analgesic and antiemetic mechanisms of DEX in surgical patients remain unclear other than its roles for reduction of noradrenaline release.[11,28] In this study, we speculated that the analgesic effects of DEX may be associated with its anti-inflammatory roles by decreasing interleukin (IL)-6, tumor necrosis factor-α and C-reactive protein (CRP),[29,30] while the antiemetic effects were in accordance with the study of total knee or hip arthroplasty.[27]

The analgesic and antiemetic mechanisms of DEX in surgical patients remain unclear other than its roles for reduction of noradrenaline release.[11,28] In this study, we speculated that the analgesic effects of DEX may be associated with its anti-inflammatory roles by decreasing interleukin (IL)-6, tumor necrosis factor-α and C-reactive protein (CRP),[29,30] while the antiemetic effects were in accordance with the study of total knee or hip arthroplasty.[27]

The analgesic and antiemetic mechanisms of DEX in surgical patients remain unclear other than its roles for reduction of noradrenaline release.[11,28] In this study, we speculated that the analgesic effects of DEX may be associated with its anti-inflammatory roles by decreasing interleukin (IL)-6, tumor necrosis factor-α and C-reactive protein (CRP),[29,30] while the antiemetic effects were in accordance with the study of total knee or hip arthroplasty.[27]

The analgesic and antiemetic mechanisms of DEX in surgical patients remain unclear other than its roles for reduction of noradrenaline release.[11,28] In this study, we speculated that the analgesic effects of DEX may be associated with its anti-inflammatory roles by decreasing interleukin (IL)-6, tumor necrosis factor-α and C-reactive protein (CRP),[29,30] while the antiemetic effects were in accordance with the study of total knee or hip arthroplasty.[27]
several studies. For example, Zhao et al. found, by meta-analysis of 8 RCTs and 2 cohort studies on breast cancer surgery, the PECS group effectively reduced the intraoperative and postoperative use of opioid drugs, incidence of PONV, need for postoperative rescue analgesia, and pain scores within 0 to 6 hours after surgery compared with the GA group. This conclusion of PECS block was also demonstrated by the analysis of 13 RCTs. The study of Tahir et al. integrated 11 RCTs and...
and suggested pain scores at 1 and 6 hours postoperatively, postoperative analgesic consumption and the incidence of PONV were significantly decreased in patients who received PVB compared with GA. Furthermore, the study performed by Kulhari et al. revealed the duration of analgesia was significantly prolonged, postoperative pain scores at 2 hours were lowered, and 24 hours morphine consumption was less in the PECS group compared with the PVB group, suggesting the analgesia superiority of PECS than PVB. In line with this result, we also found the pain score was not significantly decreased by DEX at 5 time points for the PECS group, but not one in the PVB group.

This meta-analysis has some limitations. First is the relatively small sample size in each included study, which may affect the reliability of obtained conclusions. Furthermore, the number of included studies for each outcome was also small, which may lead to the results of subgroup analyses (anesthetic technique, ethnicity) inconclusive. Second, substantial heterogeneity was present across the studies when analysis of crucial outcomes (such as the time to first request of analgesia, pain score, and PONV), which may cause potential bias. However, the trim and fill adjusted method and sensitivity analyses still confirmed their significance, indirectly indicating the robust stability of the results. Third, the lack of studies unpublished or published in other language may also result in bias for the pooled effects. Fourth, although we speculated DEX should be combined especially for the patients undergoing GA (due to the significant improvement at most time point), relative to the LA, further

| Table 5 |
| --- |
| **Adverse effects.** |
| **Adverse events** | Studies | OR (95% CI) | PA value | PH value | I² | PS value |
| PONV | Overall | 6 | 0.38 (0.16,0.93) | .034 | 57.5 | .038 |
| | GA | 3 | 0.37 (0.14,0.96) | .041 | 15.6 | .036 |
| | PVB | 3 | 0.31 (0.06,1.67) | .174 | 77.5 | .012 |
| Ethnicity | Asian | 6 | 0.38 (0.16,0.93) | .034 | 57.5 | .038 |
| | Non-Asian | 0 | — | — | — | — |
| Nausea | Overall | 7 | 0.78 (0.47,1.29) | .063 | 39.1 | .131 |
| | GA | 3 | 0.32 (0.14,0.72) | .006 | 0.0 | .678 |
| | PVB | 2 | 1.00 (0.31,3.27) | 1.000 | 0.0 | .542 |
| | PECS | 2 | 1.92 (0.62,5.53) | .136 | 0.0 | .500 |
| Ethnicity | Asian | 5 | 0.54 (0.29,1.00) | .052 | 16.0 | .312 |
| | Non-Asian | 2 | 1.71 (0.69,4.25) | .250 | 30.5 | .230 |
| Vomiting | Overall | 5 | 0.50 (0.30,1.00) | .004 | 0.0 | .615 |
| | GA | 2 | 0.34 (0.14,0.82) | .017 | 0.0 | .850 |
| | PVB | 2 | 1.00 (0.28,3.62) | 1.000 | 0.0 | .513 |
| | PECS | 1 | 0.73 (0.24,2.21) | .574 | — | — |
| Ethnicity | Asian | 3 | 0.46 (0.21,1.00) | .050 | 7.2 | .340 |
| | Non-Asian | 2 | 0.70 (0.27,2.13) | .470 | 0.0 | .911 |
| Pneumothorax | Overall | 3 | 1.00 (0.20,5.06) | 1.000 | 41.1 | .627 |
| | PVB | 2 | 1.00 (0.14,7.26) | 1.000 | 0.0 | .334 |
| | PECS | 1 | 1.00 (0.06,16.76) | 1.000 | — | — |
| Ethnicity | Asian | 1 | 3.09 (0.12,78.27) | .495 | — | — |
| | Non-Asian | 2 | 0.59 (0.08,4.61) | .615 | 0.0 | .605 |
| Bradycardia | Overall | 6 | 1.73 (0.94,3.20) | .080 | 0.0 | .682 |
| | GA | 3 | 0.34 (0.09,1.00) | .006 | 0.0 | .682 |
| | PVB | 2 | 1.07 (0.27,1.83) | .470 | 0.0 | .911 |
| | PECS | 1 | 1.97 (0.94,4.10) | .072 | 30.3 | .238 |
| Ethnicity | Asian | 5 | 0.54 (0.20,1.39) | .052 | 16.0 | .312 |
| | Non-Asian | 2 | 0.70 (0.27,2.13) | .470 | 0.0 | .911 |
| Itching | Overall | 3 | 0.26 (0.06,1.09) | .066 | 0.0 | .682 |
| | GA | 2 | 0.43 (0.08,2.50) | .350 | 0.0 | .956 |
| | PECS | 1 | 0.10 (0.01,1.88) | .123 | — | — |
| Ethnicity | Asian | 2 | 0.46 (0.09,2.50) | .350 | 0.0 | .956 |
| | Non-Asian | 1 | 0.10 (0.01,1.88) | .123 | — | — |
| Over-sedation | Overall | 3 | 0.51 (0.11,2.48) | .407 | 75.4 | .017 |
| | GA | 2 | 0.23 (0.08,0.65) | .006 | 0.0 | .957 |
| | PVB | 1 | 1.76 (0.69,4.51) | .240 | — | — |
| Ethnicity | Asian | 3 | 0.51 (0.11,2.48) | .407 | 75.4 | .017 |
| | Non-Asian | 0 | — | — | — | — |
| Hypotension | Overall | 4 | 2.17 (1.06,4.47) | .035 | 0.0 | .449 |
| | PVB | 3 | 2.30 (1.05,5.04) | .037 | 20.7 | .283 |
| | PECS | 1 | 1.56 (0.24,10.05) | .643 | — | — |
| Ethnicity | Asian | 3 | 2.30 (1.05,5.04) | .037 | 20.7 | .283 |
| | Non-Asian | 1 | 1.56 (0.24,10.05) | .643 | — | — |

CI = confidence interval, GA = general anesthesia, OR = odd ratio, PA = P value for association, PECS = pectoral nerve block, PH = P value for heterogeneity, PONV = postoperative nausea, vomiting F, fixed, PVB = paravertebral block, R = random. Bold indicated the statistical significance for association in 2 or more than 2 studies (P value < .05).
5. Conclusion

This meta-analysis suggests that DEX is a favorable anesthetic adjuvant in breast cancer surgery, which could lower postoperative pain and the risk to develop PONV. DEX should be combined especially for the patients undergoing GA relative to the LA.
Author contributions

Conceptualization: Changjun Liu, Wei Wang, Qiang Yan.
Data curation: Changjun Liu.
Formal analysis: Changjun Liu, Wei Wang.
Investigation: Zhengkun Shan, Huapeng Zhang.
Resources: Zhengkun Shan.
Software: Wei Wang.
Supervision: Qiang Yan.
Visualization: Huapeng Zhang.
Writing – original draft: Changjun Liu, Wei Wang.
Writing – review & editing: Qiang Yan.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7–34.
[2] Rapiti E, Verkooijen HM, Vlastos G, et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. J Clin Oncol 2006;24:2743–9.
[3] Kudach C, Dunwoody C, Wesmiller S. The relationship of age and postoperative pain in women after surgery for breast cancer. Pain Manage Nurs 2018;19:348–53.
[4] Kwak H, Chang YJ, Lee KC, et al. Antiemetic efficacy of dexmedetomidine versus dexmedetomidine-dexamethasone combination in patients undergoing breast surgery. J Int Med Res 2019;47:5060–9.
[5] Cortés-Flores AO, Jiménez-Tornero J, Morgan-Villela G, et al. Effects of preoperative dexamethasone on postoperative pain, nausea, vomiting and respiratory function in women undergoing conservative breast surgery for cancer: results of a controlled clinical trial. Eur J Cancer Care 2018;27:e12686.

Figure 6. Sensitivity analysis for the time to first request of analgesia. CI=confidence interval.

[6] Mohamed SA, Fares KM, Mohamed AA, et al. Dexmedetomidine as an adjunctive analgesic with bupivacaine in paravertebral analgesia for breast cancer surgery. Pain Physician 2014;17:E589–98.
[7] Shi C, Jin J, Pan Q, et al. Intraoperative use of dexmedetomidine promotes postoperative sleep and recovery following radical mastectomy under general anesthesia. Oncotarget 2017;8:79397–403.
[8] Head LK, Lui A, Boyd KU. Efficacy and safety of bilateral thoracic paravertebral blocks in outpatient breast surgery. Breast J 2018;24:561–6.
[9] Fan W, Xue H, Sun Y, et al. Dexmedetomidine improves postoperative patient-controlled analgesia following radical mastectomy. Front Pharmacol 2017;8:250.
[10] Saporito A, Aguirre J, Borgeat A, et al. Persistent postdischarge pain and chronic postoperative pain after breast cancer surgery under general anesthesia and single-shot paravertebral block: incidence, characteristics and impact on quality of life and healthcare costs. J Pain Res 2019;12:1193–9.
[11] Mantz J. Dexmedetomidine. Drugs Today (Barc) 1999;35:151–8.
[12] Schnabel A, Meyer-Freien CH, Reichl SU, et al. Is intraoperative dexmedetomidine a new option for postoperative pain treatment? A meta-analysis of randomized controlled trials. Pain 2013;154:1140–9.
[13] Bellon M, Le Bot A, Michelet D, et al. Efficacy of intraoperative dexmedetomidine compared with placebo for postoperative pain management: a meta-analysis of published studies. Pain Ther 2016;5:63–80.
[14] Liang X, Zhou M, Feng JJ, et al. Efficacy of dexmedetomidine on postoperative nausea and vomiting: a meta-analysis of randomized controlled trials. Int J Clin Exp Med 2015;8:9450–71.
[15] Mohanty M, Kalra B, Sethi AK, et al. Efficacy of dexmedetomidine as an adjuvant in paravertebral block in breast cancer surgery. J Anesth 2016;30:252–60.
[16] Mukherjee A, Das A, Mayur N, et al. Comparative evaluation of analgesic sparing efficacy between dexmedetomidine and clonidine used as adjuvant to ropivacaine in thoracic paravertebral block for patients undergoing breast cancer surgery: a prospective, randomized, double-blind study. Saudi J Anaesth 2018;12:548–54.
[17] Kaur H, Arora P, Singh G, et al. Dexmedetomidine as an adjunctive analgesic to ropivacaine in pectoral nerve block in oncological breast surgery: a randomized double-blind prospective study. J Anaesthesiol Clin Pharmacol 2017;33:457–61.

[18] Jin LJ, Wen LY, Zhang YL, et al. Thoracic paravertebral regional anaesthesia for pain relief in patients with breast cancer surgery. Medicine (Madr) 2017;96:e1107.

[19] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

[20] Shi L, Lin L. The trim-and-fill method for publication bias: practical guidelines and recommendations based on a large database of meta-analyses. Medicine (Madr) 2019;98:e15383.

[21] Bakr MA, Mohamed SA, Mohamad MF, et al. Effect of dexmedetomidine added to modified pectoral block on postoperative pain and stress response in patient undergoing modified radical mastectomy. Pain Physician 2018;21:87–96.

[22] Das R, Das RK, Sahoo S, et al. Role of dexmedetomidine as an anaesthetic adjuvant in breast cancer surgery as a day-care procedure: a randomised controlled study. Indian J Anaesth 2018;62:182–7.

[23] Goyal S, Gupta KK, Mahajan V. A comparative evaluation of intravenous dexmedetomidine and fentanyl in breast cancer surgery: a prospective, randomized, and controlled trial. Anesth Essays Res 2012;18:45–51.

[24] Jain G, Bansal P, Ahmad B, et al. Effect of the perioperative infusion of dexmedetomidine on chronic pain after breast surgery. Indian J Palliat Care 2012;18:45–51.

[25] Sun Q, Liu S, Wu H, et al. Dexmedetomidine as an adjuvant to local wound infiltration anaesthesia in abdominal surgery: a meta-analysis of randomised controlled trials. Int Wound J 2019;16:1206–13.

[26] Swami S, Ladi S, Kenya V, et al. Efficacy of dexmedetomidine as an adjuvant to local wound infiltration analgesia in abdominal surgery: a meta-analysis of randomized controlled trials. Int Wound J 2019;16:1206–13.

[27] Yang Q, Ren Y, Feng B, et al. Pain relieving effect of dexmedetomidine in patients undergoing total knee or hip arthroplasty: a meta-analysis. Medicine (Madr) 2020;99:e18538.

[28] Lehto J, Scheinin A, Johannsson J, et al. Detecting a dexmedetomidine-evoked reduction of noradrenaline release in the human brain with the alpha2C-adrenoceptor PET ligand [11C]ORM-13070. Synapse 2016;70:57–65.

[29] Wang K, Wu M, Xu J, et al. Effects of dexmedetomidine on perioperative stress, inflammation, and immune function: systematic review and meta-analysis. Br J Anaesth 2019;123:777–94.

[30] Yang W, Kong LS, Zhu XX, et al. Effect of dexmedetomidine on postoperative cognitive dysfunction and inflammation in patients after general anaesthesia: a PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore) 2019;98:e15583.

[31] Si HB, Yang TM, Zeng Y, et al. Correlations between inflammatory cytokines, muscle damage markers and acute postoperative pain following primary total knee arthroplasty. BMC Musculoskelet Disord 2017;18:265.

[32] Liu Y, Wang S, Wang Z, et al. Dexmedetomidine alleviated endoplasmic reticulum stress via inducing ER-phagy in the spinal cord of neuropathic pain model. Front Neurosci 2020;14:90.

[33] Lee BM, Jang Y, Park G, et al. Dexmedetomidine modulates transient receptor potential vanilloid subtype 1. Biochem Biophys Res Commun 2020;522:832–7.

[34] Hopwood SE, Stamford JA. Noradrenergic modulation of serotonin release in rat dorsal and median raphé nuclei via α 1 and α 2A adrenoceptors. Neuropharmacology 2001;41:433–42.

[35] Tsukagoshi S, Ohita J, Taguchi T. [An outline of 5-HT3 receptor antagonists (1)—In pharmacological actions]. Gan to Kagaku Ryoho 1993;20:2108–14.

[36] Demiri M, Antunes T, Fletcher D, et al. Perioperative adverse events attributed to α2-adrenoceptor agonists in patients not at risk of cardiovascular events: systematic review and meta-analysis. Br J Anaesth 2019;123:795–807.

[37] Zhao J, Han F, Yang Y, et al. Pectoral nerve block in anesthesia for modified radical mastectomy: a meta-analysis based on randomized controlled trials. Medicine (Baltimore) 2019;98:e13423.

[38] Versyck B, van Geffen GJ, Chin KJ. Analogic efficacy of the Pecs II block: a systematic review and meta-analysis. Anaesthesia 2019;74:663–73.

[39] Tahiri Y, Tran DQ, Bouteaud J, et al. General anaesthesia versus thoracic paravertebral block for breast surgery: a meta-analysis. J Plast Reconstr Aesthet Surg 2011;64:1261–9.

[40] Kulhari S, Bharti N, Bala I, et al. Efficacy of pectoral nerve block versus thoracic paravertebral block for postoperative analgesia after radical mastectomy: a randomized controlled trial. Br J Anaesth 2016;117:382–6.