Systematic Review and Meta-Analysis

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Dexmedetomidine as an adjuvant for patients undergoing breast cancer surgery

A meta-analysis

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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

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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subsequently depress the transmission of pain sensations and reactions of nausea and vomiting. Thus, DEX may be a potent adjuvant to exert analgesic[12,13] and antiemetic[14] 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[7] 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, pnemothorax, bradycardia, itching, sedation, hypotention). 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.[4,6,7,9,15–18,21–24]

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),

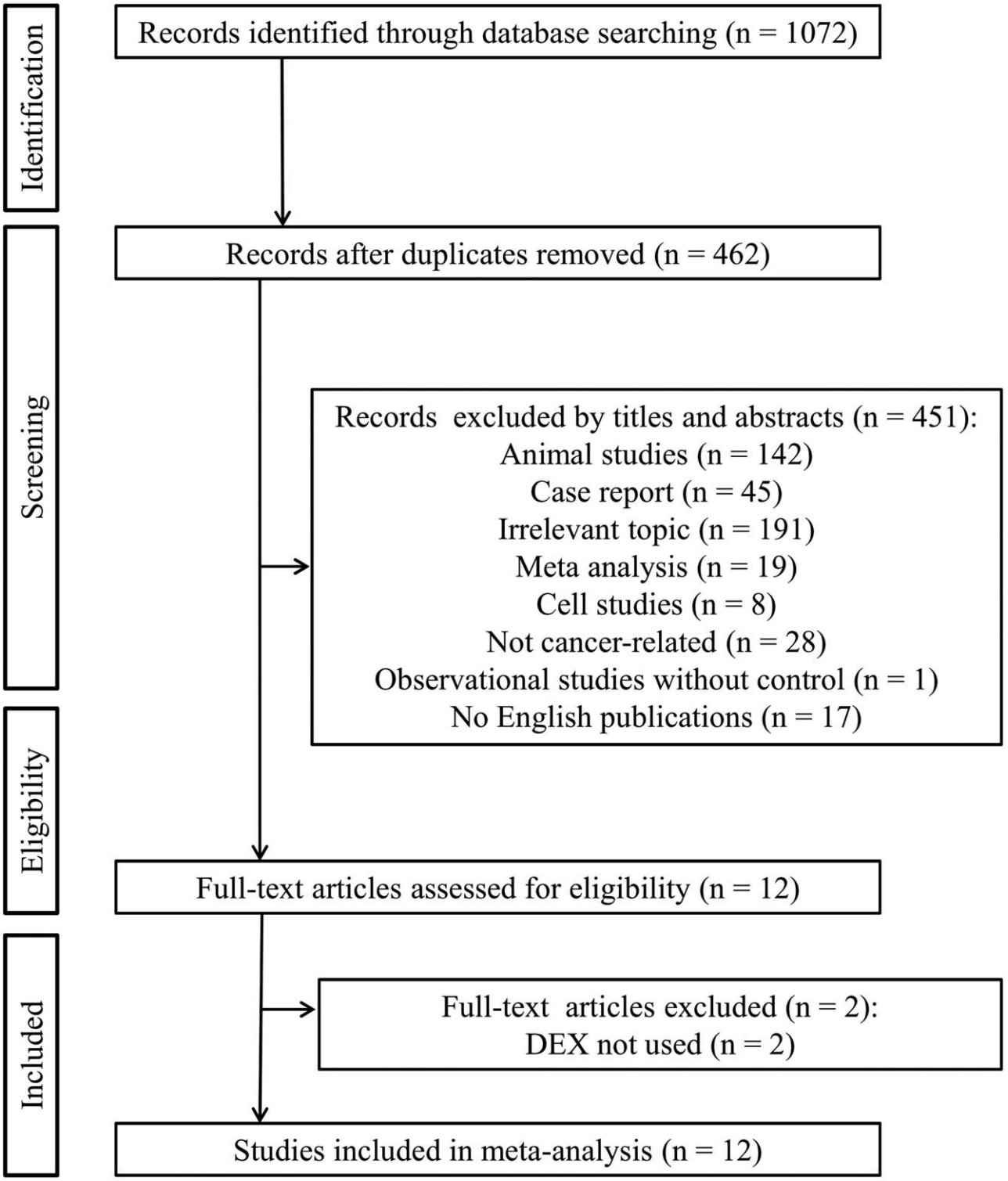

Figure 1. Flow diagram of search process.

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[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.

			Case group			Control group			
Study	Year	Country	Number	Age	Used drugs	Number	Age	Used drugs	Anesthesia using dexmedetomidine
Kaur H	2017	India	30	51.6 ± 11.0	Dexmedetomidine + Ropivacaine	30	46.2±10.6	Ropivacaine	Pectoral nerve block
Bakr MA	2018	Egypt	30	47.3±9.7	Dexmedetomidine + Bupivacaine	30	48.5±13.7	Bupivacaine	Pectoral nerve block
Mohta M	2016	India	15	46.6±10.5	Dexmedetomidine + Bupivacaine	15	49.9±10.6	Bupivacaine	Paravertebral block
Mohta M	2016	India	15	46.6±10.5	Dexmedetomidine + Bupivacaine	15	45.3±7.4	Normal saline	Paravertebral block
Jin LJ	2017	China	36	57.6±10.3	Dexmedetomidine + Bupivacaine	36	58.8±11.0	Bupivacaine	Paravertebral block
Mohamed SA	2014	Egypt	30	50.5±7.7	Dexmedetomidine + Bupivacaine	30	50.4±6.0	Bupivacaine	Paravertebral block
Mukherjee A	2018	India	44	52.4±5.6	Dexmedetomidine + Ropivacaine	30	49.9±7.0	Ropivacaine + Clonidine	Paravertebral block
Das R	2018	India	50	47.9±8.1	Dexmedetomidine	50	50.7±9.1	Normal saline	General anesthesia
Shi C	2017	China	24	49.2±8.5	Dexmedetomidine	23	47.7±8.7	Ringer solution	General anesthesia
Goyal S	2017	India	30	40.4±11.5	Dexmedetomidine	30	43.8±12.0	Fentanyl	General anesthesia
Fan W	2017	China	24	43.8±1.8	Dexmedetomidine	21	44.3±2.0	Ringer solution	General anesthesia
Jain G	2012	India	34	50.8±16.4	Dexmedetomidine	35	52.1±14.0	Normal saline	General anesthesia
Kwak H	2019	Korea	49	48.2±7.1	Dexmedetomidine	50	48.7±6.4	Normal saline	General anesthesia

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=−1.004 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, $P=.003$), 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 ($P=0.519$), 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 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 avoided	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	Yes	Unclear	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

Table 3

Analgesic effect of dexmedetomidine.

Comparison	Group	Studies	SMD (95% CI)	P_A value	I^2	P_H value
Intraoperative fentanyl requirement (μg)	Overall	6	−1.60(−2.94, −0.27)	**.018**	96.0	<.001
Anesthetic technique	GA	2	−3.15 (−9.17,2.87)	.305	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	—	—
	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	PVB	2	−1.82 (−2.58, −1.06)	<**.001**	34.4	.217
	PECS	1	−0.83 (−1.36, −0.31)	.002	—	—
Ethnicity	Asian	2	−1.82 (−2.58, −1.06)	<**.001**	34.4	.217
	Non-Asian	1	−0.83 (−1.36, −0.31)	.002	—	—
Time to first request of analgesia (min)	Overall	11	1.67 (1.02,2.32)	<**.001**	90.9	<.001
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 (0.95,3.85)	**.001**	88.8	.003
Sedation score at 1 h postoperatively	Overall	3	1.14 (0.27,2.01)	**.010**	81.0	.022
Anesthetic technique	GA	2	0.71 (0.22,1.20)	**.004**	—	—
	PECS	1	1.60 (1.02,2.18)	<.001	—	—
Ethnicity	Asian	3	1.14 (0.27,2.01)	**.010**	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	—	—
	PECS	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)	< 0.001	—	—
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 (−0.25,0.79)	.306	55.2	.135
Anesthetic technique	GA	1	0.53 (0.05,1.01)	.030	-	-
	PECS	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	—	—
	PECS	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	.841
	Non-Asian	0	—	—	—	—
Pain score at 2 h postoperatively	Overall	10	−1.45 (−2.20, −0.70)	<**.001**	90.7	<.001

(*continued*)

Table 3

(continued).

Comparison	Group	Studies	SMD (95% CI)	P_A value	I^2	P_H value
Anesthetic technique	GA	4	−1.87 (−3.35, −0.39)	**.014**	94.2	<.001
	PVB	5	−1.55 (−2.95, −0.15)	**.030**	90.7	<.001
	PECS	1	−0.28 (−0.79,0.23)	.276	—	—
Ethnicity	Asian	10	−1.45 (−2.20, −0.70)	**<.001**	90.7	.000
	Non-Asian	0	—	—	—	—
Pain score at 3 hpostoperatively	Overall	2	−0.26 (−0.61,0.08)	.133	0.0	.607
Pain score at 4 hpostoperatively	Overall	8	−2.36 (−3.30 to 1.42)	**<.001**	91.6	<.001
Anesthetic technique	GA	2	−4.37 (−5.14 to 3.59)	**<.001**	91.6	<.001
	PVB	5	−1.90 (−2.76 to 1.04)	**<.001**	0.0	.558
	PECS	1	−0.78 (−1.31 to 0.26)	0.003	—	—
Ethnicity	Asian	8	−2.36 (−3.30 to 1.42)	**<.001**	83.1	<.001
	Non-Asian	0	—	—	—	—
Pain score at 6 hpostoperatively	Overall	5	−0.63 (−1.05, −0.21)	**.003**	73.5	.005
Anesthetic technique	GA	2	−1.14 (−1.50, −0.78)	**<.001**	0.0	.531
	PVB	2	−0.38 (−0.74, −0.02)	.041	24.4	.250
	PECS	1	−0.17 (−0.67,0.34)	.519	—	—
Ethnicity	Asian	5	−0.63 (−1.05, −0.21)	**.003**	73.5	.005
	Non-Asian	0	—	—	—	—
Pain score at 8 hpostoperatively	Overall	6	−2.47 (−3.20, −1.74)	**<.001**	74.2	.002
Anesthetic technique	GA	2	−3.50 (−4.17, −2.83)	**<.001**	0.0	.696
	PVB	4	−1.94 (−2.46, −1.41)	**<.001**	28.8	.239
Ethnicity	Asian	6	-2.47 (-3.20,-1.74)	**< 0.001**	74.2	0.002
	Non-Asian	0	—	—	—	—
Pain score at 10 hpostoperatively	Overall	2	−0.31 (−0.63,0.02)	.061	0.0	.471
Pain score at 12 hpostoperatively	Overall	5	−0.81 (−1.35, −0.28)	**.003**	83.2	<.001
Anesthetic technique	GA	2	−1.51 (−1.89, −1.13)	**<.001**	0.0	.682
	PVB	2	−0.32 (−0.63, −0.01)	.044	0.0	.940
	PECS	1	−0.48 (−1.00,0.03)	.065	—	—
Ethnicity	Asian	5	−0.81 (−1.35, −0.28)	**.003**	83.2	<.001
	Non-Asian	0	—	—	—	—
Pain score at 24 hpostoperatively	Overall	11	−1.78 (−2.47, −1.08)	**<.001**	92.0	<.001
Anesthetic technique	GA	4	−2.28 (−3.72 to 0.85)	**.002**	94.3	<.001
	PVB	6	−1.72 (−2.62, −0.82)	**<.001**	89.8	<.001
	PECS	1	−0.20 (−0.71,0.31)	.440	—	—
Ethnicity	Asian	11	−1.78 (−2.47, −1.08)	**<.001**	92.0	<.001
	Non-Asian	0	—	—	—	—
Pain score at 36 h postoperatively	Overall	4	−0.92 (−1.51, −0.33)	**.002**	83.1	<.001
Anesthetic technique	GA	2	−1.41 (−1.79, −1.04)	**<.001**	0.0	.585
	PVB	2	−0.43 (−0.85, −0.02)	**.042**	42.7	.187
Ethnicity	Asian	4	−0.92 (−1.51, −0.33)	**.002**	83.1	<.001
	Non-Asian	0	—	—	—	—
Pain score at 48 hpostoperatively	Overall	4	−0.80 (−1.34, −0.26)	**.004**	80.2	.002
Anesthetic technique	GA	2	−1.27 (−1.64, −0.90)	**<.001**	0.0	.776
	PVB	2	−0.34 (−0.65, −0.03)	**.032**	0.0	.336
Ethnicity	Asian	4	−0.80 (−1.34, −0.26)	**.004**	80.2	.002
	Non-Asian	0	—	—	—	—

CI = confidence interval, F = fixed, GA = general anesthesia, P_A = *P* value for association, PCA = patient-controlled analgesia, PECS = pectoral nerve block, P_H = *P* value for heterogeneity, PVB = paravertebral block, R = random, SMD = standardized mean difference, VAS = visual analog scale. Bold indicated the statistical significance for association in 2 or more than 2 studies (*P* value <.05).

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).

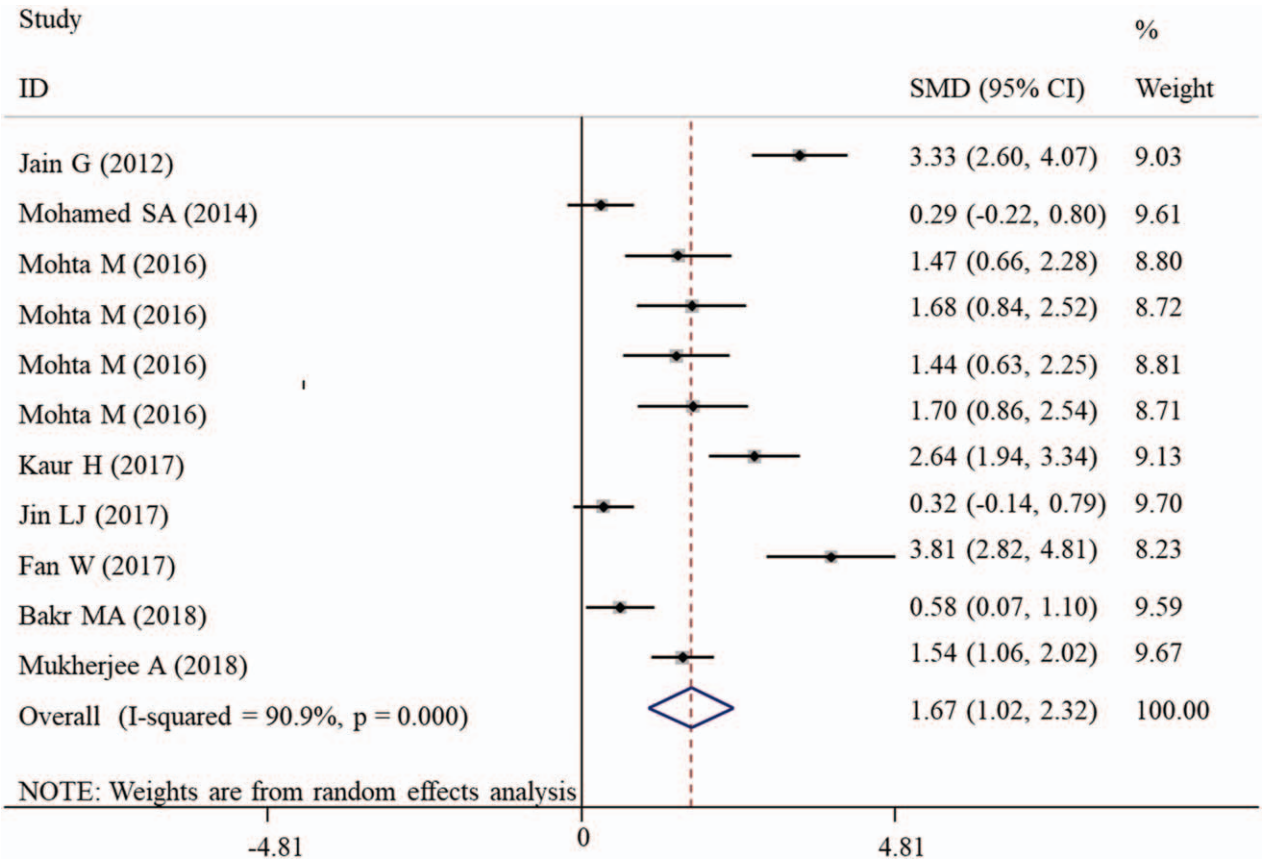

Figure 2. Forest plots showing the anesthetic effects of dexmedetomidine on the time to first request of analgesia. CI = confidence interval, SMD = standardized mean difference.

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 = 0.160–0.93, *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 3). 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, pnemothorax, bradycardia, and itching between the DEX and the control groups (Table 5). In addition, ethnicity stratification analysis revealed the incidence of hypotention 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 −3.33; 95% CI = −2.39 to −0.65; pain score at 24 hours: SMD = −1.78; 95% CI = −2.47 to −1.08; pain score at 36 hours:

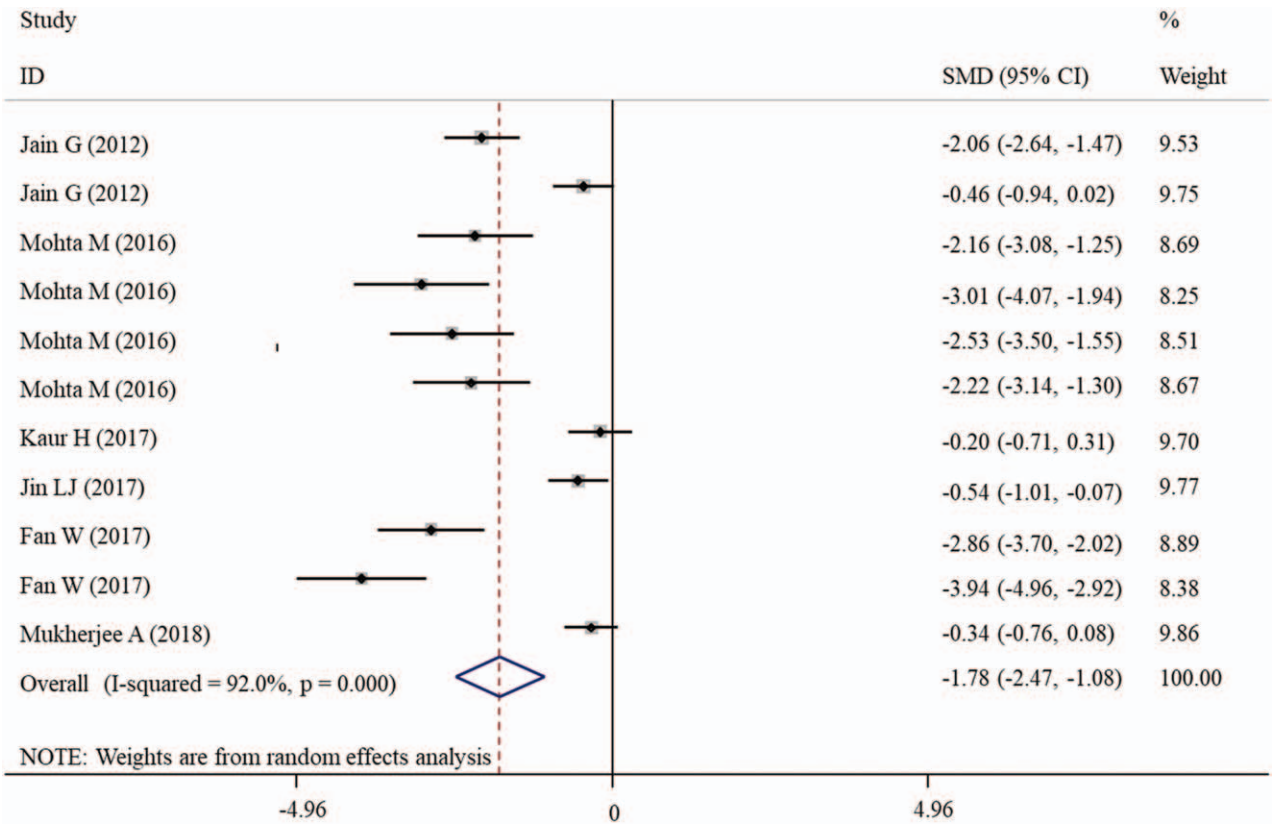

Figure 3. Forest plots showing the anesthetic effects of dexmedetomidine on the pain score at 24 h postoperatively. CI = confidence interval, SMD = standardized mean difference.

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] and increasing IL-10.[29] It was also reported that the NRS at rest was positively correlated with serum IL-6 at postoperative day 1; the NRS at walking was positively correlated with CRP at postoperative day 1 and IL-6 at postoperative day 1 to day 3.[31] Furthermore, Liu et al[32] suggested that DEX may alleviate pain via elevating endoplasmic reticulum autophagy, showing the downregulated expression of Grp78, LC3-I, p62, while upregulated expression of and FAM134B. The study of Lee et al[33] revealed that DEX may exert non-nociceptive roles by acting as an inhibitor of TRPV1 (transient receptor potential cation channel subfamily V member in the peripheral nervous system and then reducing capsaicin-induced calcium responses to block the transmission of pain signals. The previous study reported that the alpha(2)-selective agonist DEX decreased electrical stimulation-evoked 5-hydroxytryptamine (5-HT) release in the dorsal raphe nucleus and median raphe nucleus,[34] while 5-HT was demonstrated to bind with its downstream receptor to transmit impulses to the vomiting center on the chemoreceptor trigger zone in the area postrema of the central nervous system and stimulate the emetic response.[35] Thus, DEX may also mediate the antiemetic effects by blocking the 5-HT pathway.

Although patients undergoing breast surgery can benefit the analgesic and antiemetic effects from the use of DEX, it also should be noted that the incidence of hypotension seemed to be increased, which may be an adverse event induced by DEX. However, in the study of Demiri et al,[36] subgroup analysis showed that the use of low doses of DEX ($< 0.5\,\mu g\,kg^{-1}$) may reduce the risk of hypotension. Thus, low dose of DEX was suggested to be used for breast surgery in the future.

In addition to the overall results, the subgroup analysis also showed the pain relief at early time point and the decrease in the PONV was especially obvious for the GA subgroup relative to the LA subgroup (PECS and PVB). These results may be resulted from the excellent analgesic and antiemetic effects of LA itself compared with GA. This hypothesis has been demonstrated by

Table 4

Hemodynamic changes.

Comparison	Group	Studies	SMD (95%CI)	P_A value	I^2	P_H value
Intraoperative DBP at 30 min	Overall	3	−1.52 (−1.84, −1.20)	**<.001**	0.0	.891
Anesthetic technique	PVB	2	−1.56 (−1.95, −1.17)	**<.001**	0.0	.824
	PECS	1	−1.63 (−2.21, −1.04)	<.001	—	—
Ethnicity	Asian	2	−1.47 (−1.86, −1.09)	**<.001**	0.0	.780
	Non-Asian	1	−1.43 (−1.99, −0.86)	<.001	—	—
Intraoperative DBP at 60 min	Overall	3	−1.06 (−2.25,0.13)	.080	93.0	<.001
Anesthetic technique	PVB	2	−0.39 (−0.74, −0.05)	**.025**	0.0	.945
	PECS	1	−2.46 (−3.14, −1.78)	**<.001**	—	—
Ethnicity	Asian	2	−1.41 (−3.44,0.63)	.176	95.9	<.001
	Non-Asian	1	−0.41 (−0.92,0.11)	.119	—	—
Intraoperative DBP at 120 min	Overall	2	0.01 (−0.33,0.35)	.965	0.0	.968
Intraoperative SBP at 30 min	Overall	5	−1.50 (−1.78, −1.22)	**<.001**	0.0	.933
Anesthetic technique	PVB	4	−1.46 (−1.78, −1.14)	**<.001**	0.0	.907
	PECS	1	−1.64 (−2.23, −1.05)	<.001	—	—
Ethnicity	Asian	4	−1.53 (−1.86, −1.21)	**<.001**	0.0	.884
	Non-Asian	1	−1.39 (−1.95, −0.82)	<.001	—	—
Intraoperative SBP at 60 min	Overall	5	−1.05 (−1.66, −0.44)	**.001**	79.7	.001
Anesthetic technique	PVB	4	−0.74 (−1.11, −0.36)	**<.001**	33.8	.209
	PECS	1	−2.10 (−2.73, −1.46)	<.001	—	—
Ethnicity	Asian	4	−1.15 (−1.95, −0.36)	**.005**	83.5	<.001
	Non-Asian	1	−0.68 (−1.20, −0.16)	.011	—	—
Intraoperative SBP at 120 min	Overall	2	−0.60 (−0.95, −0.25)	**.001**	0.0	.886
Intraoperative HR at 30 min	Overall	7	−0.97 (−1.36, −0.58)	**<.001**	68.4	.004
Anesthetic technique	GA	2	−0.37 (−0.71, −0.03	**.033**	0.0	.771
	PVB	4	−1.26 (−1.57, −0.95)	**<.001**	0.0	.489
	PECS	1	−1.32 (−1.88, −0.76)	<.001	—	—
Ethnicity	Asian	6	−0.92 (−1.36, −0.48)	**<.001**	71.0	.004
	Non-Asian	1	−1.27 (−1.83, −0.71)	<.001	—	—
Intraoperative HR at 60 min	Overall	7	−0.71 (−0.92, −0.50)	**<.001**	27.5	.219
Anesthetic technique	GA	2	−0.47 (−0.82, −0.13	**.007**	0.0	.632
	PVB	4	−0.75 (−1.05, −0.46)	**<.001**	9.1	.348
	PECS	1	−1.18 (−1.73, −0.63)	<.001	—	—
Ethnicity	Asian	6	−0.73 (−0.96, −0.50)	**<.001**	38.2	.151
	Non-Asian	1	−0.61 (−1.13, −0.09)	.021	—	—
Intraoperative HR at 120 min	Overall	2	−0.29 (−0.63,0.06)	.101	0.0	.928
Postoperative HR at 0 h	Overall	2	−0.20 (−0.54,0.15)	.264	0.0	−.843
Postoperative HR at 2 h	Overall	2	−0.75 (−1.99,0.49)	.238	90.6	.001
Postoperative HR at 6 h	Overall	3	−0.30 (−0.58, −0.02)	**.039**	0.0	.957
Anesthetic technique	PVB	2	−0.29 (−0.63,0.06)	.101	0.0	.792
	PECS	1	−0.33 (−0.84,0.18)	.208	—	—
Ethnicity	Asian	2	−0.33 (−0.67,0.02)	.061	0.0	.997
	Non-Asian	1	−0.24 (−0.74,0.27)	.362	—	—
Postoperative HR at 12 h	Overall	3	−0.03 (−0.31,0.26)	.853	0.0	.930
Anesthetic technique	PVB	2	0.01 (−0.34,0.35)	.974	0.0	.854
	PECS	1	−0.10 (−0.61,0.41)	.703	—	—
Ethnicity	Asian	2	−0.06 (−0.40,0.28)	.741	0.0	.830
	Non-Asian	1	0.04 (−0.47,0.55)	.874	—	—
Postoperative HR at 24 h	Overall	5	.25 (−0.15,0.64)	.219	67.1	.016
Anesthetic technique	GA	2	0.60 (0.23,0.98)	**.002**	5.3	.304
	PVB	2	−0.19 (−0.53,0.15)	.271	0.0	−.727
	PECS	1	0.51 (−0.01,1.02)	.054	—	—
Ethnicity	Asian	4	0.37 (−0.03,0.77)	.068	60.1	.057
	Non-Asian	1	−0.26 (−0.77,0.25)	.320	—	—
Postoperative HR at 36 h	Overall	2	−0.08 (−0.42,0.26)	.657	0.0	.925
Postoperative HR at 48 h	Overall	2	−0.07 (−0.41,0.27)	.699	0.0	.977

CI = confidence interval, DBP = diastolic blood pressure, F = fixed, GA = general anesthesia, HR = heart rate, P_A = *P* value for association, PECS = pectoral nerve block, P_H = *P* value for heterogeneity, PVB = paravertebral block, R = random, SBP = systolic blood pressure, SMD = standardized mean difference. Bold indicated the statistical significance for association in 2 or more than 2 studies (*P* value <.05).

several studies. For example, Zhao et al[37] 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.[38] The study of Tahiri et al[39] integrated 11 RCTs

Table 5

Adverse effects.

	Adverse events	Studies	OR (95% CI)	P_A value	I^2	P_H value
PONV	Overall	6	0.38 (0.16,0.93)	**.034**	57.5	.038
Anesthetic technique	GA	3	0.37 (0.14,0.96)	**.041**	15.6	.306
	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
Anesthetic technique	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 (0.82,4.53)	.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	0.54 (0.30,1.00)	**.004**	0.0	.615
Anesthetic technique	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 (0.27,1.83)	.470	0.0	.911
Pnemothorax	Overall	3	1.00 (0.20,5.06)	1.000	41.1	.627
Anesthetic technique	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
Anesthetic technique	GA	2	1.34 (0.39,4.60)	.638	0.0	.989
	PVB	3	1.97 (0.94,4.10)	.072	30.3	.238
	PECS	1	1.00 (0.06,16.76)	1.000	—	—
Ethnicity	Asian	5	1.78 (0.95,3.34)	.073	0.0	.558
	Non-Asian	1	1.00 (0.06,16.76)	1.000	—	—
Itching	Overall	3	0.26 (0.06,1.09)	.066	0.0	.682
Anesthetic technique	GA	2	0.43 (0.08,2.50)	.350	0.0	.955
	PECS	1	0.10 (0.01,1.88)	.123	—	—
Ethnicity	Asian	2	0.43 (0.08,2.50)	.350	0.0	.955
	Non-Asian	1	0.10 (0.01,1.88)	.123	—	—
Over-sedation	Overall	3	0.51 (0.11,2.48)	.407	75.4	.017
Anesthetic technique	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	—	—	—	—
Hypotention	Overall	4	2.17 (1.06,4.47)	**.035**	0.0	.449
Anesthetic technique	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, P_A = *P* value for association, PECS = pectoral nerve block, P_H = *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).

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[40] 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

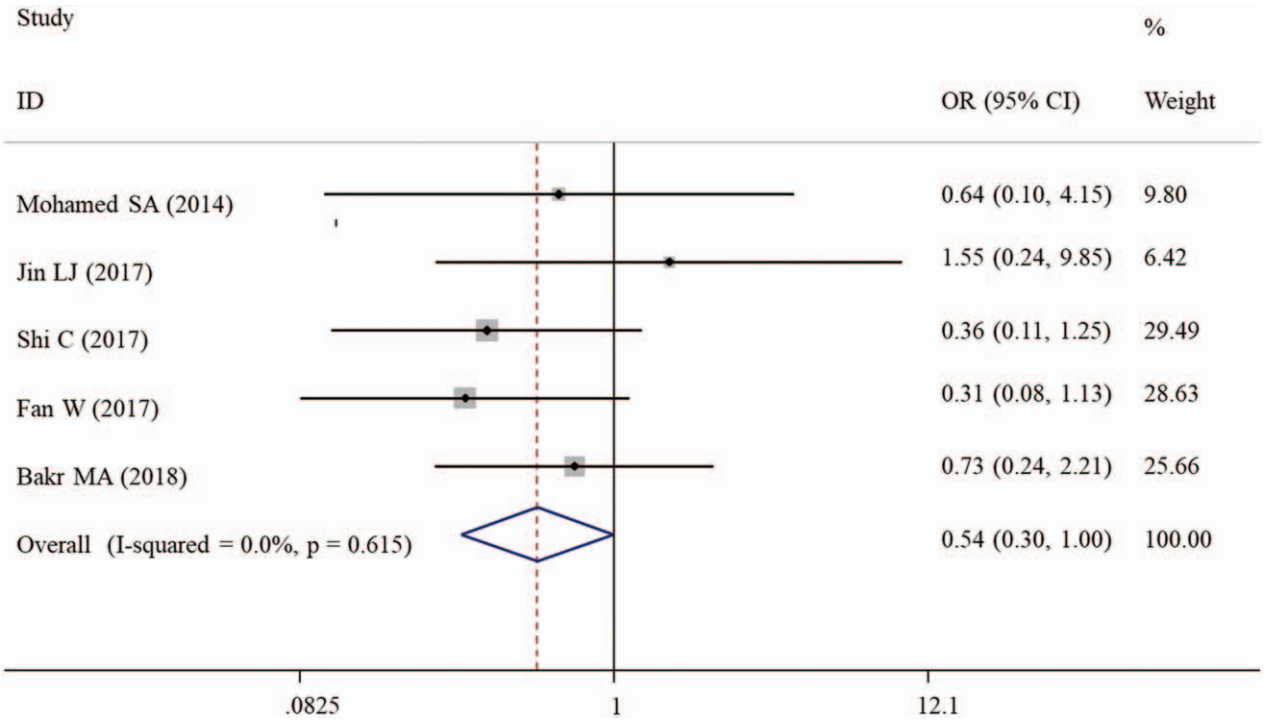

Figure 4. Forest plots showing the anesthetic effects of dexmedetomidine on the vomiting adverse event at 6 h postoperatively. CI = confidence interval, OR = odd ratio.

design to compare the difference between GA + DEX and LA + DEX should be performed to provide direct evidence. Therefore, more RCTs with larger sample size, more populations across the world, and more direct comparison groups (GA, GA + DEX, LA, LA + DEX, GA+ LA, GA + LA + DEX) should be designed to determine the idea anesthesia approach for breast surgery in clinic.

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.

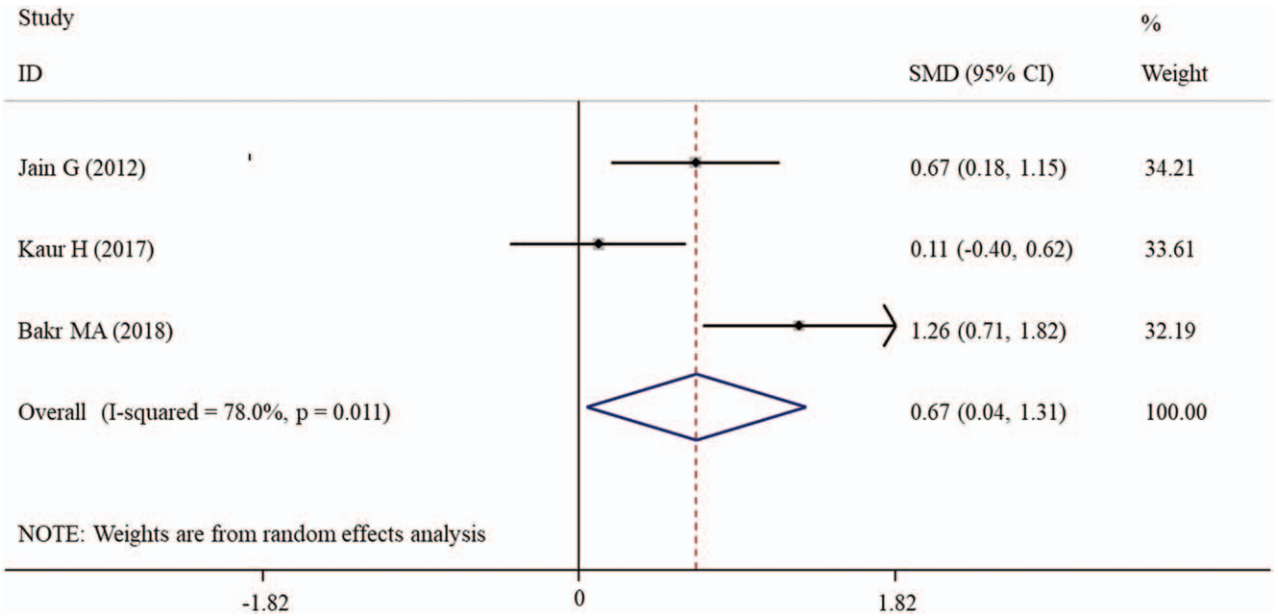

Figure 5. Forest plots showing the anesthetic effects of dexmedetomidine on the sedation score at 6 h postoperatively. CI = confidence interval, SMD = standardized mean difference.

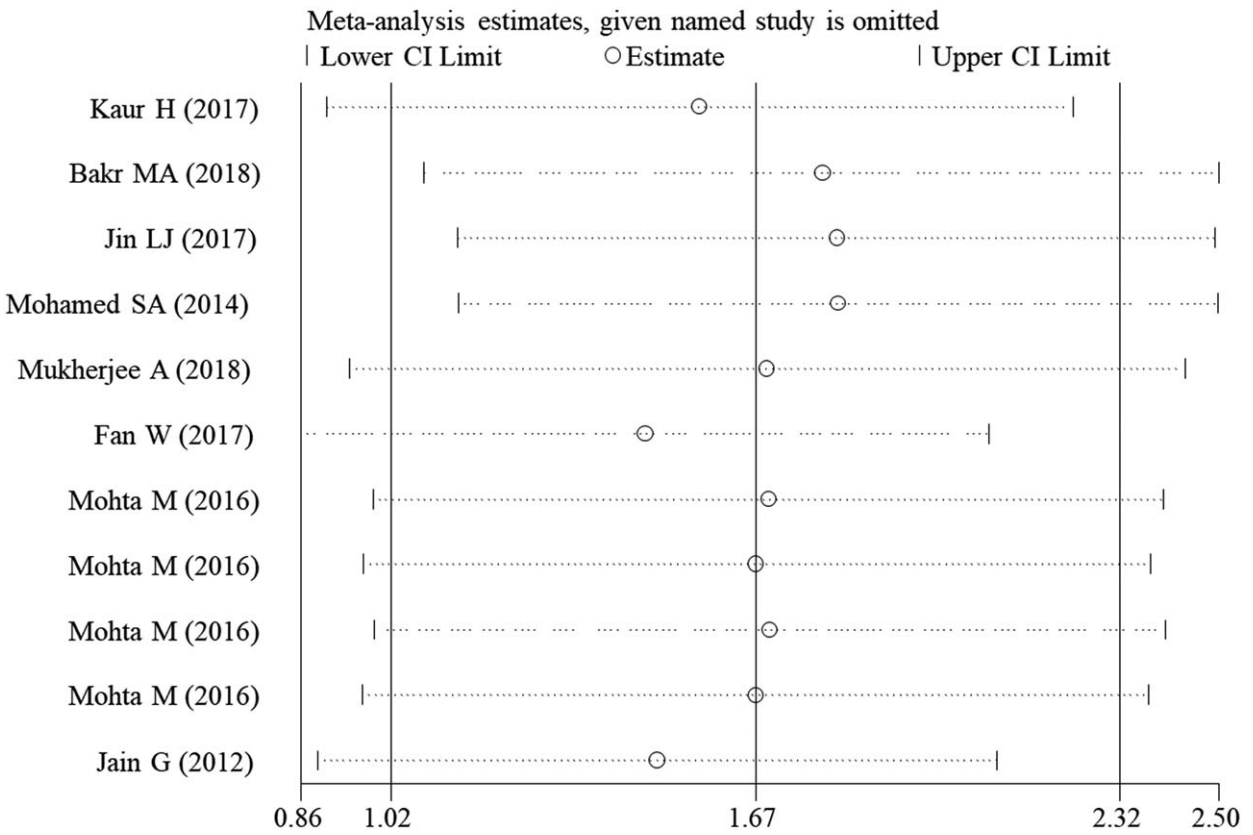

Figure 6. Sensitivity analysis for the time to first request of analgesia. CI = confidence interval.

Author contributions

Conceptualization: Changjun Liu, Wei Wang, Qiang Yan.
Data curation: Changjun Liu.
Formal analysis: Changjun Liu, Wei Wang.
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Software: Wei Wang.
Supervision: Qiang Yan.
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Writing – review & editing: Qiang Yan.

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