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The efficacy of gabapentin in reducing pain intensity and morphine consumption after breast cancer surgery
A meta-analysis

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Abstract
Background: The purpose of this meta-analysis from randomized controlled trials (RCTs) was to determine the efficacy and safety of the preoperative use of gabapentin for the treatment of acute and chronic postoperative pain following breast cancer surgery.

Methods: In November 2017, a systematic computer-based search was conducted in PubMed, Embase, Web of Science, Cochrane Library, and Google databases. RCTs comparing gabapentin with placebo in patients undergoing breast cancer surgery were retrieved. The primary endpoint was the visual analog scale (VAS) after surgery and 24 hours after surgery and total morphine consumption. The secondary outcomes were incidence of chronic pain and complications (the incidence of nausea). Software Stata 12.0 was used for meta-analysis.

Results: Finally, 9 RCTs were included in the meta-analysis. Results indicated that gabapentin was associated with reduced pain scores after surgery and 24 hours after surgery. Meanwhile, oral gabapentin was associated with a reduction of the total morphine consumption after breast cancer surgery. Similarly, gabapentin was associated with a reduction in the incidence of chronic pain and the incidence of nausea.

Conclusions: Preoperative use of gabapentin was able to reduce acute and chronic postoperative pain, total morphine consumption and the occurrence of nausea following breast cancer surgery. Further studies should determine the optimal dose of gabapentin for pain control after breast cancer surgery.

Abbreviations: CI = confidence interval, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCTs = randomized controlled trials, RR = risk ratio, SD = standard deviation, VAS = visual analog scale, WMD = weighted mean differences.

Keywords: acute pain, breast cancer surgery, chronic pain, gabepentin, meta-analysis

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1. Introduction

Breast cancer is the most commonly diagnosed cancer worldwide.[1] Modified radical mastectomy combined variably with chemotherapy or radiotherapy is currently the treatment of choice for breast cancer. Acute and chronic pain is a common complication after breast cancer surgery, with accounts between 20% to 50%, and higher.[2,3] Chronic neuropathic pain was particularly occurs after dissection of axillary lymph nodes and injury of the brachial plexus.[4] Adequate pain control after breast cancer is of vital for patient satisfaction and early mobilization.[5,6] Additionally, optimal management of the acute pain may influence the development of chronic pain[7]. Several modalities (oral opioids and patient controlled anesthesia) have been applied to reduce acute pain after breast cancer surgery.[8,9]

In recent years, gabapentin has been introduced as an adjunct in the multimodal management of postoperative pain after breast cancer surgery. Gabapentin is an anticonvulsant agent that can bind to the alpha2delta subunit of presynaptic voltage-gated calcium channels, thus reducing the calcium influx into presynaptic terminals.[10,11] However, whether perioperative oral gabapentin was effective in reducing acute pain and chronic pain among patients undergoing breast cancer surgery has not been determined.

The purpose of this meta-analysis was to systematically review randomized controlled trials (RCTs) and identify whether

preoperative oral gabapentin was associated with less acute and chronic pain among women undergoing breast cancer surgery.

2. Materials and methods

This meta-analysis was conducted in compliance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[12] and was written following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) checklist.[13]

2.1. Search strategies

The following databases were searched in March 2017 without language restriction: PubMed (1950–November 2017), Embase (1974–November 2017), Web of Science (1950–November 2017), Cochrane Library (November 2017 Issue 3), and Chinese Wanfang databases (1950–November 2017). The MeSH terms and their combinations used in the search were as follows: "analgesia" OR "pain management" OR "anesthetic agents" OR "breast cancer surgery" OR "mastectomy" OR "breast surgery" AND "gabapentin" OR "gabapentin" (MeSH terms).

The reference lists of related reviews and original articles were searched for any relevant studies, including RCTs involving adult humans. When multiple reports describing the same sample were published, the most recent or complete report was used. Because this is a meta-analysis, no ethics committee or institutional review board approval was necessary for the study.

2.2. Inclusion criteria and study selection

Patients (P): women (age >18 years) undergoing breast cancer surgery; Intervention (I): perioperative gabapentin as an intervention group; Comparison (C): placebo; Outcomes (O): visual analog scale (VAS) after surgery and 24 hours after surgery, total morphine consumption, incidence of chronic pain, and the occurrence of nausea; Study design (S): RCTs.

Two independent reviewers screened the titles and abstracts of the identified studies after removing duplicates in the search results. Any disagreements about the inclusion or exclusion of a study were resolved by discussion or consultation with an expert. The reliability of the study selection was determined by Cohen's kappa test; the acceptable threshold value was set at 0.61.[14,15]

2.3. Data abstraction

A specific extraction was performed to collect the following data from the included trials: patients' general characteristics, country, sample size of the control group and intervention group, preoperative and postoperative doses, and the timing and frequency of gabapentin use. Outcomes such as VAS after surgery and 24 hours after surgery, total morphine consumption, incidence of chronic pain and the occurrence of nausea were abstracted and recorded on a form.

Postoperative pain intensity was measured by a 110-point VAS. When the numerical rating scale (NRS) was reported, it was converted to a VAS. Additionally, a 11-point VAS was converted to a 110-point VAS.[16] Data in other forms (i.e., median, interquartile range, and mean ± 95% confidence interval (CI)) were converted to the mean ± standard deviation (SD) according to the Cochrane Handbook.[17] And opioid drugs were converted to equivalent morphine consumption according to previously published literature (iv morphine 10 mg = oral morphine 30 mg = iv hydromorphone 1.5 mg = oral hydromorphone 7.5 mg = iv

pethidine 75 mg = oral oxycodone 20 mg = iv tramadol 100 mg = iv piritramide 7.5 mg)).[18] If the data were not reported numerically, we extracted these data using the GetData Graph Digitizer software from the published figures. All data were extracted by 2 independent reviewers, and disagreements were resolved by discussion.

2.4. Quality assessment and quality evidence

The methodological quality of all included trials was independently assessed by 2 reviewers using the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (http://handbook.cochrane.org/). A total of 7 items (random sequence generation, allocation concealment, blinding to the participant and personnel, blinding to the outcome assessment, incomplete outcome, selective reporting, and other bias) were measured. Each of the items was measured as "low risk of bias," "unclear risk of bias," and "high risk of bias". The risk of bias summary and risk of bias graph were obtained using Review Manager 5.3.0 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Two reviewers (XF and KJG) independently evaluated the quality of evidence assessment in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[19] Risk of bias, inconsistency, indirectness, imprecision, and publication bias were the assessment items.[19,20] Each result was classified as high, moderate, low, or very low. GRADE Pro software was used to construct summary tables for the included studies.

2.5. Outcome measures and statistical analysis

Continuous outcomes (VAS after surgery and 24 hours after surgery, total morphine consumption) were expressed as the weighted mean differences (WMD) and respective 95% CI. Dichotomous outcomes (incidence of chronic pain and the occurrence of nausea) were expressed as the risk ratio (RR) with 95% CI. Statistical significance was set at $P < .05$ to summarize the findings across the trials. The meta-analysis was calculated by Stata software, version 13.0 (Stata Corp., College Station, TX). Statistical heterogeneity was tested using the chi-squared test and I^2 statistic. When there was no statistical evidence of heterogeneity ($I^2 < 50\%$, $P > .1$), a fixed-effects model was adopted; otherwise, a random-effect model was chosen. Publication bias was tested using funnel plots. Publication bias was assessed by funnel plot and quantitatively assessed by Begg's test. We considered there to be no publication bias if the funnel plot was symmetrical and the P value was >.05. Subgroup analysis was conducted according to the dose of gabapentin (<900 or ≥900 mg/d).

3. Results

3.1. Search results

The search result is summarized in the PRISMA flowchart (Fig. 1). In the initial research, a total of 185 papers were identified from the electronic databases (PubMed = 77, Embase = 56, Web of Science = 23, Cochrane Library = 19, and Chinese Wanfang database = 10); 0 additional records were identified through other sources. Thus, a total of 185 papers were obtained in the initial search. These bibliographical references were introduced into Endnote Software (Version X7, Thompson Reuters, CA). Duplicates were then removed and 151 papers
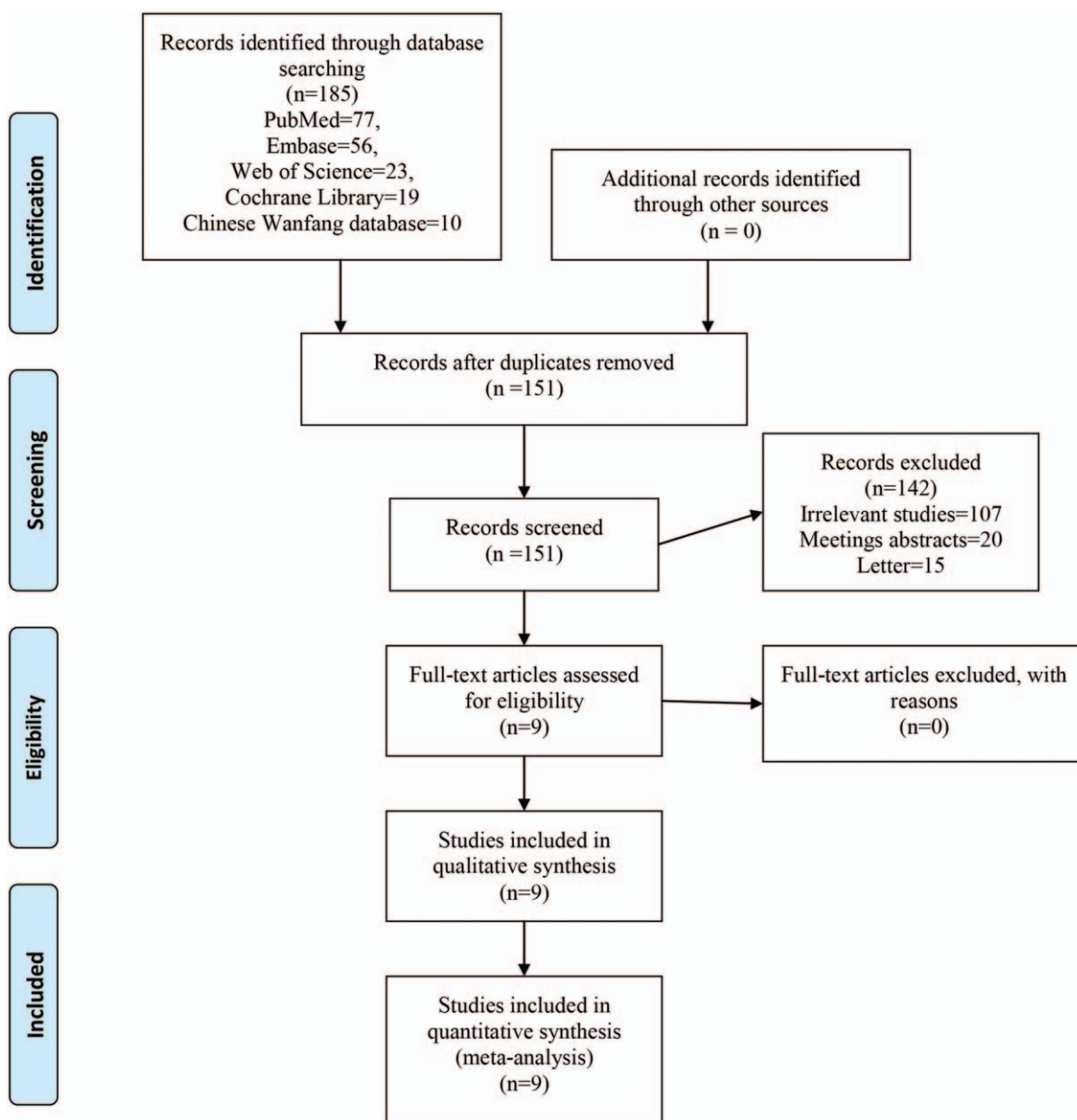
Figure 1. Flowchart of study search and inclusion criteria.

were reviewed. After screening the titles and abstracts of these 151 studies, 142 papers were excluded because they were irrelevant or did not meet the criteria. Ultimately, 9 clinical studies with 576 patients (gabapentin group = 287, placebo = 289) were finally included in the meta-analysis.[8–28] The general characteristic of the included studies can be seen in Table 1. The sample of included studies ranged from 20 to 50. And the gabapentin doses ranged from 300 mg to 1200 mg. The duration of follow-up ranged from 48 hours to 6 months.

3.2. Quality assessment

Quality assessment of the included studies can be seen in Figures 2 and 3. The risk of bias for random sequence generation, allocation concealment, blinding to the participant and outcome assessment, selection bias are all with low risk of bias. Two studies are with unclear risk of bias in other bias. Reasons for

unclear were mainly due to the sample size was not calculated and we thus did not know whether the sample was enough to reach the statistically significance.

3.3. Results of meta-analysis
3.3.1. VAS after surgery. VAS scores after surgery was reported in six studies, there was a middle heterogeneity between the included studies ($I^2 = 46.3\%$, $P = .097$). And the pooled results indicated that administration of gabapentin can decrease VAS score after surgery by 16.14 points (WMD = −16.14, 95% CI −21.85, −10.24, $P = .000$, low evidence, Fig. 4).
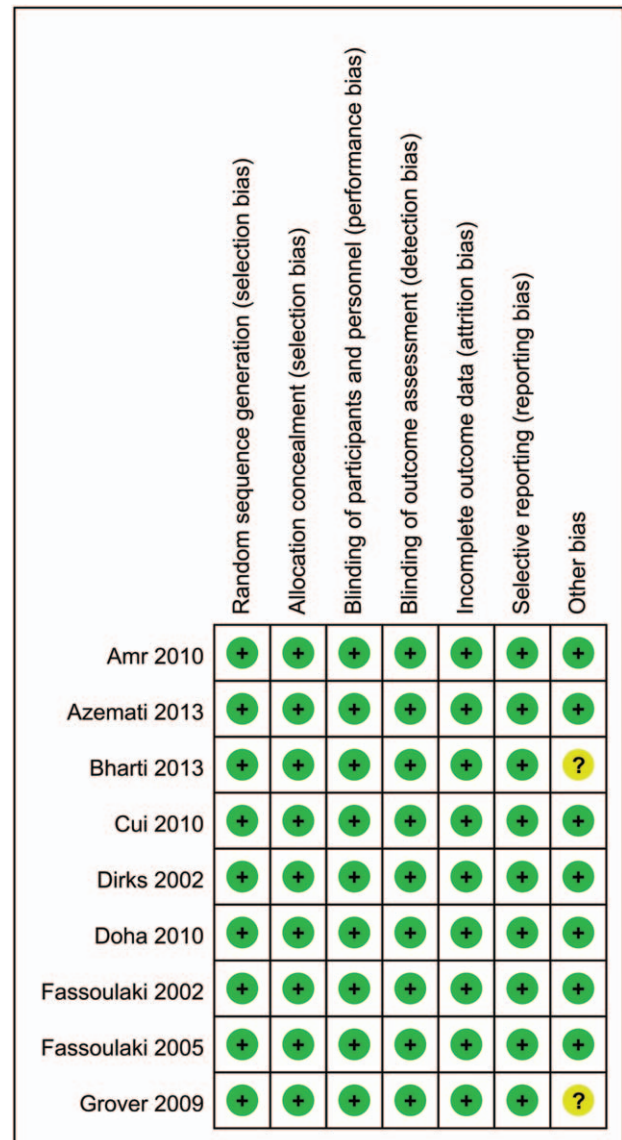
3.3.2. VAS at 24 hours after surgery. VAS scores after surgery was reported in four studies, there was a high heterogeneity between the included studies ($I^2 = 95.7\%$, $P = .000$). And the pooled results indicated that administration of gabapentin can decrease VAS score at 24 hours after surgery by 27.33 points

Table 1

The general characteristic of the included studies; 1, VAS after surgery; 2, VAS at 24 hours after surgery; 3, total morphine consumption; 4, the occurrence of nausea; 5, chronic pain incidence.

Study	Country	Control group	Surgery	No of patients	Intervention group		Outcomes	Follow-up
					Preoperative	Postoperative		
Amr 2010	Korea	Placebo (n=50)	Partial or radical mastectomy with lymph node dissection	50	Gabapentin 300-mg night before surgery continued for first 9 postop days	No	1, 2, 3, 4, 5	6 months
Azemati 2013	Japan	Placebo (n=50)	Modified radical mastectomy or quadrantectomy and axillary node dissection	50	Gabapentin 600 mg 30 min before induction of anesthesia	No	1, 2, 3, 4, 5	48 hours
Bharti 2013	Japan	Placebo (n=20)	Total mastectomy with axillary node dissection	20	Gabapentin 600 mg 2 hours before surgery	No	1, 2, 3, 5	1 month
Dirks 2002	Ireland	Placebo (n=35)	Unilateral radical mastectomy with axillary dissection	35	Gabapentin 1200 mg 1 hour before surgery	No	2, 5	3 months
Doha 2010	Italy	Placebo (n=30)	Modified radical mastectomy	30	Gabapentin 1200 mg 2 hours before surgery	No	2, 3, 4	1 year
Fassoulaki 2002	Ireland	Placebo (n=22)	Modified radical mastectomy or lumpectomy plus axillary lymph node dissection	24	Gabapentin 400 mg q6h night before surgery until postop day; concurrent use of EMLA and brachial plexus blocks	No	1, 3, 5	48 hours
Fassoulaki 2005	Korea	Placebo (n=25)	Modified radical mastectomy or lumpectomy plus axillary lymph node dissection	25	Gabapentin 400 mg tid, starting the evening before surgery and continued for first 10 postop days	No	1, 2, 5	48 hours
Grover 2009	USA	Placebo (n=27)	Total mastectomy with axillary lymph dissection	23	Gabapentin 600 mg 1 hour before surgery	No	2, 3, 5	1 month
Cui 2010	China	Placebo (n=30)	Total mastectomy with axillary dissection	30	Gabapentin 1200 mg 2 hours before induction	No	2, 3, 4, 5	7 days

EMLA = eutectic mixture of local anesthetics; VAS = visual analog scale.

Figure 2. Risk of bias of included randomized controlled trials. +, no bias; −, bias; ?, bias unknown.

(WMD = −27.33, 95% CI −51.03, −3.63, $P = .024$, low evidence, Fig. 5). We then performed sensitivity by omitting one study in turn and found that overall effects was in 95% CI limit (Fig. 6).

3.4. Total morphine consumption

Total morphine consumption after surgery was reported in 8 studies, there was a high heterogeneity between the included studies ($I^2 = 97.4\%$, $P = .000$). And the pooled results indicated that administration of gabapentin can decrease total morphine consumption after surgery by 4.59 mg (WMD = −4.59, 95% CI −7.07, −2.11, $P = .000$, middle evidence, Fig. 7).

3.5. The occurrence of nausea

The occurrence of nausea after surgery was reported in 4 studies, there was no heterogeneity between the included studies ($I^2 = 0.0\%$, $P = .711$). In addition, the pooled results indicated that
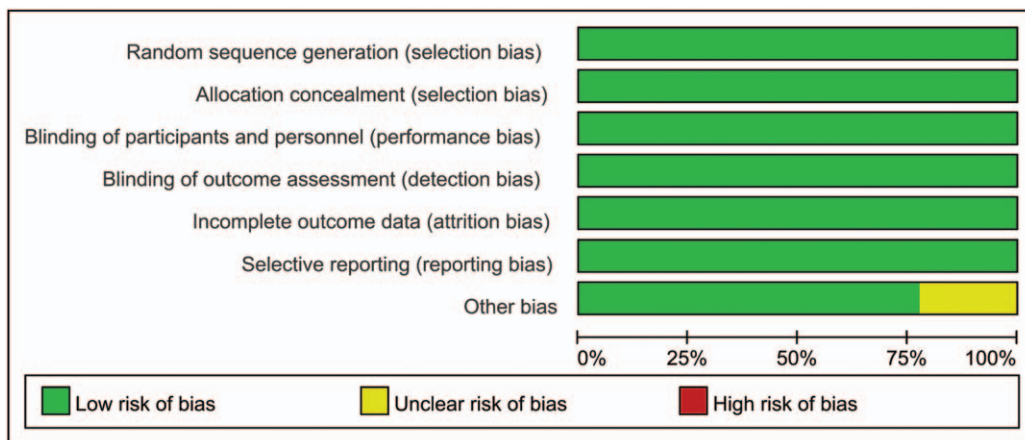
Figure 3. the risk of bias graph.

administration of gabapentin can decrease the occurrence of nausea after surgery (RR = 0.54, 95% CI 0.38, 0.78, P = .001, middle evidence, Fig. 8).

3.6. Chronic pain incidence

The chronic pain incidence after surgery was reported in 5 studies, there was no heterogeneity between the included studies (I^2 = 0.0%, P = .463). Also the pooled results indicated that adminis-

tration of gabapentin can decrease the chronic pain incidence (RR = 0.57, 95% CI 0.47, 0.68, P = .000, low evidence, Fig. 9).

3.7. Subgroup analysis, publication bias, and sensitivity analysis

Subgroup analyses were conducted according to a low dose (<900 mg/d) and a high dose of gabapentin (≥900 mg/d). The detailed results can be seen in Table 2. The pooled results
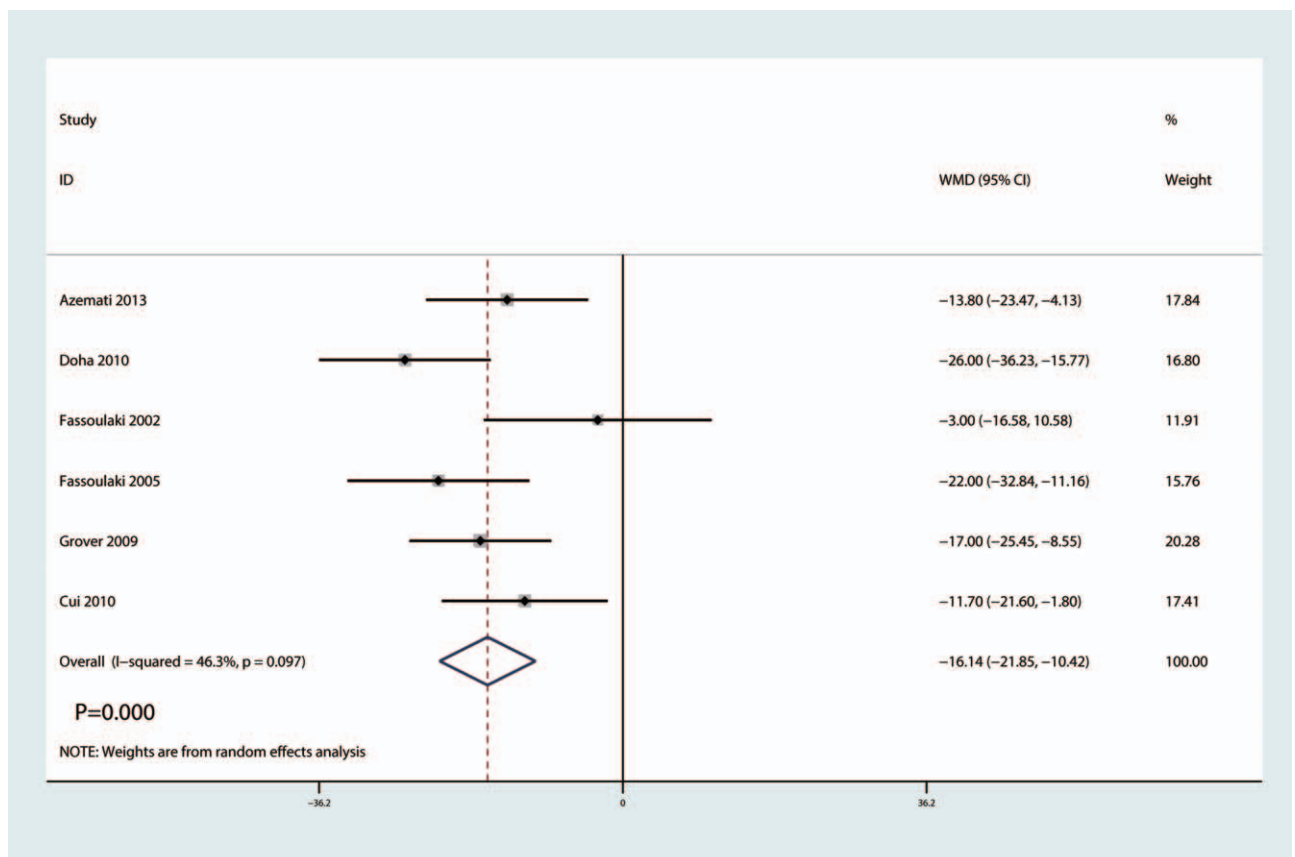

Figure 4. Forest plots of the included studies comparing the VAS after surgery. VAS = visual analog scale.
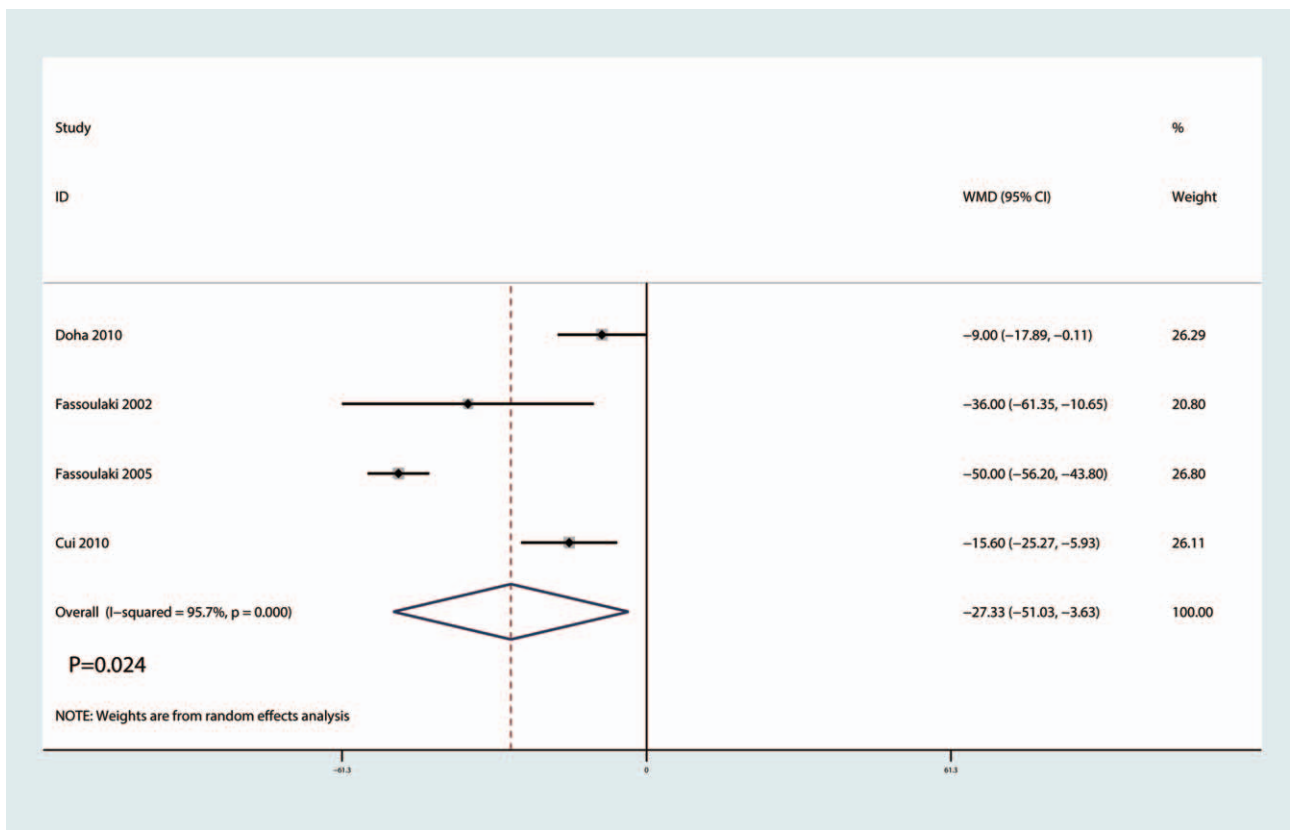
Figure 5. Forest plots of the included studies comparing the VAS at 24 hours after surgery. VAS = visual analog scale.
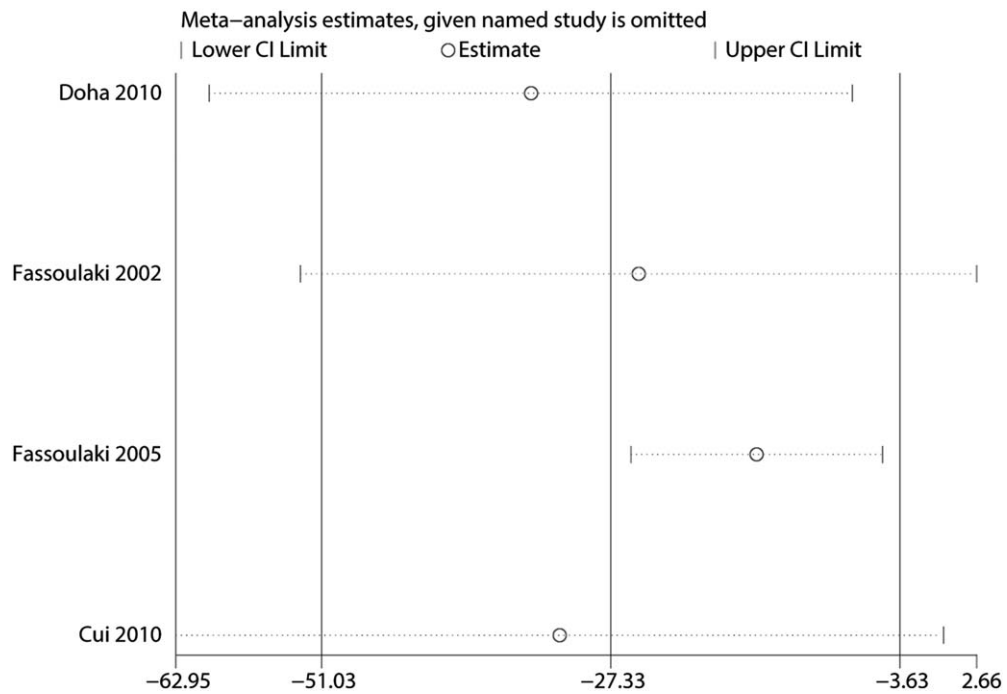

Figure 6. Sensitivity analysis of the VAS at 24 hours after surgery. VAS = visual analog scale.
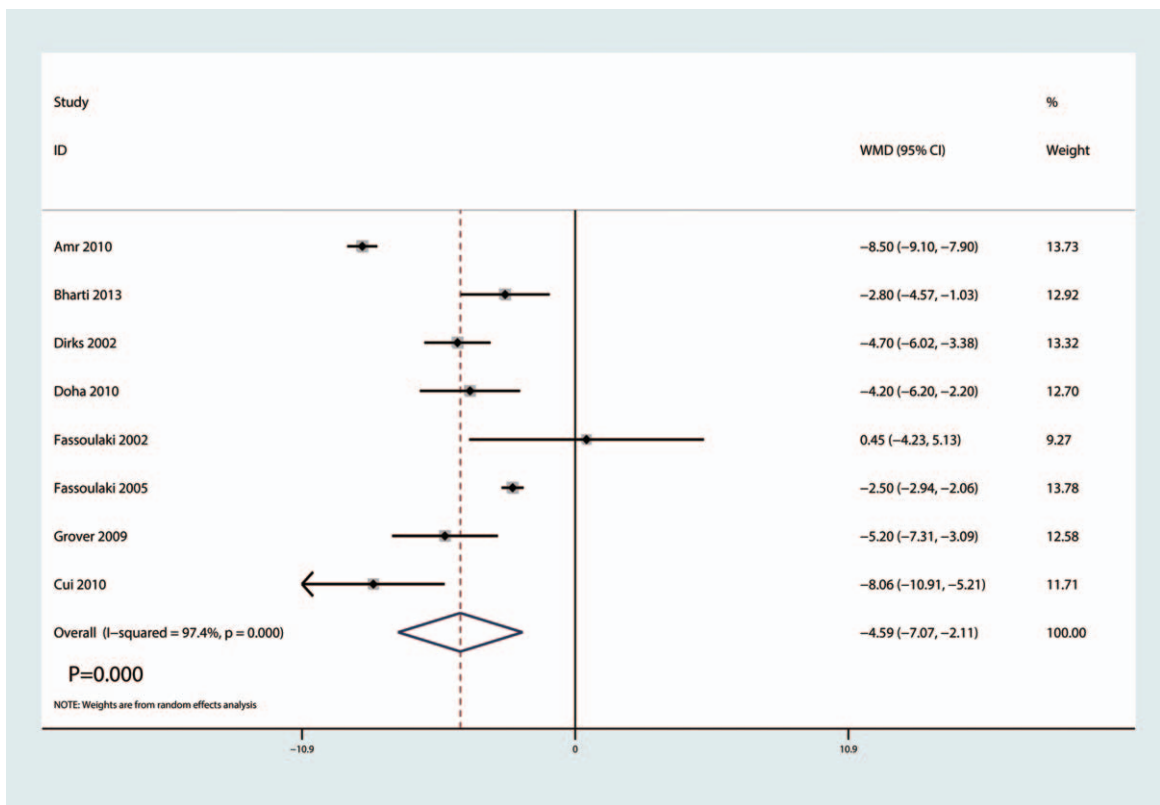
Figure 7. Forest plots of the included studies comparing the total morphine consumption.
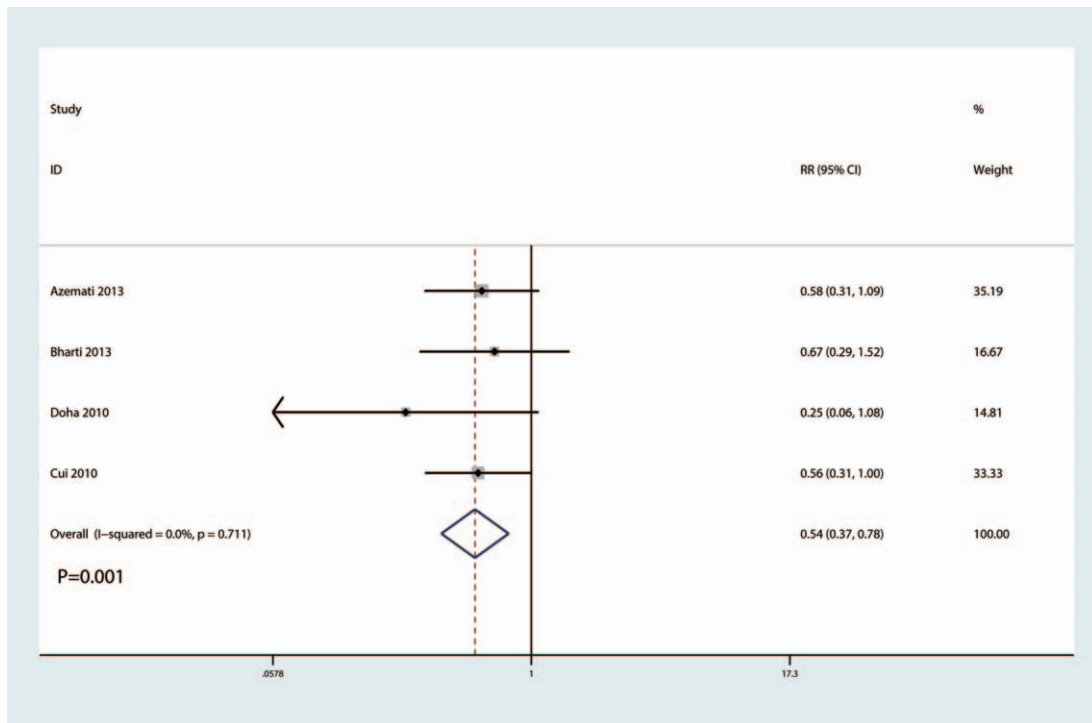

Figure 8. Forest plots of the included studies comparing the occurrence of nausea.
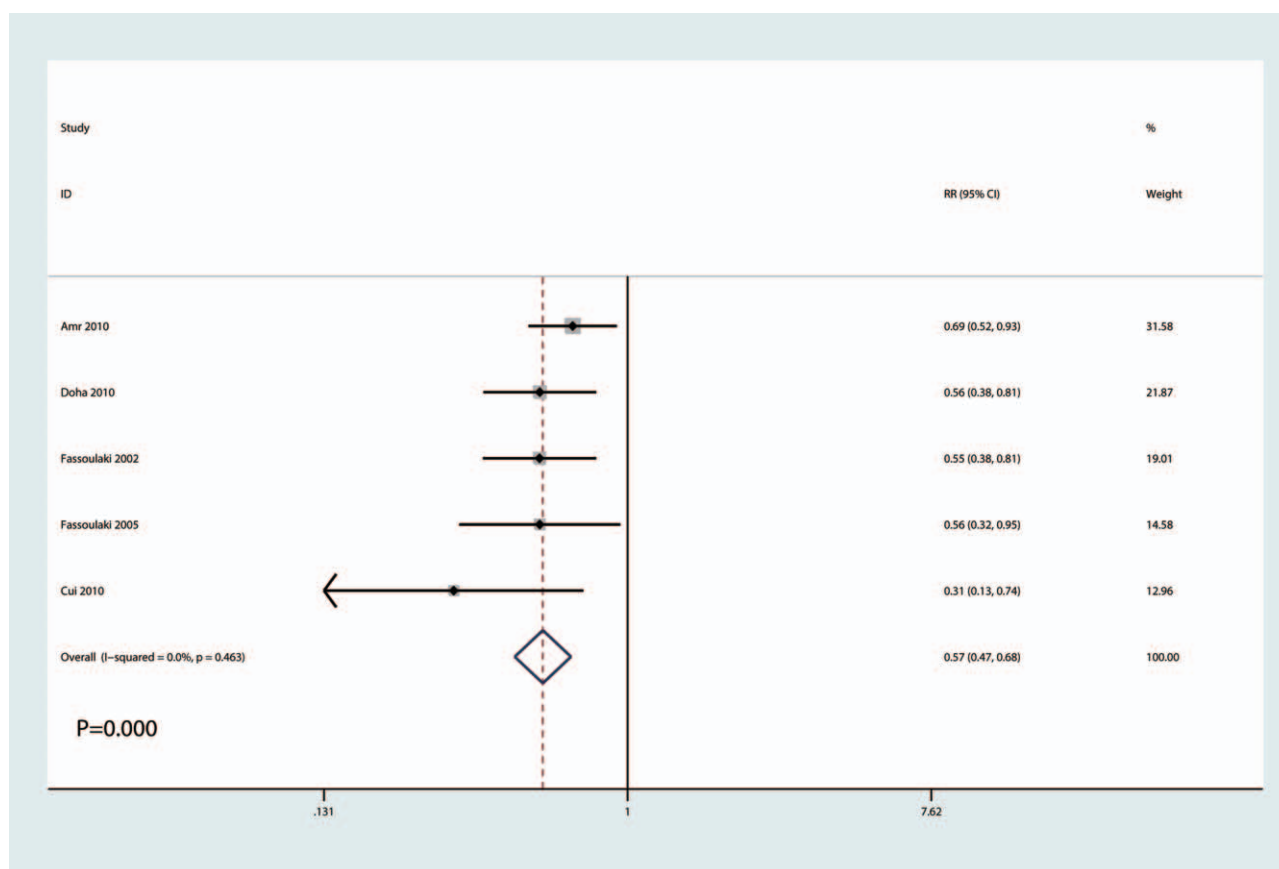
Figure 9. Forest plots of the included studies comparing the chronic pain incidence.

Table 2

Subgroup analysis for the VAS after surgery, at 24 hours after surgery, total morphine consumption, the occurrence of nausea, and chronic pain incidence.

|				Incidence			
Variables	Studies (n)	Patients (n)	P-value	Weighted mean difference (95% CI)	Heterogeneity P-value (I^2)	Model	Subgroup difference
VAS after surgery							
High dose	3	126	.000	−12.96 (−14.57, −11.35)	.764, 2	Fixed	0.016
Low dose	3	260	.009	−9.66 (−13.42, −1.89)	.006, 82.5	Random	
Time of gabapentin							
≥ 1 hours	2	186	.000	−10.05 (−12.16, −11.11)	.377, 41.6	Random	0.114
<1 hours	4	200	.000	−8.74 (−12.13, −8.55)	.015, 22.9	Fixed	
Frequency of gabapentin							
bid	3	219	.005	−9.52 (−12.16, −7.99)	.013, 46.7	Random	0.085
tid	3	167	.013	−11.83 (−12.57, −9.64)	.026, 42.9	Random	
Surgery type							
With axillary dissection	3	199	.000	−7.52 (−9.34, −9.82)	.152, 34.9	Fixed	0.109
Without axillary dissection	3	187	.000	−11.24 (−13.32, −8.52)	.012, 76.5	Random	
VAS at 24 hours after surgery							
High dose	2	251	.010	−29.23 (−15.46, −8.00)	.000, 88.3	Random	0.023
Low dose	2	180	.010	−19.50 (−36.76, −6.25)	.000, 83.9	Random	
Total morphine consumption							
High dose	3	206	.000	−5.71 (−8.55, −1.87)	.013, 89.7	Random	0.036
Low dose	5	130	.002	−2.13 (−3.85, −0.42)	.002, 87.6	Random	
The occurrence of nausea							
High dose	2	206	.011	0.45 (0.24, 0.83)	.632, 0.0	Fixed	0.001
Low dose	2	140	.560	0.81 (0.40, 1.63)	.981, 0.0	Fixed	
Chronic pain incidence							
High dose	3	270	.047	0.59 (0.40, 0.96)	.577, 0.0	Fixed	0.021
Low dose	2	106	.738	0.72 (0.64, 1.89)	.986, 0.0	Fixed	

VAS = visual analog scale.
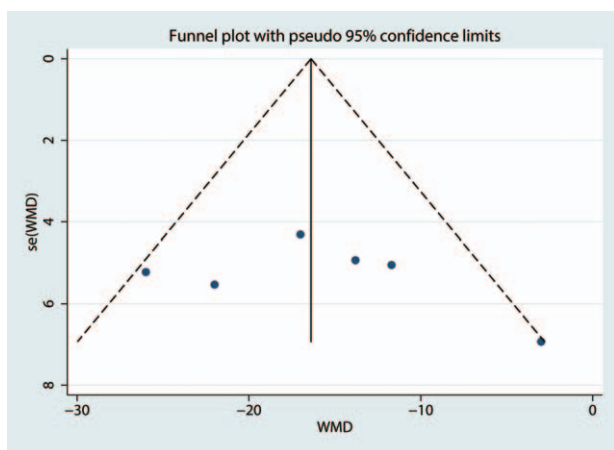
Figure 10. Funnel plot of the VAS after surgery. VAS=visual analog scale.

indicated that a high dose of gabapentin was superior than low dose of gabapentin in terms of ($P<.05$). Publication bias was detected by the funnel plot (Fig. 10) and Begg's test ($P=.216$, Fig. 11) and results revealed that there was no publication bias between the included studies for the VAS after surgery. Sensitivity analysis was then performed and results shown that the result was stable and excluded one of the study will not change the final result (Fig. 12).

4. Discussion

4.1. Main findings

Our meta-analysis indicated that gabapentin has a positive role in reducing acute pain intensity, total morphine consumption, the occurrence of nausea and the chronic pain incidence. Moreover, high dose of gabapentin was superior to low dose of gabapentin in terms of the outcomes. Our analysis found low- to middle-quality evidence that the preoperative use of gabapentin for pain control and morphine-saving.

4.2. Strength of this meta-analysis

A major strength of current meta-analysis was that we limited the inclusion criteria restricted to a surgical breast cancer population and administration with gabapentin alone. Another new knowledge of this meta-analysis was that we performed a subgroup analysis and revealed that high dose of gabapentin was effective than low dose of gabapentin for alleviating acute and chronic pain after breast cancer surgery.

4.3. Implications for clinical practice

Our meta-analysis showed that the benefit existed in gabapentin compared with control group. Therefore, preoperative oral gabapentin might be the best guide for patients prepared for breast cancer surgery. And when choosing the dosage of gabapentin, high dose of gabapentin was preferable.

The anticonvulsant gabapentin has shown promising results in relieving acute and chronic neuropathic pain.[29,30] And preoperative use of gabapentin was associated with a pain relieving in total knee and hip arthroplasty, spinal surgery and laparoscopic cholecystectomy.[31–35] Results from current meta-analysis indicated that gabapentin can decrease acute and chronic pain after breast cancer surgery. Results showed that gabapentin can decrease the pain scores by 16.14 and 27.33 points on 110-points after surgery and 24 hours, respectively. There was a high heterogeneity for pain scores at 24 hours after surgery. We performed subgroup analysis according to the dosage of gabapentin (<900 or ≥900 mg/d). The dosage of gabapentin only contributed to heterogeneity of pain scores.

Rai et al[36] reported that gabapentin has an efficacy to reduce acute pain intensity and does not reported the chronic pain. What is more, they included gabapentin and pregabalin and thus a mixed results will weak the final conclusion. Axillary node dissection was associated with a significant risk of chronic pain. Thus, the axillary node dissection may be a source of heterogeneity.[36]

We assessed the total morphine consumption and the occurrence of nausea. Final results indicated that gabapentin was associated with a significantly reduction of the total
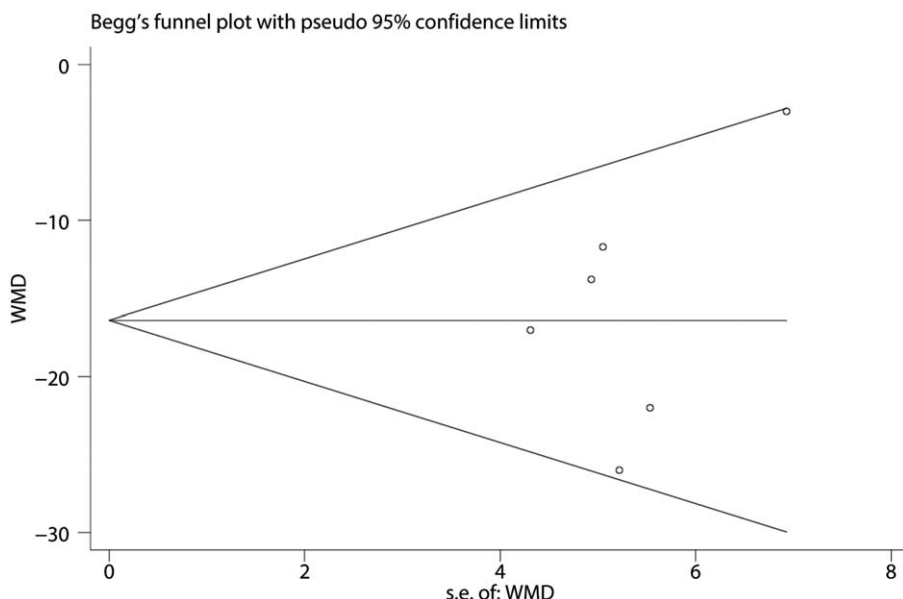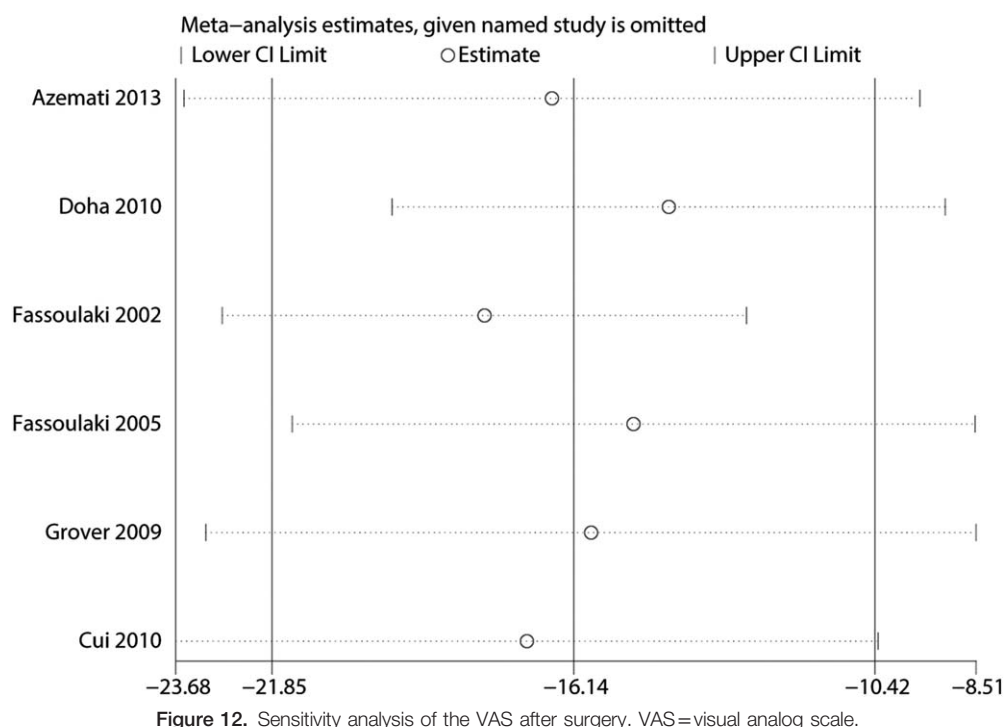

Figure 11. Begg's test of the VAS after surgery. VAS=visual analog scale.

Meta–analysis estimates, given named study is omitted

| Lower CI Limit ○ Estimate | Upper CI Limit

Figure 12. Sensitivity analysis of the VAS after surgery. VAS = visual analog scale.

morphine consumption and the occurrence of nausea. Nausea was a significant source of morbidity for patients after surgery and may contribute to delay in discharge from hospital. Khan et al[37] reported that gabapentin combined with other agents will enhance experience benefit.

The optimal dose of gabapentin for breast cancer surgery was not determined. For other surgery (total knee and hip arthroplasty), gabapentin (600 mg) given before the operation or 2 hour before operation can decrease postoperative opioid consumption and improve knee range of motion.[38] For breast cancer surgery, the dosage of gabapentin ranged from 300 to 1200 mg. And we could not determine the optimal dose of gabapentin. Future studies should be focused on the dose-response efficacy of gabapentin and the potential adverse complications.

4.4. Limitations

There were a total of 5 limitations in this meta-analysis: only 9 RCTs with small sample (20–50) were included, which might have affected the precision of the effect size estimations; follow-up was relatively short and the long-term benefit of gabapentin was unknown; dosage and timing of gabapentin administration differed between the studies and thus may cause the heterogeneity; we could not determine whether there was a publication bias for the final outcomes; different surgery with or without axillary dissection were included in this meta-analysis, which would cause selection bias.

5. Conclusion

In conclusion, immediate and chronic analgesic efficacy and opioid-sparing effects were obtained with the administration of gabapentin in breast cancer surgery. Because the sample size and the number of included studies were limited, a multicenter RCT is needed to identify the optimal dose and intervals of gabapentin.

Author contributions

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Project administration: Tongbiao Wang.
Resources: Qing Zhang.
Software: Qiaotong Huang, Shijie Zhang, Qing Zhang.
Supervision: Qiaotong Huang.
Validation: Shijie Zhang.
Visualization: Xiong Jun.
Writing – original draft: Junhong Li, Zheng Rong, Xiong Jun.
Writing – review & editing: Zheng Rong, Xiong Jun.

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