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Prophylactic efficacy of oral gabapentin on postoperative shivering

A meta-analysis of randomized controlled trials

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Abstract

Background: Postoperative shivering may lead to severe side effects during postoperative care, particularly in patients with impaired cardiopulmonary function. The efficacy of oral gabapentin as a preventive strategy for postoperative shivering has not been quantitatively analyzed. In this meta-analysis, we aimed to evaluate the effectiveness of gabapentin as a drug for treating postoperative shivering.

Methods: A review of the Cochrane Library, PubMed, and Embase was conducted by 2 researchers for randomized controlled trials (RCTs). In this meta-analysis, Review Manager was used to analyze these RCTs on oral gabapentin for postoperative shivering.

Results: Six trials with 544 patients were included in our meta-analysis. Prophylactic oral gabapentin reduced postoperative shivering compared with placebo (pooled risk ratio [RR]: 0.38, 95% confidence interval [CI]: 0.25–0.57). The anti-shivering effect could be achieved after both general anesthesia (pooled RR of 3 trails: 0.28, 95% CI: 0.14–0.56) and orthopedic surgery (pooled RR of 4 trails: 0.38, 95% CI: 0.24–0.58). Meanwhile, gabapentin also could decrease postoperative vomiting (POV; pooled RR 0.35, 95% CI 0.16–0.77).

Conclusion: Our current meta-analysis shows that compared with placebo, oral gabapentin can reduce the incidence of postoperative shivering. This result also provides new evidence to strengthen the clinical application value of gabapentin in the conventional treatment of POV.

PROSPERO registration number: CRD42022340734

Abbreviations: CI = confidence interval, PON = postoperative nausea, PONV = postoperative nausea and vomiting, POV = postoperative vomiting, RCTs = randomized controlled trials, RR = risk ratio.

Keywords: gabapentin, meta-analysis, postoperative, shivering

1. Introduction

As a physiological response in the body, shivering can effectively preserve heat through involuntary skeletal muscle contractions and peripheral vasoconstriction.[1] These mechanisms not only increase the consumption of oxygen and energy but also the production of carbon dioxide,[2] and can even lead to severe side effects during postoperative recovery,[3] especially in patients with impaired cardiopulmonary function.[4] Additionally, shivering can be particularly uncomfortable for conscious patients during anesthesia recovery, potentially increasing their anxiety.[5] Furthermore, muscle contractions during postoperative shivering can exacerbate the pain at the incision site. Therefore, to reduce related adverse events and improve the quality of postoperative rehabilitation, safe and effective treatment and prevention of shivering are essential.

Gabapentin, as the second-generation antiepileptic medicine, which resembles gamma-amino butyric acid (GABA), can relieve neuropathic pain obviously.[6] Meanwhile, gabapentin with an opioid-sparing action could be effective in preventing chronic postsurgical pain.[7] What is more, a recent study showed that

XL, MC, AH, YC, MZ, and WT contributed to this article equally.

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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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gabapentin could decrease stress reactions to harmful stimuli during the preoperative, intraoperative, and postoperative periods, and relieve anxiety before operation and prevent delirium after surgery.[8] In recent years, several randomized controlled studies[9–14] have also been conducted evaluating the efficacy of preemptive oral gabapentin before surgical incision on postoperative shivering compared with placebo; however, there has been no quantitative analysis primarily combining the related data.

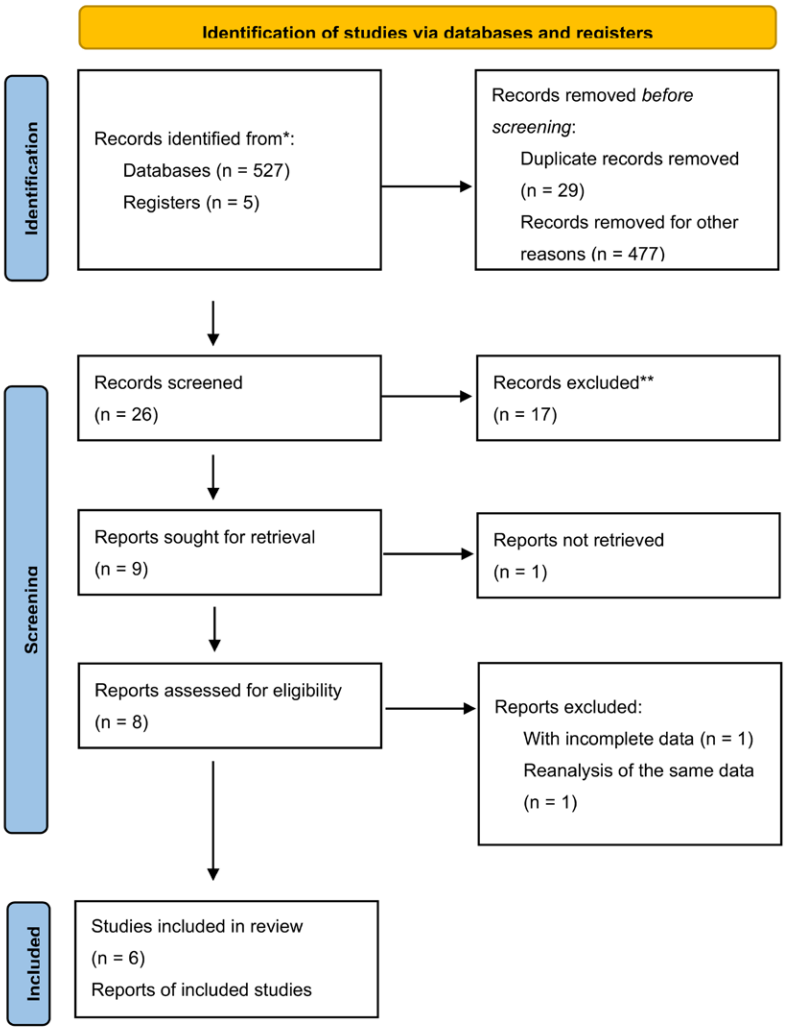
Therefore, we conducted this meta-analysis aiming to examine the evidence of prophylactic oral gabapentin in reducing postoperative shivering versus placebo, and maybe for other side effects. This could also explore the extra clinical value of oral gabapentin beyond the routine treatment for neuropathic pain.

2. Materials and methods

This meta-analysis was conducted systematically based on the recommendations of the PRISMA statement, aiming to evaluate the impact of oral gabapentin on postoperative shivering. A prespecified protocol was listed in PROSPERO (CRD42022340734). Shivering was classified using a 5-point scoring method (0 = no shivering; 1 = hair erection or peripheral vascular contraction but no noticeable shivering; 2 = activation in just 1 single group of muscle; 3 = activation in 2 or more groups of muscle but only in parts of the body; 4 = shivering all over the body).[15] And because this study is a meta-analysis of randomized controlled trials (RCTs), it does not need Ethics Committee Approval and Patient Informed Consent Form.

2.1. Search strategy

Two authors (LX and CM) systematically examined Cochrane Central Register of Controlled Trials (CENTRAL), Embase and PubMed. The following key words were included in the search strategy: (gabapentin, neurontin, GOE-3450 and AKOS 92109) and (shivering, shiver, tremor, shaking, chill, rigors or ague) and (anesthesia, anesthesia, surgery, operation or postoperative).



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Figure 1. Flow chart of the procedure about inclusion and exclusion.

The literature search was updated on December 30, 2023, with no language restriction. The reference inventories of original reports, case reports and reviews (searched electronically) were examined to identify studies not yet contained in the computerized database.

2.2. Study selection and data retrieval

Inclusion criteria: RCTs; the administration of gabapentin preoperatively, intraoperatively, or postoperatively; the presence of shivering reported; gabapentin versus placebo.

Exclusion criteria: duplications or abstracts only; missing data; patients with severe cerebrovascular disease or other contraindications of gabapentin; incorrect statistical analysis performed in the report.

Data retrieval: General information: the year of publication, the first author's name, age ranges of participants, the sum of patients and cases of shivering, interventions, type of anesthesia and surgery, duration of anesthesia and operation; Other side effects: pruritus, urine retention, bradycardia, hypotension, dizziness, headache, nausea, and vomiting (as these were defined as 2 separate phenomena, postoperative nausea and vomiting, studies should report and evaluate the variables distinctly;[16] however, the original literature rarely attempts to distinguish between them;[17] thus, if postoperative nausea and vomiting (PONV) was covered in the experiment instead of postoperative nausea (PON), we viewed the PONV variable to be a very approximate substitute for PON).

Two authors (TWQ and ZMM) independently assessed the articles for compliance with the inclusion/exclusion criteria. Disputes about this meta-analysis were settled promptly by discussion among all the authors.

2.3. Qualitative assessment

According to the guideline of Cochrane Collaboration, 2 authors (LX and CM) independently assessed the quality.[18] The guideline included 6 categories: incomplete outcome data (attrition bias), selective reporting (reporting bias), randomization sequence generation (selection bias), allocation concealment (selection bias), blinding method (performance bias and detection bias), and other bias. The last 3 categories were considered as "key domains." These categories can be summarized into 3 levels: low risk, unclear risk, and high risk. Each study was evaluated for the risk of bias based on the following levels in the 3 key areas: "high" (indicating a high risk of bias in 1 or several key areas), "unclear" (indicating an unclear risk of bias in 1 or several key areas), and "low" (indicating a low risk of bias in every key area).

2.4. Statistical method

Compared with placebo, pooled risk ratio (RR) was used to assess the effect of gabapentin on postoperative shivering, and standard mean difference (SMD) with a 95% confidence interval (CI) was used to calculate the core temperature before and after anesthesia. The overall effect concluded from W test with $P < .05$ was viewed to have statistical significance. When $I^2 \geq 50\%$, a random effects model was adopted; otherwise, a fixed effects model was used. Sensitivity analysis to test the robustness of these results can be done only by reanalyzing data from low-risk and unclear-risk studies. Subgroup analyses were based on shivering grade, type of anesthesia, and surgery, and dose of gabapentin. Begg's and Egger's Test assessed the possible publication bias. And use Review Manager (RevMan®; version 5.3.; The Cochrane Collaboration, Oxford, UK) and Stata® (version 16.0.; Stata Corp, College Station) to conduct statistical analyses.

3. Results

3.1. Study selection

As shown in Figure 1, a total of 532 articles were retrieved through PubMed, Embase, the Cochrane library and reference lists. Initially, 506 trials were eliminated, because 477 trials were non-controlled trials with reduplicative 29 trials by reading the titles. Then, 18 trails were excluded for not satisfying the inclusion criteria (17 trails) and gabapentin not on shivering (1 trail) by reviewing the abstracts. Eight papers were carefully read,

Table 1

Characteristics of the included trials.

Author	Year	Age range	Type of anesthesia	Type of surgery	Trail	Dosage regimen	Comparisons	Total (case)	Postoperative shivering (case)
Chiravanich et al[9]	2012	15–70 yr	SA	Lower extremity orthopedic surgery	2 h before spinal anesthesia	S	Oral gabapentin 600 mg	84	10
							Oral placebo capsule	84	14
Nain et al[10]	2021	20–60 yr	SA	Elective orthopedic surgery	30 min before the spinal anesthesia	S	Oral gabapentin 600 mg	50	7
							Oral placebo capsule	50	23
Nofal et al[11]	2014	No	SA	Elective cesarean section	2 h before admission to the operating room	S	Oral gabapentin 600 mg	42	0
							Oral placebo capsule	44	0
Ozgencil et al[12]	2011	18–70 yr	GA	Elective decompressive lumbar laminectomy and discectomy	2 h prior to the operation, and 10 and 22 h after the operation	M	Oral gabapentin 600 mg at each of the 3 time points	30	2
							Oral placebo capsule	30	8
Rapchuk et al[13]	2010	18–75 yr	GA	Cardiac surgery via median sternotomy	2 h prior to surgical incision and in the morning and evening for the postoperative next 2 d	M	Oral gabapentin 1200 mg before surgery and 600 mg each time after surgery	27	3
							Oral placebo capsule	27	8
Vasigh et al[14]	2016	20–60 yr	GA	Elective laminectomy	2 h before surgery and 6 h after surgery	M	Oral gabapentin 600 mg before surgery and 300 mg after surgery	38	4
							Oral placebo capsule	38	16

GA = general anesthesia, SA = spinal anesthesia, S = single dose, M = multiple doses.

we found reanalysis of the same data was reported in 1 paper, and 1 paper with incomplete data was also excluded. Finally, 6 trials[9–14] with 544 patients that met the selection criteria were included in the meta-analysis.

3.2. Study characteristic

All these studies[9–14] above explored the efficacy of gabapentin versus placebo on shivering with author name, publish year, age range, type of anesthesia including spinal anesthesia and general anesthesia, and surgery including orthopedic surgery, cesarean section and cardiac surgery, trail of drug, comparisons (study group and control group), dosage regimen, number of all patients and cases of shivering, detail in Table 1.

3.3. The methodological quality of studies included

All 6 trials,[9–14] which were all double-blind clinical experiments, described randomization detailly and reported allocation concealment as well as the end views mentioned in the Methods section (reporting bias). At the same time, the 6 tests have no incomplete outcome (attrition bias) and other deviations. Then, an overview of the risk of bias is summarized (Fig. 2).

3.4. Results of meta-analysis

Six trials,[9–14] including 544 patients, investigated the efficacy of preventing shivering after surgery, by comparing gabapentin with placebo. Postoperative shivering (pooled RR 0.38, 95% CI 0.25–0.57) in the controlled group using placebo was more obvious than the study group adopting gabapentin (Fig. 3). Begg's and Egger's Test showed that publication bias did not exist clearly when contrasting the incidence of shivering ($P = 1.000$ and $P = .435$) between gabapentin and placebo (Fig. 4).

3.4.1. Type of anesthesia. Gabapentin significantly decreased the occurrence rate of shivering after general anesthesia (combined RR of 3 trails[12–14] including 190 patients: 0.28, 95% CI: 0.14–0.56; Fig. 5B), but not spinal anesthesia (combined RR of 3 trails[9–11] including 354 patients: 0.47, 95% CI: 0.20–1.08; Fig. 5A).

3.4.2. Type of surgery. Oral gabapentin pretreatment lowered the incidence of shivering after orthopedic surgery (pooled RR of 4 trails[9,10,12,14] including 404 patients: 0.38, 95% CI: 0.24–0.58) compared with placebo (Fig. 6).

3.4.3. Dosage of gabapentin. Subgroup analysis demonstrated a single-dose bolus of 600 mg gabapentin might be more beneficial to shivering compared with placebo probably, although without statistical significance (pooled RR of 3 trials[9–11] including 354 patients: 0.47, 95% CI: 0.20–1.08; Fig. 7).

3.4.4. Other adverse effects. PON: There were 5 studies[9–12,14] including 490 patients reporting PON. Compared with placebo, a probable reduction in PON without statistical significance

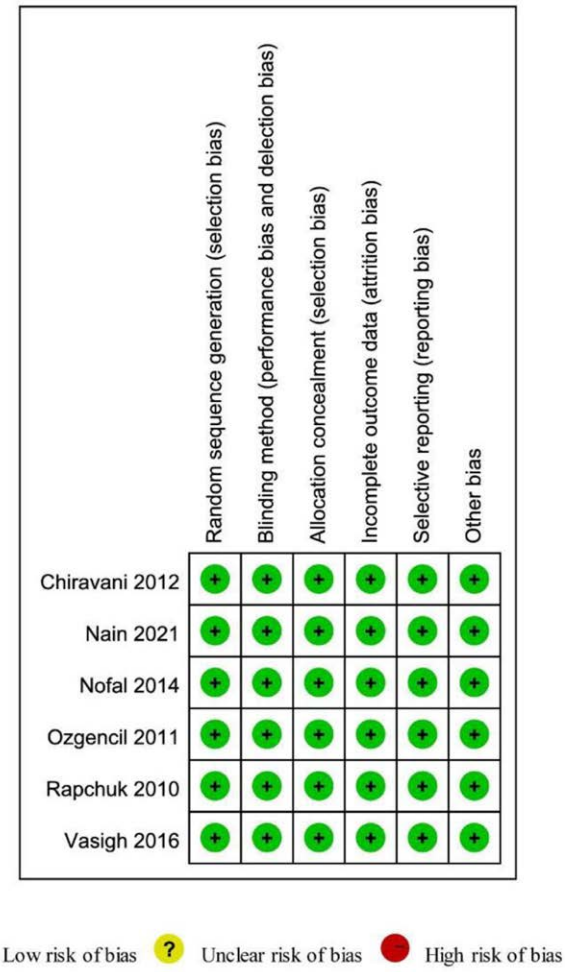


Figure 2. Risk of bias on the studies included.

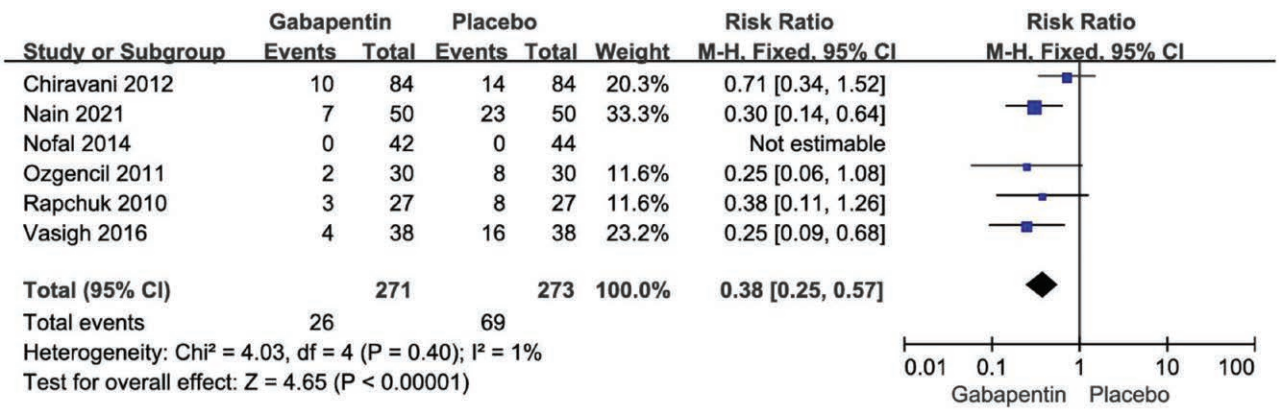


Figure 3. Results of analysis on prophylactic oral gabapentin reducing postoperative shivering compared with placebo.

(RR 0.75, 95% CI 0.38–1.41) was exposed in patients receiving gabapentin (Table 2).

Postoperative vomiting (POV): POV was involved in 2 studies including 136 patients,[12,14] the pooled estimate showed a statistical reduction in POV (RR 0.35, 95% CI 0.16–0.77) in patients who got gabapentin instead of placebo (Table 2).

Pruritus: 3 studies[9,12,14] including 304 patients assessed postoperative pruritus. The pooled analysis did not show a statistically significant decrease, while with a reduced trend in this side effect (RR 0.76, 95% CI 0.40–1.46) in gabapentin group (Table 2).

Headache: Headache was involved in 3 studies including 236 patients,[10,12,14] there was no statistical significance of reduction in this side effect (RR 1.14, 95% CI 0.58–2.24) between patients taking gabapentin orally and who got placebo (Table 2).

Urine retention: 2 studies[12,14] including 136 patients assessed urine retention after surgery, and the pooled estimate almost showed the significant reduction of postoperative urine retention (RR 0.50, 95% CI 0.24–1.03) in patients who took gabapentin orally (Table 2).

Bradycardia: There were 2 studies[9,10] including 268 patients reporting the prevention of postoperative bradycardia without statistically significant difference (RR 1.00, 95% CI 0.21–4.81) between patients using gabapentin and placebo (Table 2).

Hypotensive: Hypotensive was involved in 2 studies including 268 patients,[9,10] compared with placebo, the pooled

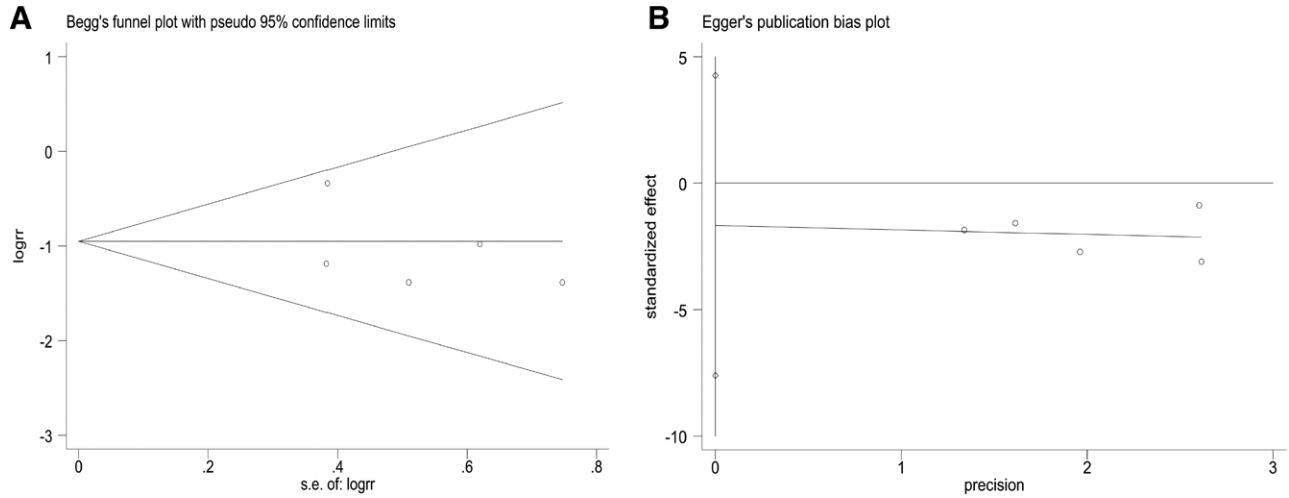


Figure 4. Begg's and Egger's test of included articles to evaluate possible publication bias.

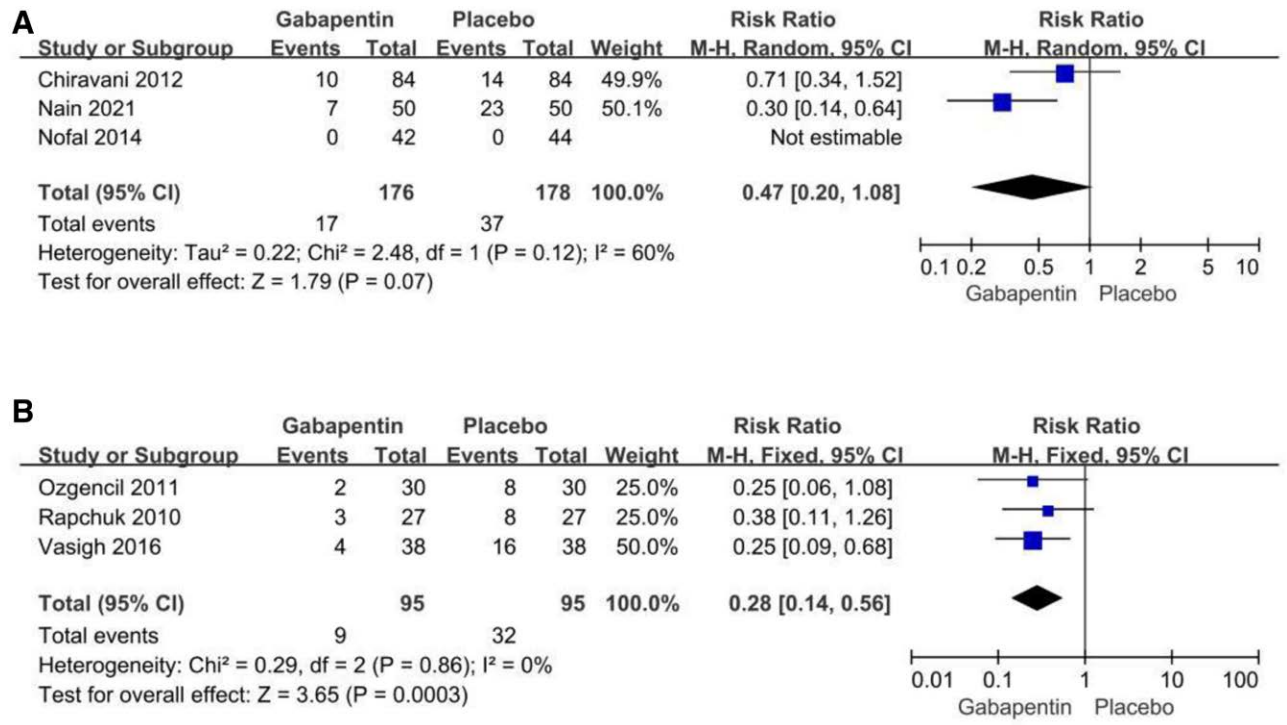


Figure 5. Consequences of subgroup analysis of the incidence of shivering after operation in kinds of anesthesia: spinal anesthesia (A) and general anesthesia (B).

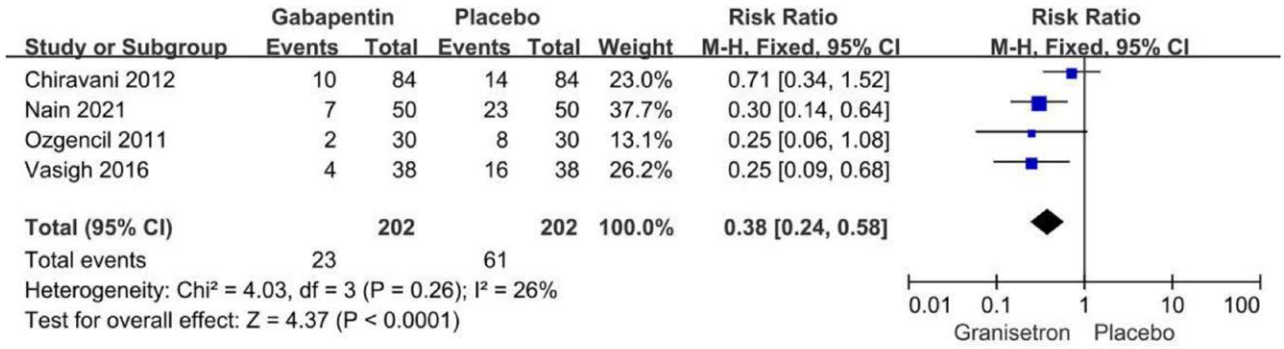


Figure 6. Consequences of subgroup analysis on incidence of shivering after orthopedic surgery.

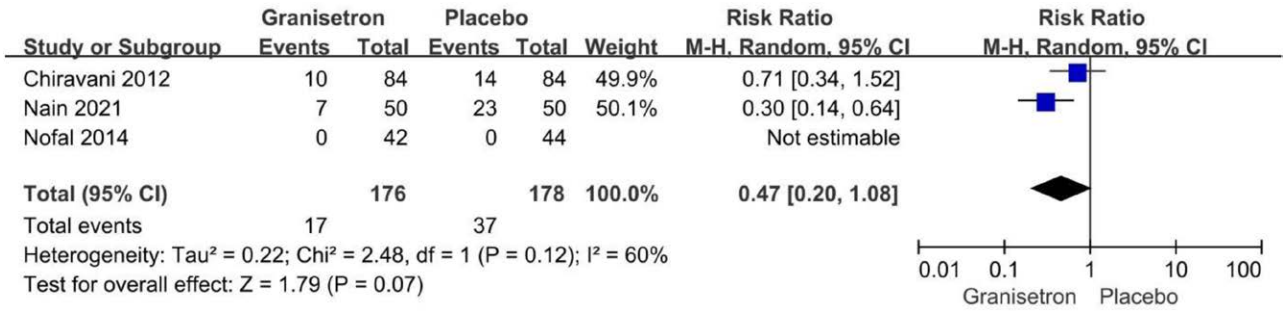


Figure 7. Consequences of subgroup analysis on incidence of shivering after operation with oral 600 mg gabapentin before anesthesia.

Table 2

Efficacy of oral gabapentin on reducing other postoperative side effects compared with placebo.

Comparison	Number of studies	Gabapentin	Placebo	RR (95% CI)	I^2	References
PON	5	49/244	68/246	0.73 (0.38, 1.41)	72%	[9–12,14]
POV	2	7/68	20/68	0.35 (0.16, 0.77)	0%	[12,14]
Pruritus	3	40/152	48/152	0.76 (0.40, 1.46)	57%	[9,12,14]
Headache	3	16/118	14/118	1.14 (0.58, 2.24)	37%	[10,12,14]
Urine retention	2	9/68	18/68	0.50 (0.24, 1.03)	0%	[12,14]
Bradycardia	2	3/134	3/134	1.00 (0.21, 4.81)	–	[9,10]
Hypotensive	2	27/134	26/134	0.87 (0.31, 2.40)	57%	[9,10]
Dizziness	2	9/72	6/74	1.50 (0.61, 3.69)	–	[11,12]

CI = confidence interval, PON = postoperative nausea, POV = postoperative vomiting, RR = risk ratio.

estimate did not exclude a statistical reduction in hypotensive (RR 0.87, 95% CI 0.31–2.40) in patients receiving gabapentin (Table 2).

Dizziness: There were 2 studies[11,12] including 146 patients reporting incidence of postoperative dizziness, compared with placebo, which was estimated without statistical reduction (RR 1.50, 95% CI 0.61–3.69; Table 2).

3.4.5. Duration of anesthesia and surgery. The difference in duration (min) of anesthesia (pooled SMD of 3 trials[10,13,14] including 230 patients: 0.35, 95% CI: −0.60 to 1.30) and surgery (pooled SMD of 4 trials[10–12,14] including 322 patients: 0.10, 95% CI: −0.29 to 0.48) did not have statistical significance (Fig. 8).

3.4.6. Sensitivity analysis. Upon the trials with high risk were eliminated by sensitivity analysis, there was no prominent dissimilarity in concludes from overall pooled estimates across all outcomes above.

4. Discussion

Postoperative shivering is one of the leading causes of discomfort for patients recovering from anesthesia, a long-standing problem with significant consequences.[19] Despite extensive research over the past decades, shivering remains a significant challenge due to its complex mechanism. Therefore, it is essential to have effective methods for the prophylaxis and treatment of shivering for patients undergoing surgery and anesthesia.

The therapeutic effect of oral gabapentin on reducing the incidence of shivering after surgery was assessed using meta-analysis, and the main results are: The efficacy of prophylactic oral gabapentin is significantly more effective than placebo in the elimination of shivering after surgery; The beneficial impact of gabapentin on shivering was observed in patients undergoing general anesthesia and orthopedic surgery; Evidence suggests that a 600 mg dose of oral gabapentin may prevent shivering after surgery; Prophylactic oral gabapentin could reduce the incidence of postoperative vomiting (POV).

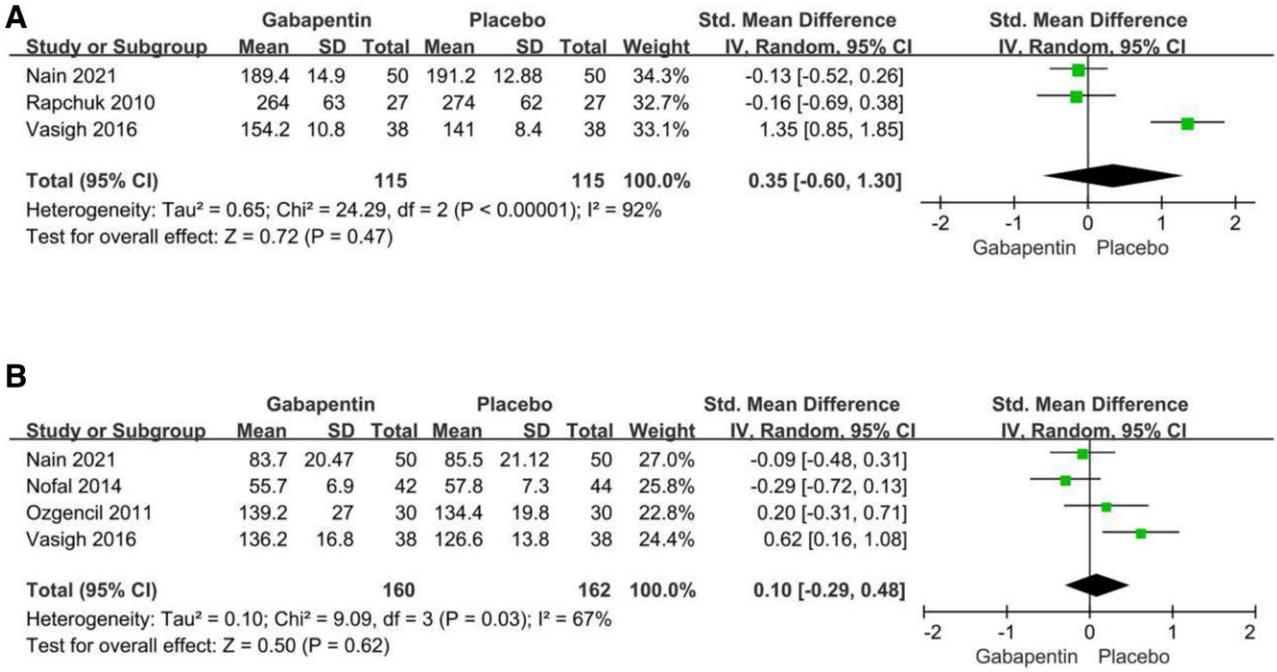


Figure 8. Results of analysis on duration of anesthesia (A) and surgery (B).

Firstly, shivering is often caused by anesthetics that inhibit thermoregulation,[20] and recent studies have suggested that a complex mechanism of thermoregulation might exist through the NMDA receptor, which may be responsible for shivering.[21] Moreover, NMDA receptor antagonists have shown significant anti-shivering effects, like MgSO4, ketamine, and so on.[21–23] Gabapentin could bind to the NMDA receptor, which might inhibit receptor activity,[24] so it could regulate the body's thermoregulatory capability, which might act as the anti-shivering effect mechanism of gabapentin.

Controversy exists in previous meta-analyses about the efficacy on shivering; several studies[10,14] suggest a superior role of gabapentin compared with placebo, but others[9,11–13] do not. We included a total of 6 articles about the efficacy of gabapentin on postoperative shivering compared with placebo with a plethora of relevant clinical outcome variables to improve the reliability of our conclusion. As far as we know, this is the first time for a meta-analysis of randomized controlled trials and placebo to elucidate multiple aspects of gabapentin's efficacy on shivering. All the studies included were well designed and rated as "Low." And these strategies were administered to come up with a solid conclusion.

The clinical usage of gabapentin to prevent shivering is still unascertained. In this meta-analysis, we found that a 600 mg oral bolus might be sufficiently effective to prevent postoperative shivering. Our study showed that gabapentin could simultaneously reduce the occurrence rate of POV, which might be due to its high binding affinity to the α2δ subunit of the presynaptic voltage-gated calcium channels.[25] By inhibiting calcium influx, it may maintain hemodynamic stability, and decrease the release of several excitatory neurotransmitters, including tachykinin. This modulation of tachykinin release probably contributes to the antiemetic effects of gabapentin.[26,27]

However, this meta-analysis has certain limitations. First, the total number of trials included might not be relatively significant, so the subgroup sample sizes are too small to ensure absolutely conclusive results. In addition, the included studies did not provide detailed information on whether effective thermal insulation measures were taken, which might indeed be a limitation of our study, as the effectiveness of gabapentin in preventing postoperative shivering could be influenced by the implementation of such measures. Finally, including only 3 trials with 2 sets of data, subgroup analysis showed that the incidence of shivering after operation in spinal anesthesia with prophylactic oral gabapentin showed a downward trend but no statistically significant difference compared to general anesthesia, which might be due to the small sample size. Therefore, more RCTs should be reasonably designed, including various patient types, doses, and administration routes for specific anesthesia or surgeries, to accurately determine the efficacy of gabapentin on postoperative shivering. We will continue to pay close attention to relevant studies in future research.

5. Conclusion

In conclusion, our present meta-analysis demonstrates that oral gabapentin may reduce the incidence of postoperative nausea and vomiting, compared with placebo. This result proves that it is valuable for gabapentin to expand its clinical usage in the routine treatment of PONV.

Acknowledgments

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Author contributions

Formal analysis: Xiao Liang, Ming Chen.
Project administration: Jing Jiang.
Resources: Zhen Gu.
Software: Aonan Hong.
Writing – original draft: Xiao Liang, Ming Chen.
Writing – review & editing: Yanchun Chen, Minmin Zhu, Weiqian Tian.

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