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5-HT_3 Receptor Antagonists for the Prevention of Perioperative Shivering: A Meta-Analysis

Wen Wang, MS[1], Xiaojing Song, MS[2], Tong Wang, BSc[3], Chaobin Zhang, MS[1], and Li Sun, MD[1]

Abstract

The aim of this meta-analysis was to evaluate the preventive efficacy and safety of 5-HT_3 receptor antagonists (5-HT_3RAs) on perioperative shivering. Relevant databases were searched to identify eligible randomized, controlled trials through January 2016. Primary outcome was the incidence of perioperative shivering, and secondary outcomes were the incidence of safety-related outcomes including postoperative nausea and vomiting (PONV), bradycardia, and hypotension. We calculated risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous data. Trial sequential analysis was performed to assess the risk of random errors and calculate the required information size. Sixteen studies with a total of 1126 patients were included in the meta-analysis. Compared with the control group, 5-HT_3RAs administered intravenously could statistically significantly reduce the incidence of perioperative shivering (RR, 0.44; 95%CI, 0.35 to 0.56; $P < .00001$; heterogeneity: $I^2 = 30\%$) as well as PONV (RR, 0.52; 95%CI, 0.28 to 0.97; $P = .04$; heterogeneity: $I^2 = 0\%$). However, they did not show superiority in lowering the rate of bradycardia (RR, 0.75; 95%CI, 0.38 to 1.49; $P = 0.42$; heterogeneity: $I^2 = 0\%$) or hypotension (RR, 0.79; 95%CI, 0.44 to 1.43; $P = .44$; heterogeneity: $I^2 = 24\%$). Trial sequential analysis of primary outcome showed that the required information size was 2634 patients and that the trial sequential monitoring boundary was crossed. Thus, more high-quality randomized, controlled trials with larger sample sizes are still required to draw a definite conclusion about the preventive efficacy of 5-HT_3RAs on perioperative shivering prevention in the future.

Keywords

5-HT_3 receptor antagonists, prevention, shivering, meta-analysis

Shivering is a common complication in intraoperative and postoperative periods.[1,2] In addition to being an uncomfortable experience for patients and interfering with many monitoring devices,[3] perioperative shivering can increase intraocular pressure, pain on the surgical site, and oxygen consumption.[4]

Although the mechanisms of perioperative shivering are still not completely understood, numerous non-pharmacological and pharmacological interventions have been raised to prevent and treat perioperative shivering with different results.[5,6] Meperidine, a type of opioid, has been widely used to treat shivering by reducing the shivering threshold twice as much as the vasoconstriction threshold over the range of clinical doses.[7,8] However, patients with intraoperative remifentanil are more likely to suffer from perioperative shivering than those with other opioids, which may be explained by the rapid metabolism of remifentanil.[9,10]

In clinical settings, 5-HT_3 receptor antagonists (5-HT_3RAs) are usually recommended for preventing and treating postoperative nausea and vomiting (PONV).[11] Many clinical studies have been conducted to investigate the effectiveness of 5-HT_3RAs on preventing perioperative shivering. However, results from relevant trials remain inconsistent.[1,2,12] Recently, the meta-analysis by Tie published in 2014 reported that ondansetron has preventive efficacy on perioperative shivering.[13] However, the preventive efficacy of other types of 5-HT_3 receptor antagonists on shivering is still unknown.

Here, we conducted a meta-analysis of randomized, controlled trials (RCTs) to assess the efficacy and safety of 5-HT_3RAs on perioperative shivering in adults. The scope of our study focused only on 5-HT_3RAs for the prevention, not treatment, of perioperative shivering.

[1]Department of Anesthesiology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[2]Department of Emergency, Peking University People's Hospital, Beijing, China
[3]Institute for Hospital Management, Tsinghua University, Beijing, China

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Corresponding Author:
Li Sun, MD, Department of Anesthesiology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17 Panjiayuannanli, Chaoyang District, Beijing, 100021, China
Email: ykyzlyysunli@126.com

Methods

Literature Search

This meta-analysis was conducted following the guidelines recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement,[14] and it was not registered in a clinical trials registry. Online databases of Pubmed, Embase, and the Cochrane Central Register of Controlled Trials were systematically searched for potentially eligible studies. The website for clinical trials registry (https://clinicaltrials.gov) was searched for published protocols. In addition, reference lists of relevant reviews and selected studies were manually scanned for additional articles. The corresponding authors were contacted by email when the full text of relevant studies could not be found. The last electronic search was on January 4, 2016. The search strategies for the 3 online databases are presented in Supplementary 1.

Inclusion and Exclusion Criteria

We searched for RCTs to compare the preventive efficacy and safety of 5-HT_3RAs versus 0.9% normal saline on the incidence of perioperative shivering in adults aged 18 years or older undergoing surgery. RCTs with full text published in English that tested prophylactic administration of 5-HT_3RAs for preventing perioperative shivering were considered. Data from experimental studies in healthy volunteers were not selected. Trials associated with the treatment of established shivering were also excluded. In view of the aim of our analysis, we did not include studies that lacked detailed information about grading or definition of perioperative shivering or methods of body temperature monitoring. Abstracts and unpublished reports were also excluded. We also excluded trials in which patients were treated with therapeutic hypothermia (eg, use of cardiopulmonary bypass). 5-HT_3RAs included ondansetron, palonosetron, ramosetron, granisetron, tropisetron, dolasetron, and alosetron.

Primary and Secondary Outcomes

The primary outcome was the incidence of perioperative shivering. Secondary outcomes were the incidence of safety-related outcomes including PONV, bradycardia, and hypotension.

Study Selection and Data Extraction

First, the titles and abstracts of all searched articles were independently screened by 2 investigators (W.W., X.J.S.) to remove duplicates and obvious ineligible studies. If studies could not be explicitly identified according to their titles or abstracts, full texts of these studies were reviewed. Finally, studies meeting the eligibility criteria were included in our meta-analysis. All controversies were settled by discussion with a third investigator.

Two researchers (T.W., C.B.Z.) individually extracted information from eligible studies using a data collection form, and any disagreement in this process was resolved by a third investigator. Because many different assessments of perioperative shivering were used in eligible trials, we extracted only dichotomous data on the presence or absence of shivering to reduce the risk of interpretational bias. In the process of data extraction, we contacted the authors for further details if the data in certain trials were inadequate or incorrect. The following data items were extracted: name of the first author, publication year, patient characteristics, operations, type of anesthesia, premedication, anesthetic regimen, comparisons, time of the injection of study agents, body temperature, assessment of perioperative shivering, and surgery time.

Quality Assessment

The risk-of-bias table for each individual study was completed independently by 2 reviewers (W.W., X.J.S.) with the Cochrane Collaboration's tool,[15] and any disagreement was settled by discussion with a third author. The tool contains the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each above domain was classified into 1 of 3 levels: high, unclear, or low risk of bias. Other biases contained comparison of baseline characteristics, reporting of power calculations, and the risk of vested financial interests (sponsoring by pharmaceutical companies). Only studies that explicitly gave method and description for each of the domains were considered as having a low risk of bias. Moreover, we used GradePro (http://gradepro.org/) to further evaluate the strength and summary of evidence about the primary outcome.

Statistical Analysis

We used Review Manager (version 5.3; the Nordic Cochrane Centre, Copenhagen, Denmark; the Cochrane Collaboration, 2014) to perform statistical analysis. The pooled risk ratio (RR) and its 95% confidence interval (CI) were calculated for the dichotomous data such as the incidence of shivering. Interstudy statistical heterogeneity was evaluated by the I^2 test. Given the clinical heterogeneity in the retrieved trials, we adopted a random-effects model for dichotomous variables. Subgroup analysis based on anesthesia protocol including general anesthesia, and neuraxial anesthesia was conducted with an a priori hypothesis that the preventive efficacy of 5-HT_3RAs on perioperative shivering would be much better in patients with neuraxial anesthesia than in patients with general anesthesia. In addition, sensitivity analysis was also undertaken to test the stability of

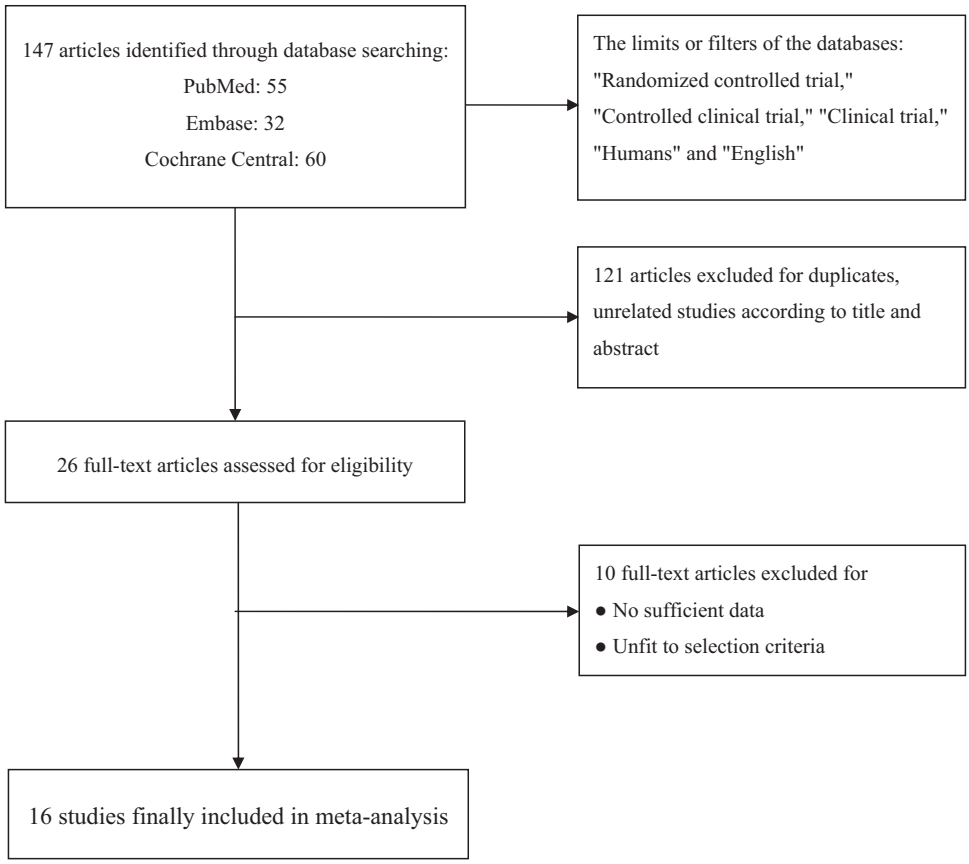

Figure 1. Flowchart of the selection process.

the results by reanalyzing the data after removing each study sequentially and by comparing the outcomes from random- and fixed-effects models. A funnel plot was used to assess the potential publication bias by using visual assessment. We performed trial sequential analysis to evaluate the risk of random errors and calculate required information size, which was conducted by using trial sequential analysis software version 0.9 beta (http://www.ctu.dk/tsa/).

Results

Study Selection

We initially identified 147 articles (55 from Pubmed, 32 from Embase, and 60 from the Cochrane Central). A total of 121 studies were excluded because they were duplicates, obviously irrelevant trials, or did not meet the selection criteria of this analysis after reviewing the titles and abstracts. Subsequently, we carefully reviewed 26 potentially eligible articles, and 10 articles were excluded, 1 for conference abstract without full text,[16] 1 for non-English study,[17] 2 for investigating the therapeutic effect of 5-HT_3RAs on established shivering,[18,19] 1 for retraction article,[20] 2 for letters to editors,[21,22] 1 for lack of detailed information about methods of body temperature monitoring,[23] 1 for with no grading or definition of perioperative shivering,[24] and 1 for lack of the full texts despite contacting the authors.[25] Finally, 16 studies were included in the meta-analysis.[1,2,12,26–38] The detailed information of our selection is summarized in Figure 1.

Study Characteristics

All adult participants in included studies were American Society of Anesthesiologists (ASA) I–II and underwent different kinds of elective operations. Among these trials, 4 studied only female patients[12,34,37,38] whereas 1 tested elderly patients.[35] Patients received neuraxial anesthesia (NA) in 7 studies,[1,26–30,38] spinal anesthesia (SA) in 6 studies,[1,26–30] and combined spinal epidural anesthesia (CSEA) in 1 study,[38] whereas patients received general anesthesia (GA) in 9 studies.[2,12,31–37] Four kinds of 5-HT_3RAs were investigated in the 16 trials: 3 studied granisetron,[1,31,32] 8 examined ondansetron,[2,26–29,33,34,38] 3 investigated ramosetron,[30,36,37] and 2 researched palonosetron.[12,35] All the included studies compared 5-HT_3RAs with a control. In the study by Powell,[2] 2 doses of ondansetron were compared with the control group. Thus, we combined the data from the 2 ondansetron groups for the shivering outcome in

Table 1. Characteristics of the Included Studies

Study	Patient Characteristics	Operations	Type of Anesthesia	Premedication	Anesthetic Regimen	Comparisons	Time of Injection	Body Temperature	Assessment of perioperative shivering	Surgery Time (min), Mean ± SD
Sagir, 2007[1]	ASA: I–II	Ureterorenoscopy	SA	No	Hyperbaric bupivacaine, 5 mg/mL, 15 mg; 25 G spinal needle	NS 3 mL IV, K 0.5 mg IV, G 3 mg IV	After SA	Tympanic and axillary temperatures	0–4 Scale	NA
Kelsaka, 2006[2,6]	ASA: I–II	Orthopedic surgery	SA	10 mg Diazepam	Hyperbaric bupivacaine, 2.5 mL 0.5%; 22 G spinal needle	NS 4 mL IV, M 0.4 mg/kg IV, O 8 mg IV	Before SA	Rectal and axillary temperatures	Pectoralis major muscles for fasciculations > 10 s	80 ± 32 76 ± 30
Safavi, 2014[2,7]	ASA: I–II	Orthopedic surgery	SA	NA	Hyperbaric bupivacaine 0.5%; 22 G spinal needle	NS IV, M 0.2 mg/kg IT,O 8 mg IV	Before SA	Tympanic and axillary temperatures	Pectoralis major muscles for fasciculations > 10 s 0–4 Scale	74 ± 28 77 ± 22 75 ± 23
Shakya, 2010[2,8]	ASA: I–II	Lower abdominal surgery	SA	0.2 mg/kg Diazepam	Hyperbaric bupivacaine, 3 mL 0.5%	NS IV, K 0.25 mg/kg IV,O 4 mg IV	After SA	Tympanic temperature	0–4 Scale	NA
Safavi, 2015[2,9]	ASA: I–II	Orthopedic surgery	SA	No	Hyperbaric bupivacaine 15 mg; 22 G spinal needle	NS 4 mL IV, K 0.25 mg/kg + Mi 37.5 μg/kg IV, O 8 mg IV	After SA	Tympanic and axillary temperatures	0–4 Scale	111 ± 2 115 ± 4 114 ± 7
Kim, 2010[30]	ASA: I–II	Knee arthroscopy	SA	NA	Hyperbaric bupivacaine, 11 mg 0.5%; 25 G spinal needle	NS 2 mL IV, R 0.3 mg IV	Before SA	Tympanic temperature	Pectoralis major muscles for fasciculations > 10 s	55 ± 18 45 ± 20
Iqbal, 2009[1,3]	ASA: I–II	Laparoscopic surgery	GA	NA	Induction: fentanyl + atracurium + propofol Maintenance: sevoflurane + atracurium	NS 5 mL IV, M 25 mg IV, G 40 μg/kg IV	Before induction	Nasopharyngeal temperature	0–4 Scale	NA
Sajedi, 2008[2,3]	ASA: I–II	Orthopedic surgery	GA	NA	Induction: thiopental + fentanyl + atracurium Maintenance: isoflurane + N_2O	NS IV, T 1 mg/kg IV, M 0.4 mg/kg IV, G 40 μg/kg IV	At the end of surgery	Tympanic temperature	0–4 Scale	NA

(*Continued*)

Table 1. Continued

Study	Patient Characteristics	Operations	Type of Anesthesia	Premedication	Anesthetic Regimen	Comparisons	Time of Injection	Body Temperature	Assessment of perioperative shivering	Surgery Time (min), Mean ± SD
Teymourian, 2015[33]	ASA: I–II	Neurosurgery	GA	5 mg/kg fentanyl, 0.02 mg/kg midazolam	Induction: thiopental + lidocaine + cisatracurium Maintenance: propofol + isoflurane	NS IV, O 4 mg IV	Before end of surgery	Nasopharynx and fingertip temperatures	Shivering movements > 10 s	308 ± 211 307 ± 196
Powell, 2000[2]	ASA: I–II	Minor general surgery	GA	No	Induction: fentanyl + propofol Maintenance: isoflurane + N_2O	NS 4 mL IV, O 4 mg IV, O 8 mg IV	Before induction	Tympanic and fingertip temperatures	Fasciculations or tremors of the face, trunk, or limbs > 15 s	NA
Asl, 2011[3,4]	ASA: I–II	Gynecologic surgery	GA	NA	Induction: fentanyl + thiopental + succinylcholine Maintenance: isoflurane + N2O	NS 2 mL IV, M 0.4 mg/kg IV, O 4 mg IV	Before induction	Tympanic and forehead temperatures	Chills for >15 s	34 ± 7 33 ± 6 36 ± 8
Jo, 2016[3,5]	ASA: I–II	Laparoscopic cholecystectomy	GA	No	Induction: alfentanil + lidocaine + propofol + rocuronium Maintenance: sevoflurane	NS 1.5 mL IV, P 75 μg IV	Before induction	Esophageal and skin temperatures	0–3 Scale	63 ± 20 57 ± 18
Jo, 2013[1,2]	ASA: I–II	Gynecological laparoscopy	GA	0.04 mg/kg Midazolam	Induction: propofol + remifentanil + rocuronium Maintenance: propofol + remifentanil	NS 1.5 mL IV, P 75 μg IV	After induction	Esophageal and index finger temperatures	0–3 Scale	95 ± 26 96 ± 26
Lee, 2015[3,6]	ASA: I–II	Thyroid surgery	GA	2–3 mg Midazolam	Induction: remifentanil + propofol Maintenance: desflurane + remifentanil	NS 3 mL IV, R 0.3 mg + Dex 5 mg IV, R 0.3 mg IV	After induction	Tympanic temperature	Fasciculation or tremors of the face, trunk, or limbs > 10 s	140 ± 35 142 ± 52 144 ± 42

(*Continued*)

Table 1. Continued

Study	Patient Characteristics	Operations	Type of Anesthesia	Premedication	Anesthetic Regimen	Comparisons	Time of Injection	Body Temperature	Assessment of perioperative shivering	Surgery Time (min), Mean ± SD
Song, 2012[3,7]	ASA: I–II	Thyroid surgery	GA	2-3 mg Midazolam	Induction: remifentanil + propofol + rocuronium Maintenance: desflurane + remifentanil	NS 2 mL IV, Dex 10 mg IV, R 0.3 mg IV	After induction	Tympanic temperature	0–3 Scale	140 ± 45 144 ± 49 142 ± 44
Browning, 2013[38]	ASA: I–II	Cesarean delivery	CSEA	No	Hyperbaric bupivacaine 0.5% 2.2–2.5 mL + fentanyl 15 μg 16 G Tuohy needle + 27 G spinal needle	NS 4 mL IV, O 8 mg IV	Before CSEA	Tympanic temperature	0–4 Scale	NA

ASA, American Society of Anesthesiologists; SA, spinal anesthesia; GA, general anesthesia; CSEA, combined spinal and epidural anesthesia; MAC, minimumalveolar concentration; NS, normal saline; K, ketamine; G, granisetron; M, meperidine; O, ondansetron; R, ramosetron; Mi, midazolam; T, tramadol; P, palonosetron; Dex, dexamethasone; IV, intravenously; IT, intrathecally; NA, not available; SD, standard deviation.
0–3 Scale: 0 = no shivering; 1 = mild fasciculations of the face or neck; 2 = visible tremors involving more than 1 muscle group; 3 = gross muscular activity involving the entire body.
0–4 Scale: 0 = no shivering; 1 = piloerection or peripheral vasoconstriction but no visible shivering; 2 = muscular activity in only 1 muscle group; 3 = muscular activity in more than 1 muscle group but not generalized; 4 = shivering involving the whole body.

this analysis. 5-HT_3RAs were given intravenously in all trials, while they were injected at different times. 5-HT_3RAs were administered before SA in 3 studies,[26,27,30] before CSEA in 1 study,[38] and after SA in 3 trials.[1,28,29] Four studies gave the intervention drug prior to induction of GA[2,31,34,35] and 3 after induction of GA.[12,36,37] One trial administered the drug 10 minutes before the end of surgery[33] and 1 at the end of surgery.[32] The detailed characteristics of 16 included studies are presented in Table 1.

Study Quality

The assessment of risk of bias within individual studies is summarized in Figure 2. There was no trial judged to be of low risk of bias in all 6 domains. Only 4 trials clearly showed the randomized sequence generation method,[12,27,32,38] and 9 studies explicitly demonstrated the allocation concealment method.[1,2,27,29–31,34,36,38] Five research studies did not clearly report the blinding of participants and personnel,[12,28,33,35,37] and 3 had no details about the blinding of outcomes assessment.[1,28,37] The risk of bias for selective reporting was considered unclear because we could not obtain the published protocol of each trial. Furthermore, 5 studies recruited only female or elderly patients,[12,34,35,37,38] and 2 studies did not report the power calculation,[28,34] resulting in high risk of other bias. Six studies carried out their power calculation without specific references.[1,27,29,31,36,37] In addition, 7 trials[12,29,30,32,33,37,38] mentioned the source of funding from universities or hospitals without pharmaceutical companies, whereas the other 9 studies[1,2,26–28,31,34–36] did not give the funding information. The summary and strength of evidence for our primary outcome according to GRADE is shown in Table 2. The quality of evidence was low for the incidence of perioperative shivering.

Meta-Analysis of Outcomes

The 16 relevant trials included 574 patients who received 5-HT_3RAs and 552 who received normal saline. All included studies, with a total of 1126 participants, compared the preventive efficacy of 5-HT_3RAs on perioperative shivering with the control. Our meta-analysis showed that 5-HT_3RAs administered intravenously was associated with a decreased risk of shivering based on a random-effects model (RR, 0.44; 95%CI, 0.35 to 0.56; $P < .00001$; heterogeneity: $I^2 = 30\%$; Figure 3) and on a fixed-effects model (RR, 0.44; 95%CI, 0.36 to 0.53; $P < .00001$).

Eight studies[1,12,28,29,31,32,34,35] reported the occurrence of PONV, the incidence of which was significantly lower in patients receiving 5-HT_3RAs than in those receiving normal saline whether it was calculated using a random-effects model (RR, 0.52; 95%CI, 0.28 to 0.97; $P = .04$; heterogeneity: $I^2 = 0\%$) or a fixed-effects model (RR, 0.44; 95%CI, 0.24 to 0.79; $P = .006$). Data from 3 studies[26,27,29] showed that risk of bradycardia was similar in the 5-HT_3RA group and the control group both in a random-effects model (RR, 0.75; 95%CI, 0.38 to 1.49; $P = .42$; heterogeneity: $I^2 = 0\%$) and in a fixed-effects model (RR, 0.75; 95%CI, 0.38 to 1.47; $P = 0.40$). Six studies[1,26–30] reported data about the

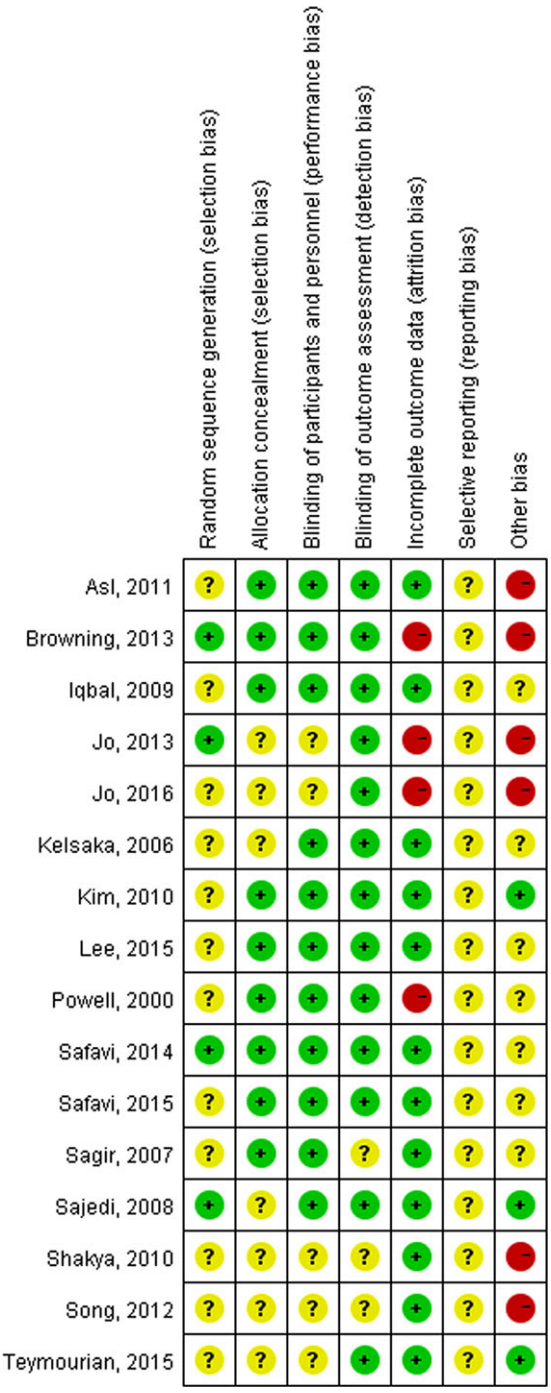

Figure 2. Risk of bias summary: each risk of bias item for each included study.

Table 2. Summary and Strength of Evidence for Primary Outcome, as Analyzed by GradePro

5-HT_3RAs Compared With Control for the Prevention of Perioperative Shivering						
Patient or population: adult patients with surgical requirement for anesthesia Setting: Intervention: 5-HT_3RAs Comparison: control						
Outcome	Anticipated Absolute Effects[a] (95%CI)		Relative Effect (95%CI)	Number of Participants (Studies)	Quality of the Evidence (GRADE)	Comments
	Risk With Control	Risk With 5-HT_3RAs				
Incidence of shivering	Study population		RR, 0.44 (0.35 to 0.56)	1126 (16 RCTs)	⊕⊕◯◯ LOW[b,c]	
	447 per 1000	197 per 1000 (157 to 251)				
	Moderate 442 per 1000	194 per 1000 (155 to 247)				

CI, confidence interval; RR, risk ratio.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI).

[b]Of 16 studies, only 4 presented adequate methods of randomization, only 9 gave detailed allocation concealment methods, 11 appropriately addressed performance bias, and 13 appropriately addressed detection bias. We therefore downgraded 1 level for study limitations.

[c]We only included studies published in English. We therefore downgraded 1 level for potential publication bias.

occurrence of hypotension; they showed that the rate of hypotension in the 5-HT_3RA group was similar to that in the control group according to a random-effects model (RR, 0.79; 95%CI, 0.44 to 1.43; $P = .44$; heterogeneity: $I^2 = 24\%$) and a fixed-effects model (RR, 0.75; 95%CI, 0.47 to 1.19; $P = .22$). We did not perform an analysis of other side effects of 5-HT_3RAs such as constipation, diarrhea, headache, and arrhythmia because only 1 included study reported that 7 patients in the study group and 1 in the control group complained of headache,[36] whereas other studies did not mention or lacked data about the incidence of these side effects.

Publication Bias

We performed a funnel plot to assess the potential publication bias by using visual assessment. The asymmetry of the funnel plot suggested the existence of publication bias (Figure 4).

Subgroup Analysis

Subgroup analysis of the efficacy of 5-HT_3RAs in reducing the incidence of perioperative shivering revealed no statistical difference between the neuraxial anesthesia and general anesthesia groups (RR, 0.39; 95%CI, 0.23 to 0.64 in the neuraxial anesthesia group vs RR, 0.45; 95%CI, 0.35 to 0.57 in the general anesthesia group; interaction $P = 0.62$; Figure 5).

Sensitivity Analysis

The relevant results were in accordance with the initial outcomes after taking out each single study sequentially and changing from a random-effects model to a fixed-effects model. In addition, sensitivity analysis was also conducted by excluding 5 articles that recruited only female and elderly patients.[12,34,35,37,38] A similar result favoring 5-HT_3RAs was shown (RR, 0.39; 95%CI, 0.31 to 0.49; $P < .00001$; heterogeneity: $I^2 = 0\%$). All these suggested the robustness of our pooled results.

Trial Sequential Analysis

We evaluated the level of evidence of the cumulative meta-analysis 5-HT_3RAs versus control by assessing the risk of random errors using trial sequential analysis. We set the parameters as follows: type I error, 5%; power, 80%; relative risk reduction, 20%; incidence in control arm, 30%; the heterogeneity correction, model variance–based, and boundary type, 2 sided. We got 30% for the control group by referring to the incidence from each included studiy and the relatively

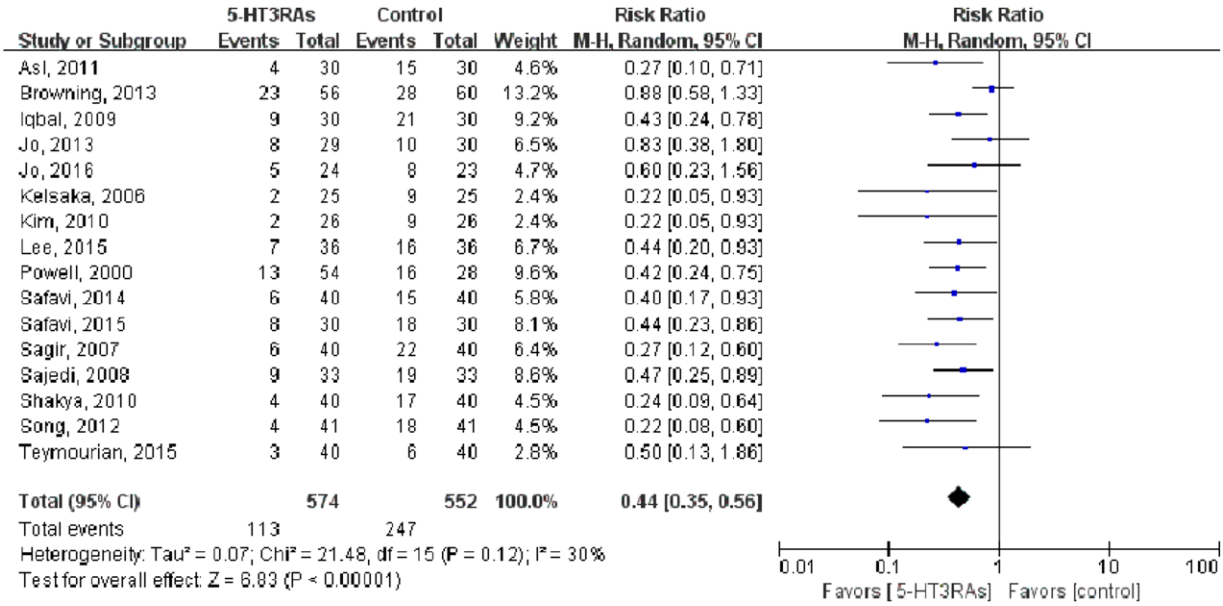

Figure 3. Forest plot of RR. 5-HT$_3$RA group and control group on preventing perioperative shivering with 95%CI. RR, risk ratio; 5-HT$_3$RAs, 5-hydroxytryptamine$_3$ receptor antagonists; CI, confidence interval.

high-quality study by Safavi,[27] which explicitly demonstrated the randomized sequence generation method, allocation concealment method, the blinding of participants and personnel, and the blinding of outcomes assessment. Trial sequential analysis showed that only 43% (1126 patients) of the required information size (2634 patients) was accrued. The cumulative z curve in random-effects models of 1126 randomized patients crossed the conventional boundary ($P < .05$) and the trial sequential monitoring boundary (Figure 6).

Discussion

We undertook this meta-analysis to evaluate the preventive efficacy and safety of 5-HT$_3$ receptor antagonists on perioperative shivering in adults aged 18 years or older undergoing surgery. Our traditional meta-analysis based on a random-effects model showed that 5-HT$_3$RAs administered intravenously can statistically significantly reduce the incidence of perioperative shivering and postoperative nausea and vomiting compared with controls, and there was no difference among the 5-HT$_3$RA and control groups in incidence of bradycardia and hypotension.

However, although meta-analyses of randomized, controlled trials (RCTs) can provide more precise estimates of the effects of health care,[39] it has been reported that almost 30% of all positive meta-analyses provide nothing but a reflection of pure chance (random error) because of lack of power.[40] Moreover, a study has shown that the required number of participants, typically termed the required information size, for a

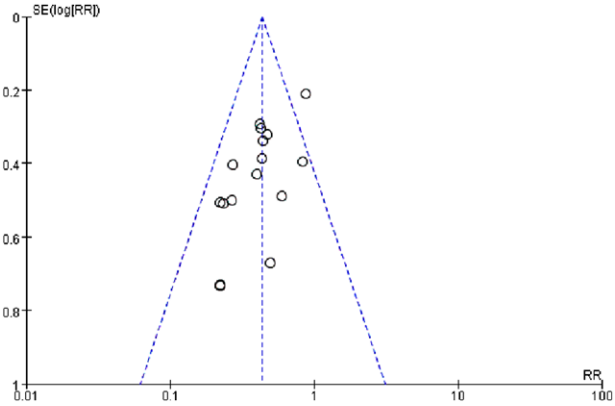

Figure 4. Funnel plot of the meta-analysis of the incidence of perioperative shivering. RR, risk ratio; log [RR], natural logarithm of RR; SE (log [RR]), standard error of the natural logarithm of the RR.

reliable and conclusive meta-analysis should at least equal the sample size of an adequately powered single trial.[41] Trial sequential analysis is a methodology that has been suggested to be applied in meta-analyses to reduce the risk of random errors and provide the required information size.[41,42] Thus, we performed trial sequential analysis to evaluate the risk of random errors and calculate required information size.

Trial sequential analysis showed that the sample size of our meta-analysis about the primary outcome was inadequate even though the cumulative z curve in random-effects models crossed the conventional boundary and the trial sequential monitoring boundary. The result of our conventional meta-analysis about the primary outcome was not confirmed in trial sequen-

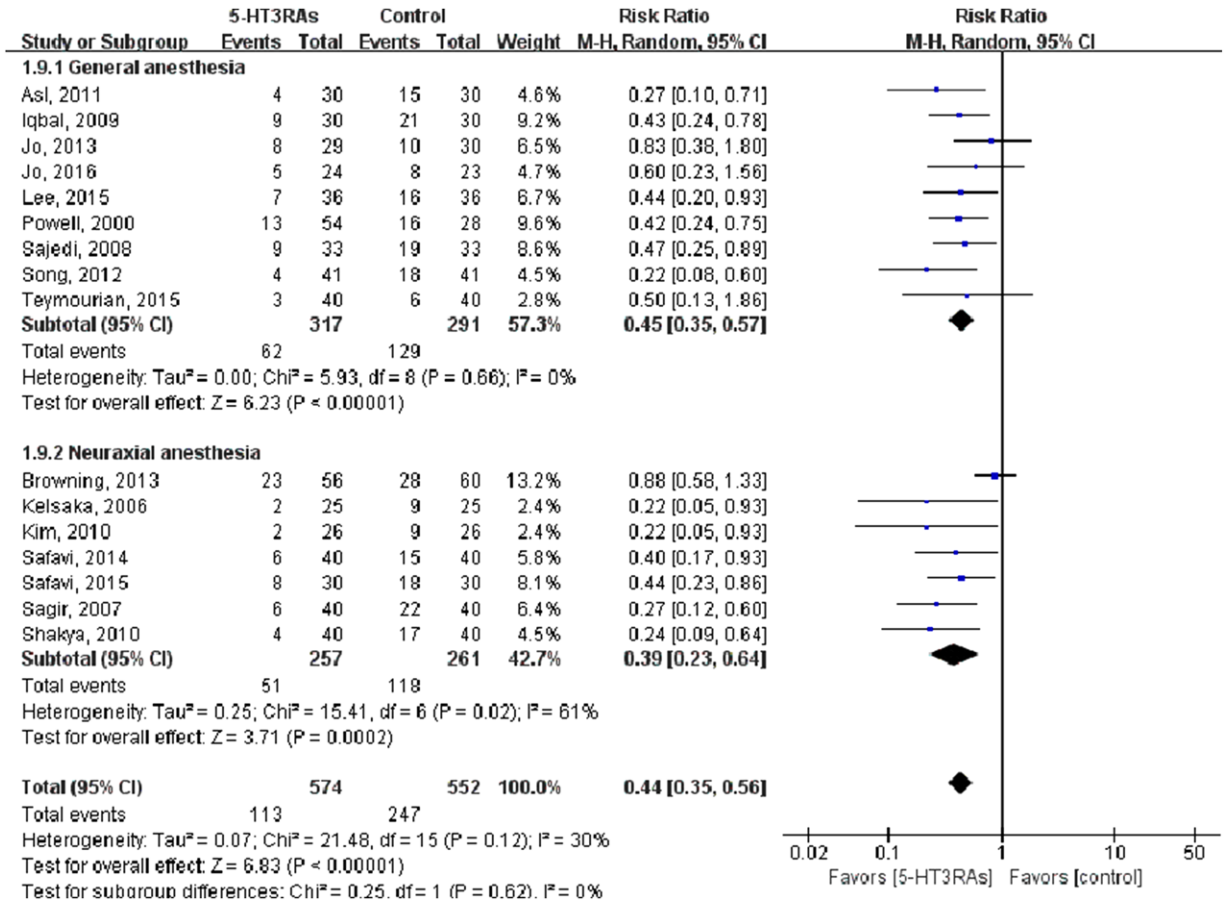

Figure 5. Forest plot of subgroup analysis of the incidence of perioperative shivering by anesthesia type. RR, risk ratio; 5-HT_3RA, 5-hydroxytryptamine$_3$ receptor antagonists; CI, confidence interval.

tial analysis. As the quality of the evidence performed by GradePro was low and trial sequential analysis cannot adjust the risk of bias, the traditionally conclusive result from our meta-analysis may be at risk of being false positive.

A similar meta-analysis was conducted by Tie et al.[13] However, it is necessary to perform this study given the following points. First, the previous meta-analysis investigated only the efficacy of ondansetron on shivering with 6 studies, whereas our analysis evaluated the preventive efficacy of 5-HT_3 receptor antagonists on shivering in 16 trials. Second, 2 studies in the previous review were excluded in our analysis because they did not meet the selection criteria, and our meta-analysis included 4 additional trials about ondansetron. Third, we undertook subgroup analysis to explore the influence of types of anesthesia on the efficacy of 5-HT_3RAs for preventing perioperative shivering. In addition, sensitivity analyses were also conducted to test the stability of our results. Fourth, GradePro was used to assess the strength of evidence about the primary outcome in our study. Fifth, we carried out trial sequential analysis and estimated the required information size for a meta-analysis to be able to reject or support a beneficial effect of 5-HT_3RAs. This method has not been used in previous systematic reviews on the prevention of perioperative shivering.

Some limitations in our study should be considered when interpreting our outcomes. First, the main limitation of our study was that we only included RCTs published in English and excluded unpublished studies and studies only published as abstract, which contributed to publication bias in our study. Second, although interstudy statistical heterogeneity was not considerable, there was obvious clinical heterogeneity among the included studies, such as variation in 5-HT_3RAs, population, type of anesthesia, dose of 5-HT_3RAs, route and time of administration, the assessment methods of perioperative shivering, surgical intervention, and so on. It is controversial to combine the results of different protocols and various interventions in a pooled RR estimate because of the risk of trial heterogeneity. Third, there were no included studies that had low risk of bias across all domains, and GradePro was used to evaluate the strength of evidence about our primary outcome. Evidence was low for the

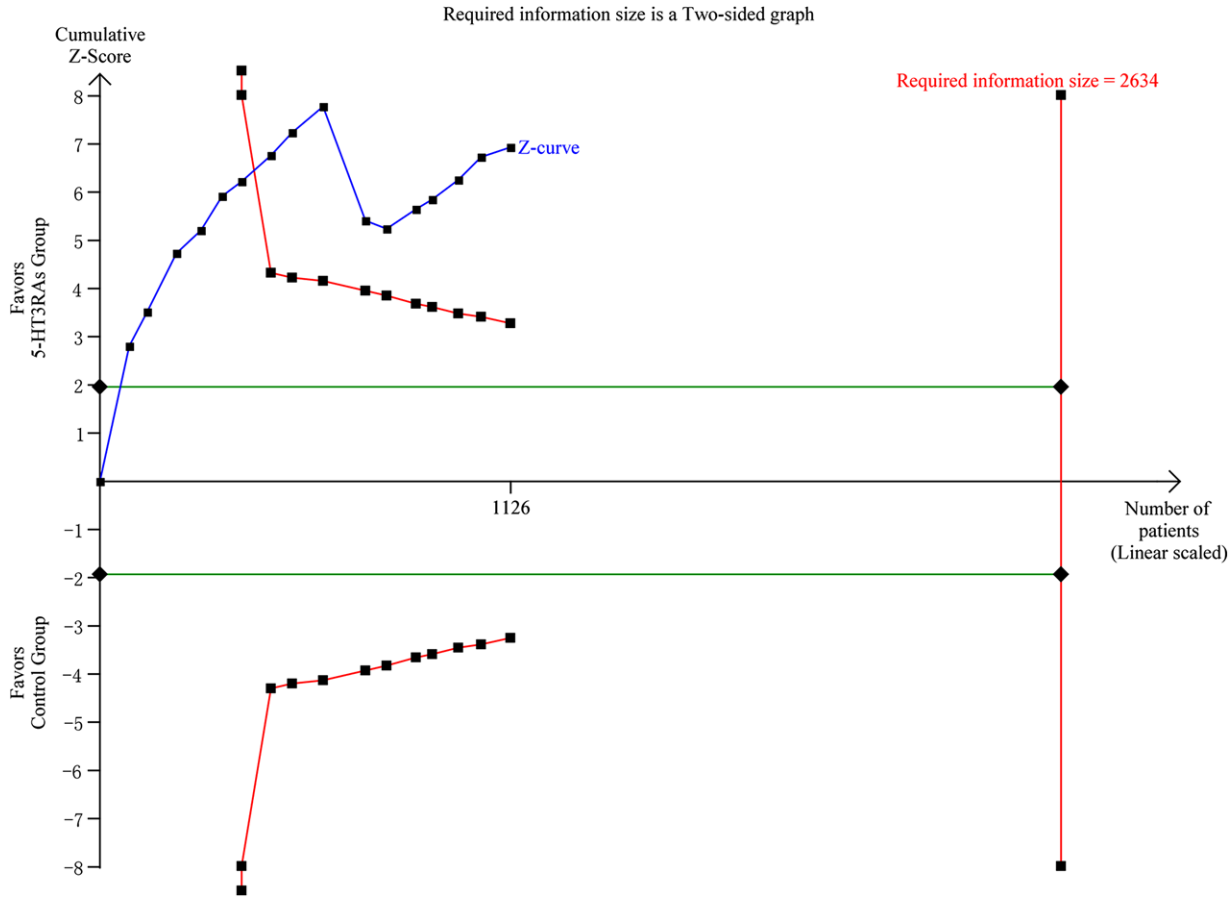

Figure 6. Trial sequential analysis of the preventive efficacy of 5-HT3RAs on perioperative shivering. 5-HT_3RAs, 5-hydroxytryptamine$_3$ receptor antagonists; perioperative shivering.

incidence perioperative shivering, indicating that more well-designed and high-quality RCTs are needed in the future. Finally, we did not register this study in a clinical trials registry.

Conclusions

Although our conventional meta-analysis demonstrated that 5-HT_3 receptor antagonists can prevent perioperative shivering in adults aged 18 years or older under general and neuraxial anesthesia, it should be interpreted carefully, as this evidence was not confirmed in trial sequential analysis. Therefore, more high-quality randomized, controlled trials with larger sample size are still required to draw a definite conclusion about the preventive efficacy of 5-HT_3RAs on perioperative shivering in the future.

Declaration of Conflicting Interests

None.

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Supporting Information

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