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5-HT$_3$ receptor antagonists for the prevention of perioperative shivering undergoing spinal anaesthesia: a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Objective Perioperative shivering (POS) is a common complication in patients undergoing spinal anaesthesia. The present study investigated the efficacy of 5-HT$_3$ receptor antagonists in preventing POS following spinal anaesthesia.

Design Systematic review and meta-analysis.

Data sources Pubmed, Embase, the Web of Science and Cochrane Library were searched from database establishment on 31 July 2019.

Eligibility criteria Randomised controlled trials that reported the effects of 5-HT$_3$ receptor antagonists in the prevention of POS in patients after spinal anaesthesia.

Data extraction and synthesis Two reviewers independently extracted data. The primary outcome of the present study was the incidence of POS. The risk of bias for the included studies was assessed according to the Cochrane Handbook. The quality of primary outcome was evaluated by Grading of Recommendations Assessment, Development and Evaluation. Trial sequential analysis for the primary outcome was performed to reduce the type 1 error caused by repeated meta-analysis and the required information size was calculated.

Results A total of 13 randomised controlled trials consisting of 1139 patients were included. The overall incidence of POS was significantly lower in the 5-HT$_3$ receptor antagonists group (risk ratio 0.31; 95% CI 0.26 to 0.38; p<0.01; I^2=0%). Subgroup analysis for different types of 5-HT$_3$ receptor antagonists and timing of administration produced similar results. Also, patients had a lower incidence of postoperative nausea and vomiting after administrating 5-HT3 receptor antagonists. No statistically significant differences in drug-related adverse effects were observed. Grading of Recommendations Assessment, Development and Evaluation revealed a high level of evidence. The cumulative z-curve crossed the trial sequential monitoring boundary.

Conclusions The present study revealed that prophylactic 5-HT$_3$ receptor antagonists were an effective measure for reducing the incidence of POS in patients after spinal anaesthesia. However, further studies investigating the different types of surgeries are required.

PROSPERO registration number CRD42019148191.

Strengths and limitations of this study

- ► This systematic review and meta-analysis assessed the effectiveness of 5-HT$_3$ receptor antagonists for preventing perioperative shivering and was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.
- ► Grading of Recommendations Assessment, Development and Evaluation was performed to evaluate the quality of the evidence.
- ► We conducted trial sequential analysis for the primary outcome to reduce the type 1 error.
- ► There was a lack of subgroup analysis for different types of surgery.

INTRODUCTION

Perioperative shivering (POS) is a common complication in patients undergoing spinal anaesthesia and has a reported incidence of up to 77.5%.[1] Although shivering is a protective reflex to increase the core temperature by the involuntary contraction of muscles, it also leads to adverse effects such as increasing oxygen consumption and affecting wound healing.[2 3] Unlike general anaesthesia, patients undergoing spinal anaesthesia remain awake during the surgery, and shivering is therefore more likely to cause discomfort in such patients. In addition, severe shivering may affect the procedure itself. The mechanisms of POS have not been fully elucidated. Eberhart *et al* postulated that shivering is more likely to occur in children, hypothermic states and long surgical procedures.[4] Various pharmacological interventions have been revealed to prevent POS, including dexmedetomidine,[5] meperidine[6] and opioids.[7] However, these agents are associated with side effects such as hypotension, constipation, respiratory depression and postoperative nausea and vomiting (PONV).

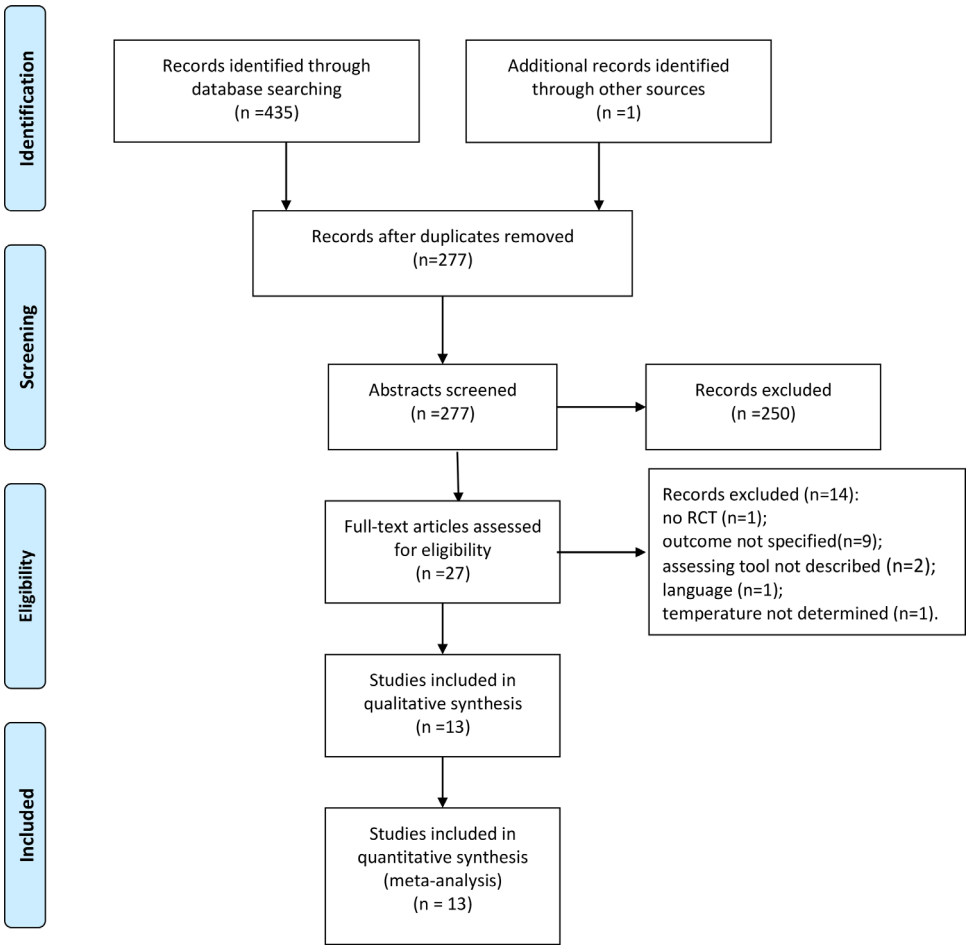

Figure 1 Diagram of the review process. RCT, randomised controlled trial.

Several studies have reported that preoperative 5-HT_3 receptor antagonists effectively prevent POS after spinal anaesthesia.[8–10] However, Rashad and Farmawy did not report any statistically significant differences in the occurrence of shivering between patients administered prophylactic 5-HT_3 receptor antagonists and controls.[11] Previous meta-analyses[12 13] revealed that 5-HT_3 receptor antagonists prevented POS; however, these studies investigated both general and spinal anaesthesia. Furthermore, the aforementioned studies were limited by a small sample size. Therefore, the present meta-analysis was performed to evaluate the role of 5-HT_3 receptor antagonists in the prevention of POS after spinal anaesthesia.

MATERIALS AND METHODS

The present systematic review and meta-analysis was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[14]

Systematic literature search

Two independent investigators (LHF and YXZ) searched Pubmed, Embase, the Cochrane Library and Web of Science to identify eligible randomised controlled trials (RCTs) from database establishment on 31 July 2019. The search was restricted to articles published in the English language. Additionally, references of the included studies, medical textbooks and clinical guidelines were retrieved manually. The corresponding authors of the studies were contacted to obtain important information that was not available during retrieval. RCTs that reported the incidence of shivering after the administration of 5-HT_3 receptor antagonists compared with placebo were retrieved. The search strategy of Pubmed was reported in Supplement Digital Content.

Selection criteria and data extraction

Studies meeting the following criteria were included: (1) population: patients undergoing spinal anaesthesia, (2) intervention: 5-HT_3 receptor antagonists as a POS prophylactic agent, (3) comparison: the comparison that 5-HT_3 receptor antagonists verse placebo was investigated, (4) outcome: evaluated the effectiveness of 5-HT_3 receptor antagonists for POS and (5) study design: RCT. The exclusion criteria included (1) other type of anaesthesia, (2) lack of the tool required for assessing POS and (3) lack of temperature monitoring. Two reviewers (LHF and YXZ) independently extracted the following items from the studies: name of the first author, year of publication, age of patients, surgery type, sample size, anaesthetic techniques, timing of medication, assessment tools and outcomes. Discrepancies were resolved by a third reviewer (ZXY).

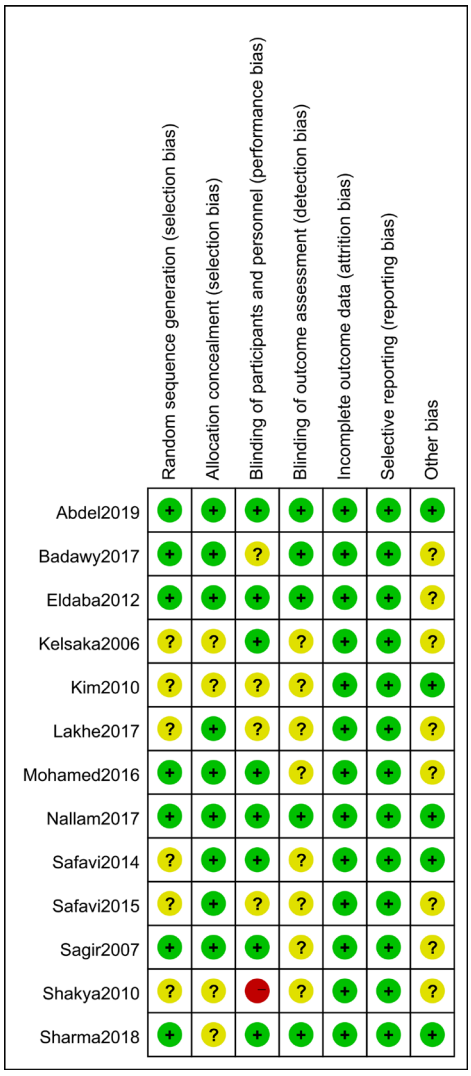

Figure 2 The summary of risk of bias.

Risk of bias assessment.

The risk of bias for the included studies was assessed according to the Cochrane Handbook. The criteria were as follows: random sequence generation, allocation concealment, double blinding, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Each trial was classified as low, high or unclear. Furthermore, two reviewers independently assessed the trials, and discrepancies were resolved by a third reviewer (ZXY).

Methodological quality appraisal.

The quality of primary outcomes was evaluated by Grading of Recommendations Assessment, Development and Evaluation (GRADE)[15 16] according to the following criteria: study design, risk of bias, rating inconsistency in results, rating indirectness of evidence, imprecision and others. The evidence quality was classified as high, moderate, low or very low. Finally, the overall evaluations were included in a summary of findings table.

Primary and secondary outcomes

The primary outcome of the present study was the incidence of POS. The occurrence of shivering was defined by the author of each study. The incidence of adverse effects, including PONV, hypotension and bradycardia, were secondary outcomes.

Statistical analysis

The meta-analysis was conducted using Review Manager (V.5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and Stata V.12.0 (StataCorp LP, USA). For dichotomous outcomes, a pooled risk ratio (RR) and 95% CIs were calculated. $p<0.05$ was considered to indicate a statistically significant difference. The heterogeneity of the trials was assessed using the I^2 index. High heterogeneity most likely existed due to clinical and methodological factors; therefore, the random effect model was applied even in cases of low I^2 values. Subgroup analysis was performed according to the different types of 5-HT_3 receptor antagonists and timing of administration. Funnel plots and the Begg test were used to evaluate publication bias. Trial sequential analysis (TSA) for the primary outcome was performed to reduce the type 1 error caused by repeated meta-analysis and the required information size (RIS) was calculated. The risk of type 1 error was maintained at 5% with a power of 80%. TSA was performed using Trial Sequential Analysis Viewer (V.0.9.5.10 Beta. Copenhagen: Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, 2016). In addition, sensitivity analysis was performed by sequentially deleting trials to check the stability of the primary outcome.

Patient and public involvement

No patient and public were involved in this study.

RESULTS

Search results

The literature screening process is presented in figure 1. Initially, 436 relevant studies were identified using the aforementioned search strategy. After excluding duplicated studies, 277 studies were screened based on their abstracts. A total of 27 full-text articles were subsequently assessed for eligibility.[1 8–11 17–38] Finally, 13 studies were included in the present meta-analysis.[1 20–31] There were no disagreements among the authors as to whether the aforementioned studies should be included in the present meta-analysis.

Assessment of quality and bias

A total of seven of the included studies[1 20 21 25 26 29 31] clearly described the method of random sequence generation, while nine of the trials[1 20 21 24–29] reported allocation concealment. Double blinding of the participants and personnel was mentioned in eight studies.[1 21 22 25 26 28 29 31] Only five studies reported that the assessors were blinded.[1 20 21 26 31] No selective reporting and attrition bias were reported. The summary of risk of bias is shown in figure 2.

Study characteristics

The detailed information of the studies included in the present meta-analysis is presented in table 1. The

Table 1 The details of included studies

Studies	Age (year)	Sample size (n)	Type of surgery	Anaesthetic regimen	Interventions	Timing of medication	Assessment tool	Outcomes
Abdel-Ghaffar and Moeen[1]	20–40	222	Caesarean section	8–10 mg hyperbaric bupivacaine	G 1 mg vs G 0.7 mg vs saline	Before SA	5-point scale	POS PONV
Badawy and Mokhtar[20]	20–38	75	Caesarean section	12.5 mg hyperbaric bupivacaine	O 8 mg vs saline	Before SA	5-point scale	POS PONV
Eldaba and Amr[21]	2–5	80	Lower limb surgery	0.5 mg/kg hyperbaric bupivacaine	G 10 ug/kg vs saline	Before SA	4-point scale	POS
Kelsaka *et al* [22]	20–60	50	Orthopaedic surgery	12.5 mg hyperbaric bupivacaine	O 8 mg vs saline	Before SA	Pectoralis major muscles for fasciculations > 0 s	POS hypotension bradycardia
Kim *et al*[23]	18–62	52	Knee arthroscopy	11 mg hyperbaric bupivacaine	R 0.3 mg vs saline	Before SA	Pectoralis major muscles for fasciculations > 10 s	POS
Lakhe *et al*[24]	18–65	60	Gynaecological orthopaedic surgery	15 mg hyperbaric bupivacaine	O 4 mg vs saline	After SA	5-point scale	POS
Mohamed[25]	18–65	160	Vascular plastic andrology orthopaedics urological gynaecology	15 mg hyperbaric bupivacaine	G 40 µg/kg vs saline	Before SA	5-point scale	POS PONV hypotension
Nallam *et al*[26]	22–32	80	Caesarean section	12.5 mg hyperbaric bupivacaine	O 8 mg vs saline	Before SA	5-point scale	POS PONV
Safavi *et al*[27]	18–65	60	Orthopaedic surgery	15 mg hyperbaric bupivacaine	O 8 mg vs saline	After SA	5-point scale	POS PONV bradycardia hypotension
Safavi *et al*[28]	16–65	80	Orthopaedic surgery	0.5% hyperbaric bupivacaine	O 8 mg vs saline	Before SA	5-point scale	POS bradycardia hypotension
Sagir *et al*[29]	18–65	160	Ureterorenoscopy	15 mg hyperbaric bupivacaine	G 3 mg vs saline	After SA	5-point scale	POS hypotension
Shakya *et al*[30]	Adult patients	80	Lower abdominal surgical	15 mg hyperbaric bupivacaine	O 4 mg vs saline	After SA	5-point scale	POS hypotension
Sharma *et al*[31]	20–60	70	Various elective surgeries	10–15 mg hyperbaric bupivacaine	O 8 mg vs saline	Before SA	5-point scale	POS PONV hypotension

G, granisetron; O, ondansetron; PONV, postoperative nausea and vomiting; POS, perioperative shivering; R, ramosetron; SA, spinal anaesthesia.

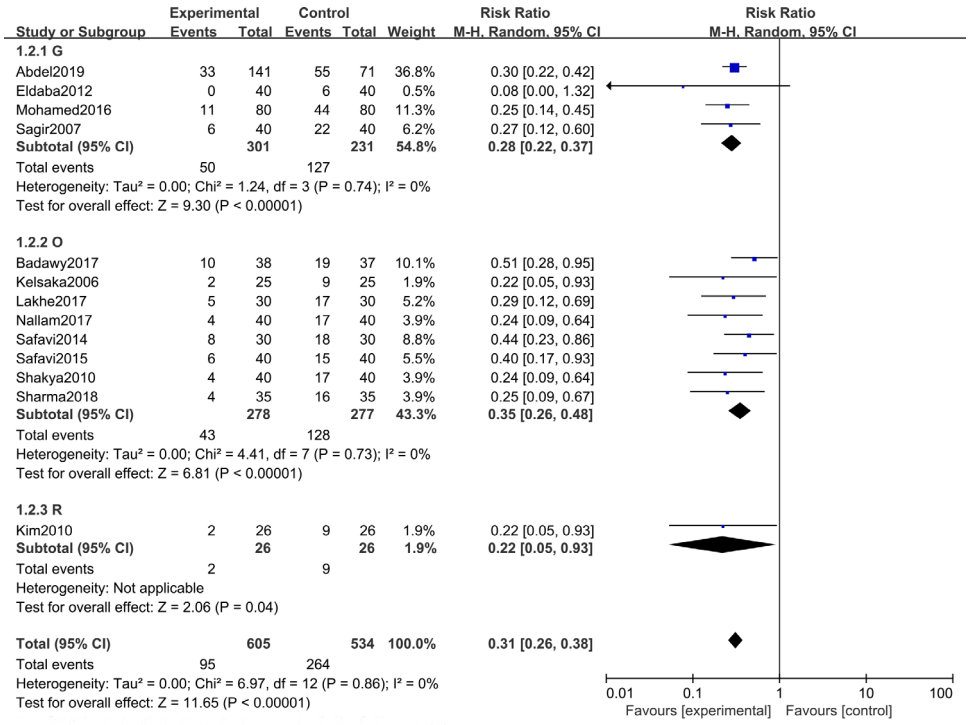

Figure 3 Forest plot of the meta-analysis of the incidence of perioperative shivering between 5-HT3 RAs and control groups. 1.2.1 Granisetron; 1.2.2 Ondansetron;1.2.3 Ramosetron. 5-HT3 RAs, 5-HT3 receptor antagonists; M-H, Mantel-Haenszel.

patients in one trial were described as adults,[30] while the other trials included patients with an age range of 2–65 years. Hyperbaric bupivacaine for spinal anaesthesia was administered in all the RCTs. 5-HT_3 receptor antagonists were administered before or after spinal anaesthesia. The 5-HT_3 receptor antagonists administered included ondansetron, ramosetron and granisetron. A 5-point scale was used for assessing shivering in 10 studies,[1 20 24–31] fasciculations in the pectoralis major muscles were used in two studies[22 23] and a 4-point scale was used in another trial.[21]

Primary outcome

The 13 RCTs investigated in the present study included 605 patients who received 5-HT_3 receptor antagonists and 534 who received a placebo. The efficacy of 5-HT_3

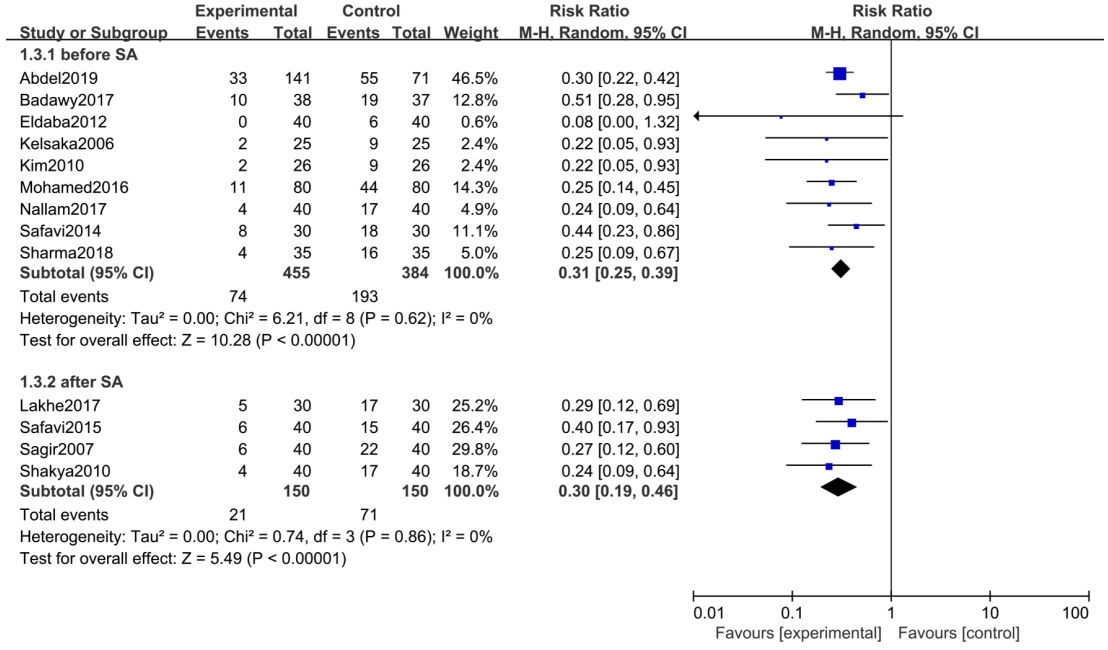

Figure 4 The subgroup analysis of perioperative shivering incidence with different medication timing. M-H, Mantel-Haenszel; SA, spinal anaesthesia.

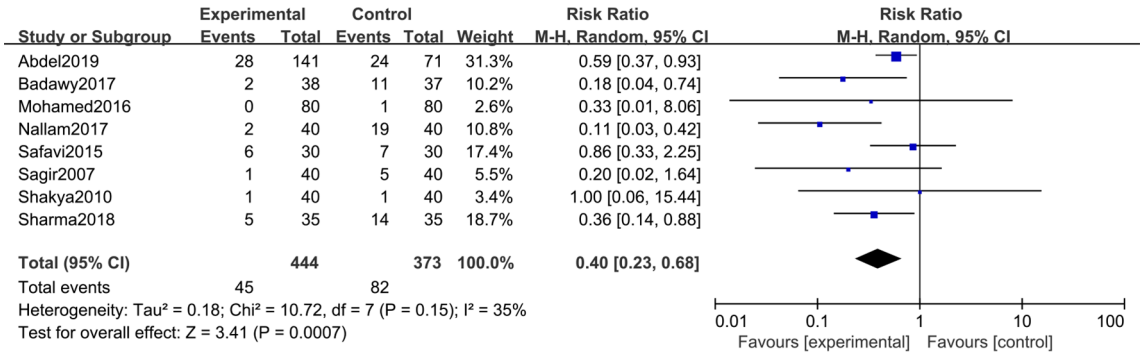

Figure 5 Forest plot of the meta-analysis of the incidence of postoperative nausea and vomiting between 5-HT3 receptor antagonist and control groups. M-H, Mantel-Haenszel; PONV, postoperative nausea and vomiting.

receptor antagonists in preventing POS was compared with that of a placebo in all studies. In the study by Abdel-Ghaffar and Moeen,[1] ondansetron was compared at two different doses (0.7 mg and 1.0 mg), and both groups were included in the 5-HT_3 receptor antagonists group for the purpose of the present meta-analysis. The meta-analysis showed a lower incidence of POS in patients who received 5-HT_3 receptor antagonists (RR 0.31; 95% CI 0.26 to 0.38; p<0.01; I^2=0%; figure 3).

Subgroup analysis

Subgroup analysis for the different types of 5-HT_3 receptor antagonists produced similar results. The incidence of POS was significantly reduced in patients treated with ondansetron (RR 0.35; 95% CI 0.26 to 0.48; p<0.01; I^2=0%), granisetron (RR 0.28; 95% CI 0.22 to 0.37; p<0.01; I^2=0%) or ramosetron (RR 0.22; 95% CI 0.05 to 0.93; p<0.01). Further subgroup analysis was performed based on the different timing of medication. The results revealed that patients who received 5-HT_3 receptor antagonists before (RR 0.31; 95% CI 0.25 to 0.39; p<0.01; I^2=0%; figure 4)[1 20–23 25 26 28 31] or after spinal anaesthesia (RR 0.30; 95% CI 0.19 to 0.46; p<0.01; I^2=0%) exhibited a decreased risk of POS.[24 27 29 30]

Secondary outcomes

A total of eight trials reported PONV.[1 20 25–27 29–31] The forest plot revealed a lower incidence of PONV in the 5-HT_3 receptor antagonists group (RR 0.40; 95% CI 0.23 to 0.68; p<0.01; I^2=35%; figure 5). Drug-related adverse effects that have been reported in the trials include hypotension and bradycardia. Hypotension was mentioned in 10 RCTs,[1 22 23 25–31] although the experimental group tended to increase hypotension, no significantly statistical difference was observed (RR 0.69; 95% CI 0.46 to 1.04; p=0.08; I^2=47%; figure 6). Bradycardia was recorded in three studies,[22 27 28] and meta-analysis revealed no significant difference between patients who received 5-HT_3 receptor antagonists or a placebo (RR 1.18; 95% CI 0.61 to 2.25; p=0.63; I^2=0%; figure 7).

Trial sequential analysisTSA

TSA revealed that the number of patients investigated had reached the RIS of 759. The cumulative z-curve crossed the trial sequential monitoring boundary (figure 8), suggesting that adequate data were available to confirm the POS-preventive effect of 5-HT_3 receptor antagonists.

Sensitivity analysis and publication bias

Sensitivity analysis was performed for the primary outcome and the effect estimate remained unchanged, which indicated the robustness of the pooled results (online supplemental figure 1). Although the funnel plot was asymmetrically distributed (online supplemental figure 2), the Begg test revealed no potential publication bias (0.259).

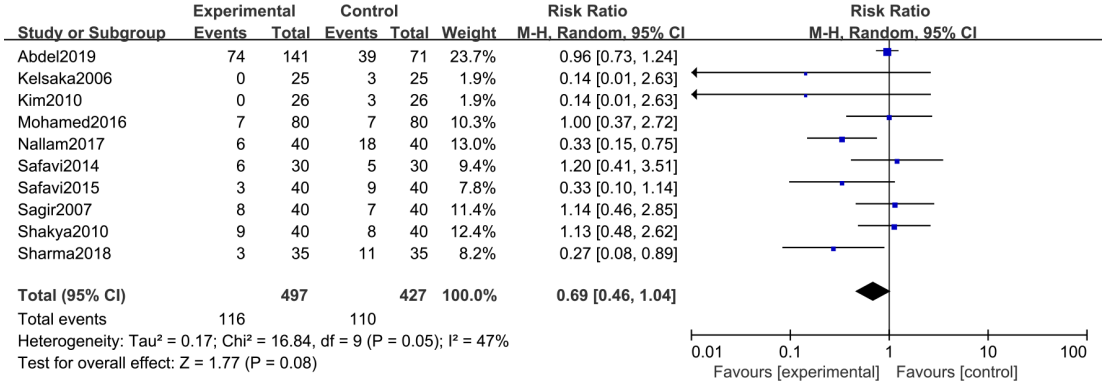

Figure 6 Forest plot of the meta-analysis of the incidence of hypotension between 5-HT3 receptor antagonist and control groups. M-H, Mantel-Haenszel.

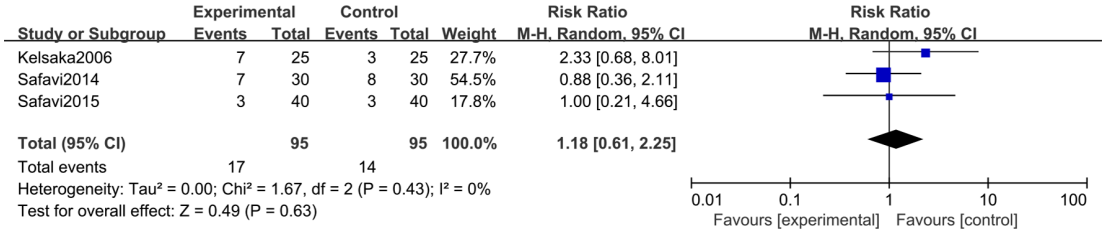

Figure 7 Forest plot of the meta-analysis of the incidence of bradycardia between 5-HT3 receptor antagonist and control groups. M-H, Mantel-Haenszel.

GRADE evaluation

All the studies were RCTs, and the I^2 was 0% in the primary outcome. As rating inconsistency in the results and rating indirectness of evidence were 'not serious'. TSA suggested adequate data to support the prophylactic effect, and imprecision of evidence was graded to 'not serious'. No potential publication bias was reported. The overall GRADE score for the primary outcomes was high (online supplemental table).

DISCUSSION

The present meta-analysis was performed to explore the prophylactic effect of 5-HT_3 receptor antagonists on POS following spinal anaesthesia. The results demonstrated that the prophylactic use of 5-HT_3 receptor antagonists significantly reduced the incidence of POS (GRADE; high) and PONV compared with placebo. Subgroup analysis for different types of 5-HT_3 receptor antagonists and timing of administration revealed similar results. No statistically significant differences in adverse effects were observed although the experimental group tended to increase hypotension. TSA demonstrated that data of 5-HT_3 receptor antagonists for preventing POS were sufficient.

Subgroup analysis was performed for different types of 5-HT_3 receptor antagonists and timing of administration. However, the type of surgery was not analysed as one study did not specify the type of surgery performed.[31] The corresponding author was contacted for further clarification, however, no response was received.

The mechanism of shivering after spinal anaesthesia remains unclear. A study investigating seven healthy women suggested that spinal anaesthesia significantly decreased the threshold for shivering.[39] During spinal anaesthesia, vasodilatation and redistribution of the core temperature are restricted to the lower body below the level of the block, while vasoconstriction and shivering are restricted to the upper body.[40] Voronova *et al*[41] suggested that the activation of central 5-HT3 receptors is more effective in hypothermia induction due to a marked decrease in thermogenesis and increased heat loss, indicating that 5-HT3-associated pathways may play an important role in controlling shivering. The mechanism of 5-HT3 receptor antagonists to prevent

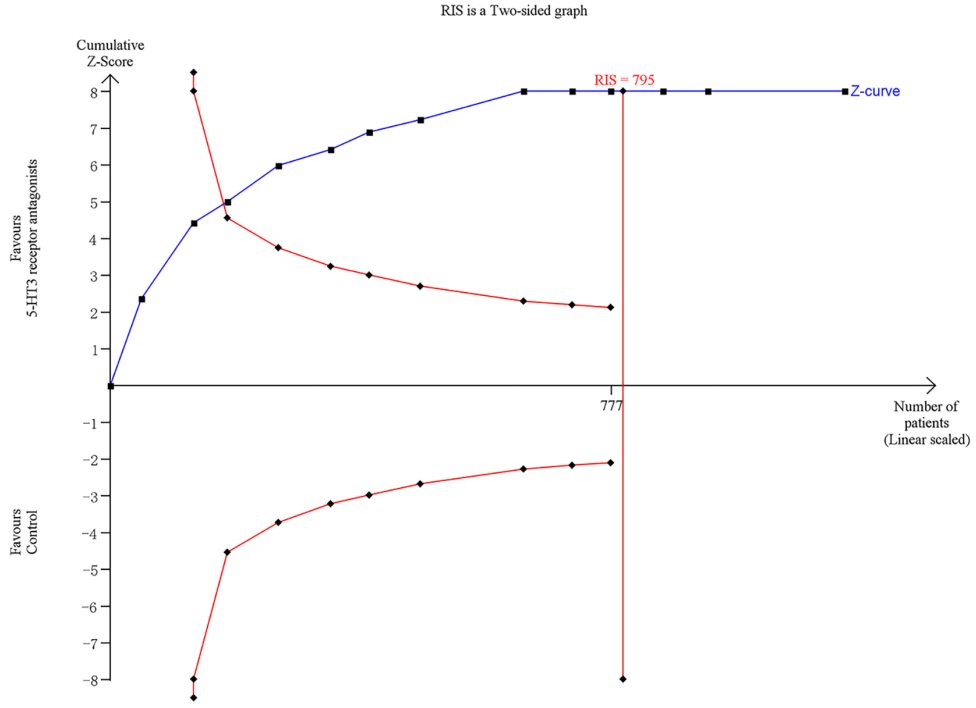

Figure 8 Trial sequential analysis of the preventive efficacy of 5-HT3RAs on POS. 5-HT3RAs, 5-HT_3 receptor antagonists; POS, perioperative shivering; RIS, required information size.

chills might be related to the inhibition of neurotransmission required for hypothalamic temperature regulation .[42]

Various types of 5-HT_3 receptor antagonists have been administered to prevent POS. Previous meta-analysis focused on 5-HT_3 receptor antagonists for the prevention of POS.[12 13] However, this study differed to the present meta-analysis. First, the previous studies included trials investigating both general and spinal anaesthesia. Second, the present meta-analysis included a trial that reported data in children.[12] Third, Zhou *et al* had not performed subgroup analysis for different kinds of 5-HT_3 receptor antagonists.[13] In addition, new RCTs were published over the past few years. Therefore, an updated meta-analysis was required.

The I^2 index was low in the majority of the outcomes, which indicated that there was no substantial statistical heterogeneity in the trials. However, varying doses of bupivacaine, surgery types, different timings of medication, different assessment tools, the experience of the surgeon and premedication all led to a potential high clinical heterogeneity in the present study. Therefore, random effect and subgroup analyses were performed to test the stability of the outcomes.

The results of our meta-analysis showed that 5-HT3 receptor antagonists can be recommended to prevent POS in patients after spinal anaesthesia, and the GRADE evaluation for this evidence was high. TSA demonstrated that the existing RCTs are sufficient to confirm the effectiveness of 5-HT3 receptor antagonists prevention, however, only five studies declared that the ratings were blinding, further, high-quality researches should pay more attention to the universality of the application for different types of surgeries.

LIMITATIONS

Several limitations in the present study should be acknowledged. First, only studies published in English were included in the meta-analysis, which potentially led to language bias. Second, certain studies did not mention the blinding of the assessor, allocation concealment or methods of randomisation, possibly resulting in selection and performance biases. Third, a subgroup analysis for different types of surgeries was not performed. Fourth, the present study does not yet have a registered protocol, and finally, publication bias was present.

CONCLUSION

In summary, the perioperative administration of 5-HT_3 receptor antagonists may be an effective measure for the prevention of POS in patients undergoing spinal anaesthesia. However, further studies investigating different types of surgeries are required.

Contributors Q-HS conceived and designed the review. H-FL and XZ performed the data extraction and preparation. H-FL and XZ contributed to the assessment of risk of bias. X-ZY contributed to resolve the disagreement. Q-HS and X-ZY conducted the data analysis. Q-HS and YL wrote the paper, which was critically reviewed and approved by all the authors. Q-HS and XZ had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Q-HS is the guarantor of the study.

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Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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