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5-HT3 receptor antagonists for the prevention of postoperative shivering: a meta-analysis

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Abstract

Objective: We evaluated the efficacy of 5-HT3 receptor antagonists for the prevention of postoperative shivering.

Methods: We searched PubMed, the Cochrane Library, EMBASE and Web of Knowledge to find randomized controlled trials (RCT) of 5-HT3 receptor antagonists for the prevention of postoperative shivering. Two researchers independently screened studies, extracted data, and assessed quality in accordance with the inclusion and exclusion criteria, and then conducted a meta-analysis using RevMan 5.2.

Results: Ultimately, 14 RCTs that included 980 patients were included in the analysis. We found that: 1) the incidence of shivering was significantly lower in 5-HT3 groups than placebo groups (relative risk, [RR] = 0.48, 95% confidence interval [CI] 0.40 – 0.58); 2) there was no significant difference in the incidence of shivering between 5-HT3 groups and meperidine groups (RR = 0.89, 95% CI 0.60 – 1.34).

Conclusion: 5-HT3 receptor antagonists appear to prevent postoperative shivering, with a broadly comparable efficacy to meperidine.

Keywords

HT3 receptor antagonists, shivering, meta-analysis, randomized controlled trial, meperidine, anesthesia

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Introduction

Postoperative shivering reportedly complicates emergence from anaesthesia in 5% to 60% of cases.[1] Postoperative shivering can provoke elevation in cellular metabolism, oxygen consumption and carbon dioxide production; hypoxaemia and lactic acidosis may occur in severe cases. Physical and

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pharmacologic methods have been used to prevent postoperative shivering, with variable success. Opioid and non-opioid drugs are often used to treat postoperative shivering, but they have potential side effects, including hypotension, hypertension, sedation, respiratory depression, nausea and vomiting.[2,3] More recently, 5-HT3 receptor antagonists have emerged as a means of preventing postoperative shivering. We undertook a meta-analysis of controlled clinical trials of 5-HT3 receptor antagonists for the prevention of postoperative shivering to assess their efficacy.

Materials & methods

Inclusion criteria

We identified randomized controlled trials (RCTs) of patients undergoing elective surgery under general or spinal anaesthesia. The intervention in the experimental group was an intravenously administered 5-HT3 receptor antagonist; the control groups included an intravenous injection of placebo (physiologic saline), or meperidine. The main outcome indicator in eligible studies was the occurrence of postoperative shivering.

Exclusion criteria

We excluded studies in which 5-HT3 antagonists were administered in combination with other drugs to prevent shivering, those with incomplete information or data, and articles for which we could not obtain the full text.

Search strategy

We searched articles published from inception to May 2016 in the Cochrane Library, PubMed, EMBASE and Web of Knowledge. A combination of subject headings with keyword searching was employed and document types were not restricted. English search terms included ''ondansetron'', ''5-HT3receptor antagonists'', ''Łpalonosetron'', ''granisetron'', ''tropisetron'', ''postoperative shivering'', ''postanaesthetic shivering'', ''Łshivering'' and ''anesthesia''. *et cetera*.

Literature screening and quality evaluation

Two researchers independently screened studies and extracted data, then cross-checked with each other. The two resolved disagreements by discussion or consulted a third party when consensus could not be reached. We evaluated methodologic quality of the RCTs identified using a modified Jadad scale.[4] Evaluation included randomization, allocation concealment, and blinding of implementers and participants.

Data extraction

Two researchers independently extracted data using tables designed in advance, and then cross-checked with each other. The two resolved disagreements by discussion or consulted a third party when consensus could not be reached. Extracted data included: names of the researchers, year of publication, study design, interventions, control measures, outcome indicators, target events and the overall sample size.

Statistical methods

Statistical analysis was conducted via using the RevMan 5.2 program, provided by the Cochrane Collaboration (London, UK). First, heterogeneity was tested using the chi-squared and I^2 tests: when there was no heterogeneity ($P > 0.1$ and $I^2 < 50\%$, respectively), we adopted a fixed-effects model. When we detected heterogeneity, we employed a random-effects model and we subsequently made an assessment of stability by undertaking further meta-analyses while eliminating studies one by one. For continuous variables, the weighted mean difference

was used, and for enumeration data, relative risk (RR) was calculated. All effect sizes were represented by 95% confidence intervals (CI), and when $P < 0.05$, the results were considered statistically significant. We used funnel plots to establish whether there was publication bias.

Results

Search results

We identified 248 articles using our search strategy; 17 were selected for further screening against our inclusion and exclusion criteria after reading the titles and checking for duplicate publication. One was excluded as the full text was not available,[5] another because the 5-HT3 antagonist was administered in combination with other drugs[6] and another because the number of shivering patients was not provided.[7] Ultimately, 14 RCTs were included in the meta-analysis.[8–21] Figure 1 shows our literature screening process.

Characteristics of included studies

The included studies comprised 980 participants, 499 of whom were allocated to experimental groups and 481 to control groups. Cases included in the study are presented in Table 1.

Quality assessment of included studies

The 14 included studies all employed a randomized group model. The implementation of the blinding method was not described in three studies.[8,15,16] None of the studies was assessed to exhibit selective reporting (Table 1).

Meta-analysis results

All studies reported the incidence of shivering, but each study defined shivering differently and the durations of observation for shivering were inconsistent. We elected to analyse the total incidence of shivering only, and did not seek to quantify the extent of shivering.

The incidence of postoperative shivering. All studies compared the incidence of postoperative shivering. No statistical heterogeneity ($P = 0.20$, $I^2 = 24\%$) was found

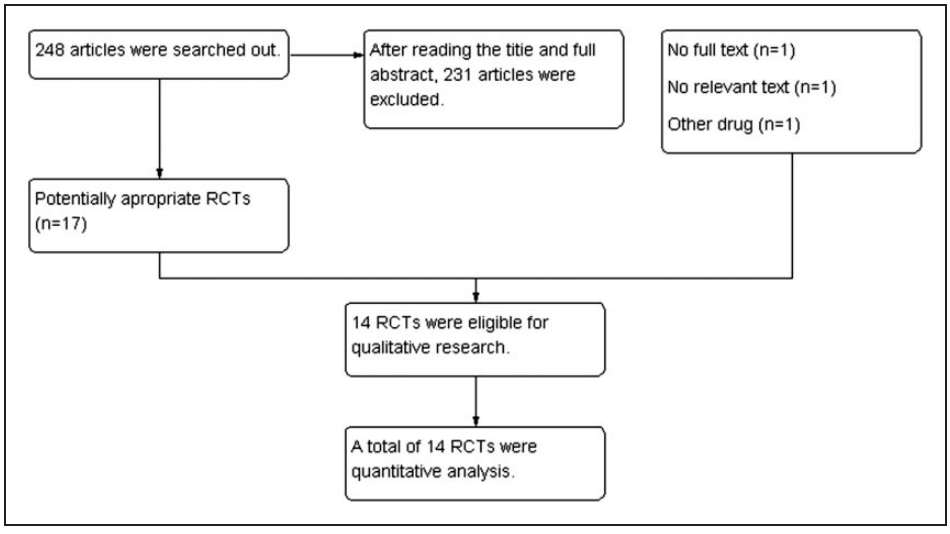

Figure 1. Study flow diagram.

Table 1. Characteristics of the studies included in the meta-analysis.

Author (publication year)	Headcount	Grouping	Anaesthetic technique	Jadad core
Kelsaka (2006)	75	ondansetron 8 mg meperidine 0.4 mg/kg normal saline	spinal anaesthesia	5
Teymourian (2015)	80	ondansetron 4 mg normal saline	general anaesthesia	5
Asl (2011)	90	ondansetron 4 mg meperidine 0.4 mg/kg normal saline	general anaesthesia	4
Powell (2000)	82	ondansetron 4 mg ondansetron 8 mg normal saline	general anaesthesia	6
Lin (2016)	59	ondansetron 4 mg normal saline	general anaesthesia	4
Safavi (2014)	120	ondansetron 8 mg meperidine 0.2 mg/kg normal saline	spinal anaesthesia	5
Browning (2013)	118	ondansetron 8 mg normal saline	combined spinal-epidural anaesthesia	6
Abdollahi (2012)	90	ondansetron 8 mg meperidine 0.4 mg/kg normal saline	general anaesthesia	5
Sagir (2007)	160	granisetron 3 mg ketamine 0.5 mg normal saline ketamine 0.25 mg + granisetron 1.5 mg	spinal anesthesia	5
Sajedi (2008)	132	40 μg/kg granisetron 0.4 mg/kg meperidine 1 mg/kg tramadol normal saline	general anaesthesia	5
Eldaba (2012)	80	10 μg/kg granisetron normal saline	spinal anaesthesia	5
Iqbal (2009)	90	granisetron 40 μg/kg meperidine 25 mg normal saline	general anaesthesia	5
Jo (2013)	60	0.075 mg palonosetron normal saline	general anaesthesia	5
Jo (2016)	48	0.075 mg palonosetron normal saline	general anaesthesia	5

among 14 studies, therefore, a fixed effects model was applied to conduct the meta-analysis. The incidence of postoperative shivering was significantly lower in experimental groups than control groups ($RR = 0.48$, 95% CI 0.40 – 0.58, $P < 0.00001$; Figure 2). We identified heterogeneity in the studies of postoperative

Table 2. Results of subgroup meta-analysis by anaesthetic technique.

Group	No. of studies	Relative risk (95% confidence interval)	I^2 (%)	$P_{heterogeneity}$	Effect model
General	9	0.48 (0.38–0.60)	0	0.86	Fixed
Spinal	5	0.38 (0.18−0.82)	69	0.01	Random

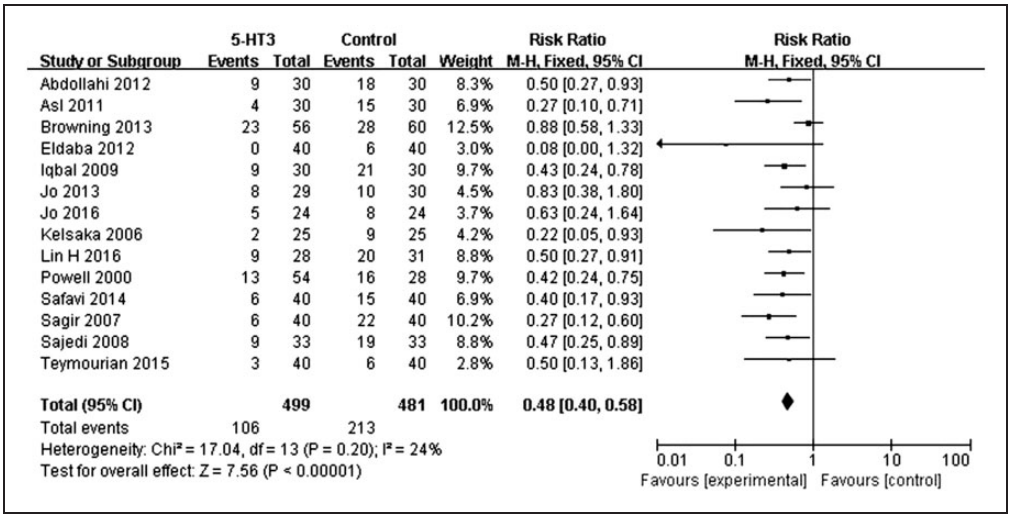

Figure 2. Pooled estimate of the 14 included studies.

shivering after spinal anaesthesia, but not those of general anaesthesia (Table 2). Subgroup meta-analysis by aesthetic technique, using random and fixed effects models, respectively, demonstrated that 5-HT3 receptor antagonists were associated with significant reductions in the risk of postoperative shivering in patients undergoing both modes of anaesthesia (Table 2).

Six studies, totalling 376 patients, compared 5-HT3 receptor antagonists with meperidine for postoperative shivering.[11,14,16,18,20] We identified an acceptable lack of heterogeneity between the studies ($P = 0.16$, $I^2 = 36\%$), so used a fixed effects model for meta-analysis. We found that no statistically significant difference between the incidence of shivering in the 5-HT3 receptor antagonist and meperidine groups (RR = 0.89, 95% CI 0.60–1.34, $P = 0.59$; Figure 3).

Sensitivity and funnel plot analysis

Funnel plot analysis indicated that the results were symmetrical, suggesting that there was no publication bias (Figure 4). After the complete meta-analysis, we undertook subsequent meta-analyses excluding studies one by one, and found that the results were consistent with those obtained before exclusion, implying that stability was satisfactory.

Discussion

This meta-analysis indicated that 5-HT3 receptor antagonists appear to prevent

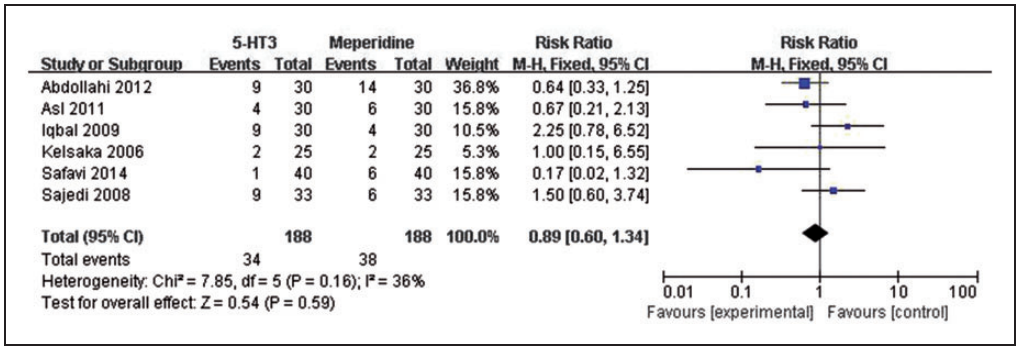

Figure 3. The anti-shivering effect of 5HT3 receptor antagonists compared with meperidine.

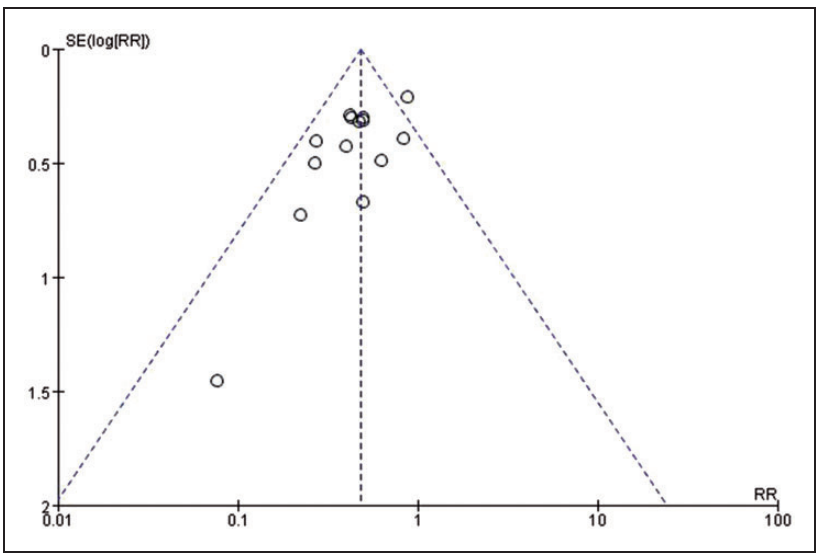

Figure 4. Funnel plot.

postoperative shivering, with a broadly comparable efficacy to meperidine. Shivering is a common complication of emergence from anaesthesia. Shivering is generally considered to be a thermoregulatory phenomenon, a physiologic response to lowering of core body temperature during anaesthesia. Nonetheless, heat preservation and administration of warmed fluids does not eliminate shivering.[22] Under spinal anaesthesia, shivering occurs as a thermoregulatory response to lowering of core body temperature and reductions in blood supply to the upper body. Thermoregulation is controlled by central nervous system neurotransmitters in the hypothalamus; the preoptic area of the hypothalamus releases 5-HT3 to activate heat production pathways, and thus increase body temperature. In mouse models, intravenous administration of 5-HT3 reportedly provokes vaso-dilation and shivering,[23] suggesting that 5-HT3-mediated pathways play an import-ant role in the control of postoperative shivering. 5-HT3 antagonists may

prevent postoperative shivering by inhibiting reuptake of 5-HT in the preoptic area.[1]

Shivering after general anaesthesia and after spinal anaesthesia may have different causes. General anaesthesia likely impairs central thermoregulation, while spinal anaesthesia impairs peripheral and central thermoregulation by increasing the inter-threshold range, increasing the sweating threshold, and reducing the shivering and vasoconstriction thresholds.[24] Core temperature reduction reportedly peaks 3 – 4 hours after induction of general anaesthesia, but no such peak occurs after spinal anaesthesia; vasoconstriction will occur when the core temperature reaches the vasoconstriction threshold in general anaesthesia, but not in spinal anaesthesia.[25] Interestingly, despite the potential differences in mechanisms, our meta-analysis found that 5-HT3 antagonists effectively prevent postoperative shivering after general anaesthesia and spinal anaesthesia. We found no significant difference between the efficacy of 5-HT3 antagonists and meperidine for the prevention of shivering. However, our study had some limitations. First, only 14 RCTs were included. Second, a variety of 5-HT3 receptor antagonists were used at different doses and times in the experimental groups. These factors may have introduced bias and affected the reliability of our results. Consequently, more rigorously designed, detailed, high-quality RCTs are needed to verify our conclusions.

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Declaration of conflicting interests

The Authors declare that there is no conflict of interest.

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