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

Chengmao Zhou¹², Yu Zhu², Zhen Liu¹ and Lin Ruan¹,*

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

Date received: 24 June 2016; accepted: 19 August 2016

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

¹Department of Anesthesiology, Affiliated Tumor Hospital of Guangxi Medical University, Nanning 530021, China
²Department of Surgery, Zhaoqing Medical College, Zhaoqing 526000, China

Corresponding author:
Lin Ruan, Department of Anesthesiology, Affiliated Tumor Hospital of Guangxi Medical University, River Road No. 71, Nanning, Guangxi, China.
Email: RuanLin187@163.com

Creative Commons CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
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. 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-HT3 receptor antagonists”, “Lpalonosetron”, “granisetron”, “tropisetron”, “postoperative shivering”, “postanaesthetic shivering”, “Lshivering” 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. 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 I² tests: when there was no heterogeneity (P > 0.1 and I² < 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, another because the 5-HT3 antagonist was administered in combination with other drugs and another because the number of shivering patients was not provided. Ultimately, 14 RCTs were included in the meta-analysis. 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. 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.
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 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 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 anaesthesia | 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          |
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.\textsuperscript{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

| 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       |

**Table 2. Results of subgroup meta-analysis by anaesthetic technique.**
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.\textsuperscript{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,\textsuperscript{23} suggesting that 5-HT3-mediated pathways play an important role in the control of postoperative shivering. 5-HT3 antagonists may
prevent postoperative shivering by inhibiting reuptake of 5-HT in the preoptic area.\textsuperscript{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 interthreshold range, increasing the sweating threshold, and reducing the shivering and vasoconstriction thresholds.\textsuperscript{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.\textsuperscript{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.

Acknowledgements
The authors are grateful to You-Jing Luo, MD for her extensive support throughout the drafting and approval of the article, which substantially improved the quality of the manuscript.

Declaration of conflicting interests
The Authors declare that there is no conflict of interest.

Funding
This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

References
1. Sagir O, Gulhas N, Toprak H, et al. Control of shivering during regional anaesthesia: prophylactic ketamine and granisetron. \textit{Acta Anaesthesiol Scand} 2007; 51: 44–49.
2. Horn EP, Standl T, Sessler DI, et al. Physostigmine prevents postanesthetic shivering as does meperidine or clonidine. \textit{Anesthesiology} 1998; 88: 108–113.
3. Kayalha H, Roushanfekr MG and Ahmadi M. The comparison of ondansetron and meperidine to prevent shivering after anesthesia in patients undergoing lower limb orthopedic surgeries with general anesthesia. \textit{Journal of Zanjan University of Medical Sciences and Health Services} 2014; 22: 14–22.
4. Jadad, A. R. et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? \textit{Control Clin Trials} 1996; 17: 1–12.
5. Mei W, Li M, Yu Y, et al. Tropisetron alleviate early post-operative pain after gynecological laparoscopy in sevoflurane based general anaesthesia: a randomized, parallel-group, factorial study. \textit{Eur J Pain} 2014; 18: 238–248.
6. Komatsu R, Orhan-Sungur M, In J, et al. Ondansetron does not reduce the shivering threshold in healthy volunteers. \textit{Br J Anaesth} 2006; 96: 732–737.
7. Lin H, Wang J, Jin Z, et al. Preventative effect of ondansetron on postanesthesia shivering in children undergoing caudal anesthesia: a randomized double-blinded clinical trial. \textit{Pediatr Res} 2016; 79: 96–99.
8. Jo YY, Kim YB, Lee D, et al. Implications of palonosetron in elderly patients undergoing laparoscopic cholecystectomy with respect to its anti-shivering effect. \textit{Aging Clin Exp Res} 2016; 28: 83–88.
9. Teymourian H, Mohajerani SA, Bagheri P, et al. Effect of ondansetron on postoperative shivering after craniotomy. \textit{World neurosurg} 2015; 84: 1923–1928.
10. Safavi M, Honarmand A, Negahban M, et al. Prophylactic effects of intrathecal Meperidine and intravenous Ondansetron on shivering in patients undergoing lower extremity orthopedic surgery under spinal anesthesia. *J Res Pharm Pract* 2014; 3: 94–99.

11. Browning RM, Fellingham WH, O’Loughlin EJ, et al. Prophylactic ondansetron does not prevent shivering or decrease shivering severity during cesarean delivery under combined spinal epidural anesthesia: a randomized trial. *Reg Anesth Pain Med* 2013; 38: 39–43.

12. Jo YY, Kwak HJ, Lee MG, et al. Effect of palonosetron on postanesthetic shivering after propofol-remifentanil total intravenous anesthesia. *J Anesth* 2013; 27: 535–540.

13. Abdollahi MH, Forouzannia SK, Bagherinasab M, et al. The effect of ondansetron and meperidin on preventing shivering after off-pump coronary artery bypass graft. *Acta Med Iran* 2012; 50: 395–398.

14. Eldaba AA and Amr YM. Premedication with granisetron reduces shivering during spinal anaesthesia in children. *Anaesth Intensive Care* 2012; 40: 150–153.

15. Asi ME, Isazadefar K, Mohammadian A, et al. Ondansetron and meperidine prevent postoperative shivering after general anesthesia. *Middle East J Anaesthesiol* 2011; 21: 67–70.

16. Iqbal A, Ahmed A, Rudra A, et al. Prophylactic granisetron vs pethidine for the prevention of postoperative shivering: a randomized control trial. *Indian J Anaesth* 2009; 53: 330–334.

17. Sajedi P, Yaraghi A and Moseli HA. Efficacy of granisetron in preventing post-anesthetic shivering. *Acta Anaesthesiol Taiwan* 2008; 46: 166–170.

18. Sagir O, Gulhas N, Toprak H, et al. Control of shivering during regional anaesthesia: prophylactic ketamine and granisetron. *Acta Anaesthesiol Scand* 2007; 51: 44–49.

19. Kelsaka E, Baris S, Karakaya D, et al. Comparison of ondansetron and meperidine for prevention of shivering in patients undergoing spinal anaesthesia. *Reg Anesth Pain Med* 2006; 31: 40–45.

20. Powell RM and Buggy DJ. Ondansetron given before induction of anesthesia reduces shivering after general anesthesia. *Anesth Analg* 2000; 90: 1423–1427.

21. Sessler DI, Rubinstein EH and Moayeri A. Physiologic responses to mild perianesthetic hypothermia in humans. *Anesthesiology* 1991; 75: 594–610.

22. Dawson NJ and Malcolm JL. Initiation and inhibition of shivering in the rat: interaction between peripheral and central factors. *Clin Exp Pharmacol Physiol* 1982; 9: 89–93.

23. Alfonsi P. Postanaesthetic shivering: epidemiology, pathophysiology, and approaches to prevention and management. *Drugs* 2001; 61: 2193–2205.

24. Kurz A. Physiology of thermoregulation. *Best Pract Res Clin Anaesthesiol* 2008; 22: 627–644.

25. Lenhardt R. The effect of anesthesia on body temperature control. *Front Biosci (Schol Ed)* 2010; 2: 1145–1154.