Abstract: Purpose: Postoperative shivering is a long-standing problem, resulting in serious consequences. The current meta-analysis aimed to explore the prophylactic use of granisetron as an efficacious agent for postoperative shivering. Methods: Two researchers searched Cochrane Library, PubMed, and Embase databases for controlled clinical trials, independently. This meta-analysis of randomized controlled trials (RCTs) was performed with Review Manager. Results: Eight trials, including 839 patients, were examined in the current meta-analysis. Granisetron reduced postoperative shivering, compared with a placebo (pooled risk ratio [RR]: 0.30, 95% confidence interval [CI]: 0.24 to 0.39), especially with a higher incidence of grade 0 shivering (no shivering) (pooled RR 2.04, 95% CI 1.48 to 2.80) and a lower incidence of grade 3 shivering (pooled RR 0.43, 95% CI 0.27 to 0.69). Anti-shivering effects can be achieved after general anesthesia (GA) and regional anesthesia (SA), as well as after both laparoscopic surgery and open surgery. Not only 40 ug/kg but also 2 mg of granisetron reduced incidence rates of shivering, compared with a placebo. Additionally, granisetron decreased postoperative nausea, vomiting, and pruritus. Conclusion: The present meta-analysis demonstrates that intravenous prophylactic infusions with granisetron may prevent postoperative shivering. Present results provide new evidence, expanding the clinical value of granisetron in addition to routine usage for postoperative nausea and vomiting.

Keywords: Granisetron, shivering, meta-analysis, postoperative

Introduction

A physiological response of the body, shivering can effectively preserve heat via involuntary skeletal muscle and peripheral vascular contraction [1]. Shivering can increase oxygen and energy consumption, as well as carbon dioxide production [2]. It may even lead to severe side effects during postoperative recovery [3], especially in patients with impaired cardiopulmonary function [4]. In addition, for conscious patients, shivering may be an especially uncomfortable experience during anesthesia recovery [5]. Thus, in reducing related adverse events and improving postoperative quality of rehabilitation, safe and effective treatments and prevention of shivering are crucial.

Granisetron is a 5-hydroxytryptamine 3 (5-HT3) receptor antagonist. It has been used as an antiemetic to treat nausea and vomiting following chemotherapy, radiotherapy, and operations [6]. It can reduce the activity of the vagus nerve, a nerve that activates the vomiting center in the medulla oblongata [7]. Moreover, some clinical researchers have already studied the administration of granisetron to prevent shivering [8]. However, controversy remains concerning the effectiveness of magnesium in arresting shivering. Different results have been reported in different studies [9-16].

To the best of our knowledge, no quantitative analysis has been conducted on the combination of related data primarily. Therefore, the cur-
rent meta-analysis was conducted, aiming to explore the prophylactic use of granisetron as an efficacious agent for postoperative shivering.

Materials and methods

Classification of shivering scores

Aiming to assess the roles of granisetron in shivering, this meta-analysis was performed according to recommendations of the PRISMA statement. Shivering was graded using a five point scale (0 = No shivering; 1 = Piloerection or peripheral vasoconstriction but no visible shivering; 2 = Muscular activity in only one muscle group; 3 = Muscular activity in more than one muscle group but not generalized shivering; and 4 = Shivering involving the whole body) [17], validated in the postoperative period. It was defined as real ‘shivering’ with grades ≥ 3.

Search strategy

Two authors (M.J.N. and W.Z.P.) systematically searched Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and PubMed. The search strategy included the following key words: (granisetron) and (shivering, shiver, tremor, shaking, chill, rigors, or ague) and (anesthesia, anesthesia, surgery, operation, or postoperative). The literature search was updated on September 30, 2018, with no language and initial time limitations. Reference lists of the reviews, original reports, and case reports (retrieved through the electronic searches) were checked, identifying studies that had not yet been included in the computerized databases.

Study selection and data retrieval

Study selection criteria were pre-established. Inclusion criteria: (1) Randomized controlled trials (RCTs); (2) Administration of granisetron prophylactically; (3) Presence of shivering reported; and (4) Granisetron versus placebo.

Exclusion criteria: (1) Duplicates or abstracts only; (2) Missing data; (3) Patients with severe cerebrovascular disease or other contraindications of granisetron; and (4) Incorrect statistical analysis performed in the report.

Data retrieval included name of the first author, publication year, participants, type of anesthesia and surgery, interventions, number of total patients and shivering cases, length of operation, and other side effects [hypotensive, pruritus, nausea, and vomiting (because nausea and vomiting were defined as two separate phenomena, studies should report and evaluate the variables distinctly)] [18]. Since few patients will experience vomiting without nausea, incidence rates of postoperative nausea and vomiting (PONV) and postoperative nausea (PON) are similar. Thus, original papers often do not try to distinguish between these variables [19]. If PONV but not PON was reported in trails, PONV variables were considered as a very close substitute for PON. When both PONV and PON were reported simultaneously, this study assessed the nausea values.

Two authors (S.B. and L.X.), independently, assessed the articles for compliance with inclusion/exclusion criteria. Disputes were settled promptly by group discussion.

Qualitative assessment

Quality of the studies was evaluated, independently, according to the guidelines of Cochrane Collaboration [20], containing six categories (randomization sequence generation (selection bias), blinding method (performance bias and detection bias), allocation concealment (selection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias, with the first three categories considered as “key domains”). The categories above could be summarized into three levels, high risk, unclear risk, and low risk. The risk of bias of each study was evaluated according to the levels of the three key domains: “High” (high risk of bias for one or more key domains), “Unclear” (unclear risk of bias for one or more key domains), and “Low” (low risk of bias for all key domains).

Statistical methods

The efficacy of granisetron on shivering, compared with a placebo, was estimated by calculating pooled risk ratios (RR). Core temperature, before and after anesthesia, was assessed by pooled standard mean difference (SMD), with 95% confidence intervals (CI). Overall effects were determined by w tests, with P < 0.05 indicating statistical significance. When I² ≤ 50%, a fixed-effects model was adopted. Otherwise, a random-effects model was used. Sensitivity
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analysis was performed to test the robustness of these results, reanalyzing the data of low-risk and unclear-risk studies only. Subgroup analyses were based on shivering grades, type of anesthesia, and surgery and dose of granisetron. Potential publication bias was assessed via Begg's and Egger's tests. Review Manager (RevMan®) (Version 6.0.; The Cochrane Collaboration, Oxford, UK) and Stata® (Version 14.0.; Stata Corp, TX, USA) was used to perform statistical analysis.

**Results**

**Study selection**

As shown in Figure 1, the search of PubMed, Embase, Cochrane Library, and reference lists yielded 145 articles. Initially, 117 trials were discarded. A total of 88 trials were not controlled trials, while the other 29 trials were duplicates. Another 13 trials were excluded for times: 107±12.37 min, 105±8.59 min [12], 132.4±52 min, 134.5±49 min [15]. The pooled estimate did not show statistical differences (RR 1.90, 95% CI -1.86 to 5.67) (Table 1).

**Methodological quality of studies included**

All eight included trials [9-16] provided a detailed description of randomization. Six studies [9-11, 13, 15, 16] were double-blinded. Seven trials [9-14, 16] reported allocation concealment. All studies [9-16] reported the end points mentioned in the Methods section (reporting bias), without incomplete outcomes (attrition bias) and other biases. An overview of the risk of bias is summarized in Figure 2.

**Results of the meta-analysis**

Eight trials [9-16], including 839 patients, investigated the efficacy of preventing postoperative shivering, comparing granisetron with a placebo.
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<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Participants</th>
<th>Type of anesthesia</th>
<th>Type of surgery</th>
<th>Trail</th>
<th>Dosage regimen</th>
<th>Comparisons</th>
<th>Total (case)</th>
<th>Shivering</th>
<th>Anesthesia time (Mean ± SD, min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdel-Ghaffar [9] 2018</td>
<td>Adult</td>
<td>RA</td>
<td>Caesarean Section</td>
<td>Over 1 min, 5 min before the spinal block</td>
<td>S Granisetron 1 mg IV</td>
<td>69 Granisetron 0.7 mg IV</td>
<td>72 Placebo IV</td>
<td>11</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eldaba [10] 2012</td>
<td>Children</td>
<td>RA</td>
<td>Lower limb surgery</td>
<td>Over a five minute period just before spinal puncture</td>
<td>S Granisetron 10 µg/kg IV</td>
<td>40 Placebo IV</td>
<td>40 Placebo IV</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Iqbal [11] 2009</td>
<td>Adult</td>
<td>GA</td>
<td>Laparoscopic surgery</td>
<td>Before induction of anaesthesia</td>
<td>S Granisetron 40 anise IV</td>
<td>30 Placebo IV</td>
<td>30 Placebo IV</td>
<td>6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Khan [12] 2006</td>
<td>Adult</td>
<td>GA</td>
<td>Laparoscopic Cholecystectomy</td>
<td>Before induction of anaesthesia</td>
<td>S Granisetron 40 anise IV</td>
<td>60 Placebo IV</td>
<td>60 Placebo IV</td>
<td>0</td>
<td>107±12.37</td>
<td>105±8.59</td>
</tr>
<tr>
<td>Ma [13] 2009</td>
<td>Adult</td>
<td>GA</td>
<td>Gynecological laparoscopic operation</td>
<td>Before induction of anaesthesia</td>
<td>S Granisetron 2 mg IV</td>
<td>50 Placebo IV</td>
<td>50 Placebo IV</td>
<td>9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sagir [14] 2007</td>
<td>Adult</td>
<td>RA</td>
<td>Urological surgery</td>
<td>After intrathecal injection</td>
<td>S Granisetron 3 mg IV</td>
<td>40 Placebo IV</td>
<td>40 Placebo IV</td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sajedi [15] 2008</td>
<td>Adult</td>
<td>GA</td>
<td>Elective orthopedic surgery</td>
<td>At the end of surgery</td>
<td>S Granisetron 40 µg/kg IV</td>
<td>33 Placebo IV</td>
<td>33 Placebo IV</td>
<td>8</td>
<td>132±452</td>
<td>134.5±49</td>
</tr>
<tr>
<td>Singh [16] 2011</td>
<td>Adult</td>
<td>GA</td>
<td>Elective surgery</td>
<td>Before induction of anesthesia</td>
<td>S Granisetron 2 mg IV</td>
<td>25 Placebo IV</td>
<td>25 Placebo IV</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.30 (0.24, 0.39)</td>
<td>1.90 (-1.86, 5.67)</td>
<td></td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>I²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0%</td>
<td>0%</td>
<td></td>
<td></td>
<td>0%</td>
</tr>
</tbody>
</table>

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Incidence of shivering (pooled RR 0.30, 95% CI 0.24 to 0.39) in the granisetron group was significantly lower than that in the placebo group (Table 1), especially with a higher incidence of grade 0 shivering (no shivering) (pooled RR 2.04, 95% CI 1.48 to 2.80) and a lower incidence of grade 3 shivering (pooled RR 0.43, 95% CI 0.27 to 0.69) (Table 2). Begg’s and Egger’s tests suggested no significant publication bias existed in comparisons of shivering (P = 0.835 and P = 0.924) between granisetron and the placebo (Figure 3).

Types of anesthesia

Granisetron significantly reduced incidence rates of shivering after general anesthesia (GA) (pooled RR of five trails [11-13, 15, 16]: 0.34, 95% CI: 0.23 to 0.50) and regional anesthesia (SA) (nausea: pooled RR of three trials [9, 10, 14]: 0.29, 95% CI: 0.21 to 0.39) (Figure 4).

Types of surgery

Granisetron pretreatment lowered incidence rates of shivering after laparoscopic surgery (pooled RR of three trails [11-13]: 0.31, 95% CI: 0.19 to 0.51) and open surgery (pooled RR of five trails [9, 10, 14-16]: 0.30, 95% CI: 0.23 to 0.40), compared with the placebo (Figure 5).

Dosage of granisetron

Subgroup analysis demonstrated beneficial effects of a single-dose bolus of 40 ug/kg granisetron, compared with a placebo, on shivering (pooled RR of three trials [11, 12, 15]: 0.30, 95% CI: 0.16 to 0.55). Moreover, 2mg granisetron also reduced incidence rates of shivering (pooled RR of two trials [13, 16]: 0.31, 95% CI: 0.17 to 0.58) (Figure 6).

Other adverse effects

PON: There were eight studies in seven trials [9, 11-16] reporting PON. Compared with the placebo, a reduction in PON, with statistical significance (RR 0.38, 95% CI 0.26 to 0.54), was exposed in patients receiving granisetron (Table 3).

Postoperative vomiting (POV): POV was involved in four studies [11-14]. Pooled estimates showed a statistical reduction in POV (RR 0.41, 95% CI 0.23 to 0.72) in patients receiving granisetron, compared with the placebo (Table 3).

Hypotensive: Hypotension was involved in three studies [9, 14], compared with a placebo. The pooled estimate did not exclude a statistical reduction in hypotension (RR 0.97, 95% CI 0.78 to 1.20) in patients receiving granisetron (Table 3).

Pruritus: Two studies in one trial [9] assessed postoperative pruritus. Pooled analysis showed a statistically significant decrease (RR 0.03, 95% CI 0.00 to 0.22) in this side effect in the granisetron group (Table 3).

Core temperature before and after anesthesia

Differences between core temperatures before (pooled RR 0.32, 95% CI: -0.29 to 0.94) and after (pooled RR -0.25, 95% CI: -0.59 to 0.08)
Prophylactic granisetron prevents postoperative shivering

Table 2. Efficacy of intravenous granisetron in reducing shivering compared with a placebo

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Number of studies</th>
<th>Granisetron</th>
<th>Placebo</th>
<th>RR (95% CI)</th>
<th>I²</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shivering grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>55/70</td>
<td>27/70</td>
<td>2.04 (1.48, 2.80)</td>
<td>0%</td>
<td>[11, 14]</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3/70</td>
<td>9/70</td>
<td>0.47 (0.03, 7.31)</td>
<td>68%</td>
<td>[11, 14]</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>3/103</td>
<td>6/103</td>
<td>0.50 (0.13, 1.94)</td>
<td>0%</td>
<td>[11, 14, 15]</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>18/103</td>
<td>42/103</td>
<td>0.43 (0.27, 0.69)</td>
<td>0%</td>
<td>[11, 14, 15]</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>0/103</td>
<td>5/103</td>
<td>0.09 (0.01, 1.58)</td>
<td>0%</td>
<td>[11, 14, 15]</td>
</tr>
</tbody>
</table>

Discussion

Postoperative shivering, one of the leading causes of discomfort in patients recovering from anesthesia, is a long-standing problem, resulting in serious consequences. Although lots of research has been conducted in past decades, shivering remains an extremely significant challenge due to the complex mechanisms.

The present meta-analysis was undertaken to evaluate the efficacy of prophylactic granisetron on prevention of shivering. Main findings are as follows: (1) Granisetron showed superiority to placebos on the prevention of shivering without different core temperatures in all common anesthesia and surgeries; (2) The beneficial effects of granisetron on shivering were expressed primarily through more patients without shivering and lower incidence rates of grade 3 shivering; (3) The most commonly used dose in published articles, both intravenous 4 μg/kg and 2 mg bolus infusions showed a preventive effect on shivering; and (4) Granisetron reduces incidence of PON, POV, and postoperative pruritus.

Sensitivity analysis

Since studies with high risk were excluded for sensitivity analysis, there were no significant differences in results from overall pooled estimates across all outcomes.
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Shivering usually results from anesthesia inhibiting the body’s thermoregulatory capability [21]. Cutaneous vasodilation may also be a causative factor [22]. First, thermoregulation is controlled by central nervous system neurotransmitters in the hypothalamus where the...
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The preoptic area releases 5-HT3 to activate heat production pathways [23-25]. This increases body temperature through shivering [26]. In addition, other studies have demonstrated that 5-HT could be an excitatory transmitter acting on the warm receptor-heat loss pathways [27]. Moreover, intravenous administration of 5-HT has been reported to provoke vasodilation in mouse models [28]. Thus, its beneficial anti-shivering effects may be explained by the fact that granisetron, as a 5-HT3 receptor antagonist, may decrease not only heat loss, but also heat production, augmenting vasoconstriction.

Table 3. Efficacy of intravenous granisetron in reducing other operative side effects compared with a placebo

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Number of studies</th>
<th>Granisetron</th>
<th>Placebo</th>
<th>RR (95% CI)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PON</td>
<td>8</td>
<td>32/379</td>
<td>87/380</td>
<td>0.38 (0.26, 0.54)</td>
<td>[9, 11-16]</td>
</tr>
<tr>
<td>POV</td>
<td>4</td>
<td>44/199</td>
<td>36/200</td>
<td>0.41 (0.23, 0.72)</td>
<td>[9, 15, 16]</td>
</tr>
<tr>
<td>Hypotensive</td>
<td>3</td>
<td>82/181</td>
<td>85/182</td>
<td>0.97 (0.78, 1.20)</td>
<td>[9, 14]</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2</td>
<td>0/141</td>
<td>32/141</td>
<td>0.03 (0.00, 0.22)</td>
<td>[9]</td>
</tr>
</tbody>
</table>

Figure 6. Results of subgroup analysis concerning incidence of postoperative shivering by dosage of granisetron.

Figure 7. Results of analysis of the core temperature before (A) and after (B) anesthesia.
Controversy remains concerning the efficacy on shivering. Several studies [9, 11, 13-15] have suggested a superior role of granisetron, compared with a placebo, but others [10, 12, 16] have not. The current study included total eight articles about the efficacy of granisetron on postoperative shivering, compared with a placebo, with plenty of relative clinical outcome variables. These improved the reliability of present conclusions. To the best of our knowledge, this is the first study to shed light on the efficacy of granisetron on shivering from a variety of aspects, via meta-analysis of RCTs compared with placebos. Almost all included studies were well-designed and assessed as “Low”. These strategies led to solid conclusions.

The clinical use of granisetron to prevent shivering remains unclear. The current meta-analysis found that both 40 ug/kg and 2 mg bolus infusions were effective in preventing postoperative shivering. Granisetron has been applied as an antiemetic to treat PONV through reducing the activity of the vagus nerve, a nerve that activates the vomiting center in the medulla oblongata [7]. The current study showed the definite pharmacological effects above. Results showed that granisetron could reduce the incidence of postoperative pruritus simultaneously. The anti-pruritic efficacy of granisetron has been previously investigated. The reason may be that pruritus is related to direct stimulation of 5-HT3 receptors in the dorsal horn of the spinal cord and medulla. Therefore, 5-HT3 antagonists may be beneficial in its treatment [29].

However, the current meta-analysis had several limitations. First, the total number of trails included was significant, but the amounts in subgroups were too small to secure conclusive results. In addition, significant heterogeneity existed in the number of patients with shivering grade 1 and core temperatures before anesthesia, possibly due to the instability of evaluation and measurements. Therefore, more RCTs, including kinds of patients and various doses or routes of administration in specific anesthesia or surgeries, should be designed to confirm the efficacy of granisetron on postoperative shivering.

In conclusion, the present meta-analysis demonstrates that intravenous prophylactic infusions of granisetron may prevent postoperative shivering. Results provide new evidence, expanding the clinical value of granisetron in addition to routine usage for PONV.

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Disclosure of conflict of interest

None.

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