Effect of Ondansetron on Postoperative Shivering After Craniotomy

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INTRODUCTION: Postoperative shivering (POS) is an early complication after craniotomy. Preventive pharmacologic drugs are the mainstay of treatment. Meperidine is the drug of choice but with increased risk of apnea, nausea, and increased intracranial pressure. Some reports have suggested that ondansetron and meperidine have similar anti-shivering effects.

OBJECTIVES: To assess the preventive effect of ondansetron on POS after craniotomy.

METHODS: In a randomized, double-blind, placebo-controlled trial, 80 patients with American Society of Anesthesiologists status I to II between 20 and 60 years of age scheduled for elective craniotomy were enrolled in the study. Patients received either intravenous ondansetron 4 mg (n = 40) or saline (n = 40) 10 minutes before the end of surgery.

RESULTS: POS was observed in 3 patients (7.5%) in the ondansetron group, significantly lower than in the control group (6 patients [15%]; P = 0.048). Ondansetron decreased the relative risk of occurrence of POS after craniotomy from 4.42 (95% confidence interval [CI], 2.3–8.5; P = 0.0021) in the control group to 1.05 (95% CI, 0.76–2.20; P = 0.074). In the ondansetron group, the mean (± standard deviation) core temperature in the preoperative phase (36.6°C ± 0.66°C) was significantly higher than in the postoperative phase (34.2°C ± 0.56°C) (P = 0.001). In addition, the mean (± standard deviation) peripheral temperature in the preoperative phase (36.5°C ± 0.72°C) was significantly higher than in the postoperative phase (34.4°C ± 0.51°C) (P = 0.001).

CONCLUSIONS: Ondansetron can effectively decrease POS after craniotomy. This effect is not mediated through maintenance of the core or peripheral temperature. Ondansetron probably acts by a central inhibitory mechanism on POS through 5-hydroxytryptaminergic pathways, not by changing thermoregulatory set points.

INTRODUCTION

Shivering is an early postoperative complication after neurosurgical procedures.¹ The incidence of POS after anesthesia varies between 5% and 65%.² Perioperative hypothermia is a common problem in anesthesia practice. General anesthesia influences the thermoregulatory process. Sustained shivering augments metabolic heat production by 90%–100% in adults; however, this increase is trivial in comparison with the heat loss during general anesthesia and thus is surprisingly ineffective.

The exact cause of POS is still unclear; certainly, much POS is simply normal shivering. It is always preceded by core hypothermia and thermoregulatory disturbance. The 4- to 8-cycle/minute waxing and waning pattern of normal shivering is apparently a simple thermoregulatory response to intraoperative hypothermia. On the other hand, it may result from anesthetic-induced disinhibition of normal descending control over spinal reflexes. The neurotransmitter pathways involved in the mechanism of POS are poorly understood.

Preventive pharmacologic measures are the mainstay of treatment. Nonpharmacologic approaches such as maintaining ambient temperature, warming air blankets,³ and intravenous infusions are as effective as pharmacologic measures⁴. Mild

Key words
- Craniotomy
- Ondansetron
- Postoperative shivering

Abbreviations and Acronyms
- 5-HT: 5-Hydroxytryptamine
- CI: Confidence interval
- POS: Postoperative shivering

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perioperative hypothermia does not necessarily induce POS, but more severe hypothermia has higher probability of the incidence of shivering. Length of anesthesia and type of surgery are definitely determinants for POS. POS has some unwanted consequences such as patient discomfort, increase in oxygen consumption, and cardiovascular events.

Mepetidine, clonidine, and physostigmine are all effective treatments, indicating that opioid, alpha 2-adrenergic, and anticholinergic receptors are probably involved. Other drugs such as tramadol and nefopam are inhibitors of amine reuptake; ketanserin is a 5-hydroxytryptamine (5-HT) 2 antagonist. Nefopam has also been used for prevention of shivering during spinal anesthesia with more stable hemodynamics. Although tramadol and meperidine are available for prevention of POS, both drugs can increase intracranial pressure and induce seizure. Therefore, clinicians are disinclined to use them in postcraniotomy shivering. Alpha 2-adrenergic dexmedetomidine may decrease cerebral perfusion pressure (CPP = mean arterial pressure – intracranial pressure) as it attenuates blood pressure.

5-HT3 antagonists can inhibit or prevent shivering, but their effect on POS is still debated. Ondansetron is a 5-HT3 receptor antagonist. Some reports have suggested that ondansetron and meperidine have similar anti-shivering effects. Although several studies have reported that ondansetron may be effective in the prevention of POS, the results remained controversial.

Objectives
The aim of this study was to assess the preventive effects of ondansetron on POS in neurosurgeries.

METHODS

Study Design and Patient Selection
This study was a double-blind design with placebo control, and it was checked and approved by the University Review Board and Hospital Ethic Committee. Information about the trial was given to the patients in both oral and written forms. All patients were enrolled in the study on the basis of informed consent according to the University and Hospital Ethic Board Committee.

In a randomized, double-blind, placebo-controlled trial, 80 patients with American Society of Anesthesiologists status I to II between 20 and 60 years of age scheduled for elective neurosurgery were enrolled in the study and randomly assigned to the ondansetron group or the placebo group based on accidental numbers. Patients with obesity (body mass index >30 kg/m²), preoperative fever (temperature >38°C), hyper- or hypothyroidism, Parkinson disease, irregular heart rhythm, requiring blood transfusion during surgery, and receiving medications to alter thermoregulation were excluded from the study.

Patients received either intravenous ondansetron 4 mg (2 mg/mL) manufactured by Hikma Farmacêutica (S.A. Estrada do Rio da MO, Terrugem SNT, Portugal) or saline 10 minutes before the end of surgery.

Method of Anesthesia
Patients were pre-oxygenated with 5 L/minute 100% O₂ for 3–5 minutes. Anesthesia was induced by the same method in all patients. For premedication, fentanyl 5 µg/kg and midazolam 0.02 mg/kg were administered. Anesthesia was induced by sodium thiopental 4–6 mg/kg, lidocaine 1.5 mg/kg, and cisatracurium 0.2 mg/kg. Intubation was performed under smooth direct laryngoscopy after 60–90 seconds when train of four was 0. The size of endotracheal tube was selected after laryngoscopy under direct visualization. Anesthesia was maintained with propofol 75–150 µg/kg and under 1 minimum alveolar anesthetic concentration of isoflurane and 100% oxygen. Ten minutes before surgery ended, ondansetron or saline was infused. Extubation was performed using the same method in both groups; after surgery, when train of four >0.7 and the patient was fully awakened, neuromuscular block was reversed (neostigmine 0.06 mg/kg + atropine 0.02 mg/kg) and the patient was extubated. If patients had bucking during extubation then they were excluded from study. In recovery, patients only had O₂ 5 L/minute via face mask.

Fluid therapy was performed using standard methods. Patients were covered with 3 layers of surgical drapes. The ambient temperature was measured by a wall thermometer and room temperature was maintained at 23°C via the operating room air conditioner.

Shivering, Core, and Peripheral Temperature Measurements
Shivering was evaluated during the postoperative period by observation of shivering movements of more than 10 seconds duration. The occurrence of shivering was documented clinically during recovery by nursing staff, who were unaware of the group assignment.

Core (nasopharynx) and skin temperature (dorsum of middle finger) were recorded. Patients’ temperature was measured before anesthesia and then every 2 hours during and after surgery. The difference between the preoperative core and skin temperature was determined. Blood pressure, heart rate, and oxygen saturation were recorded before surgery and every 2 hours after anesthesia.

Statistical Analysis
Statistical calculations were conducted using SPSS 20 (Chicago, Illinois, USA). The parametric variables were presented as means ± standard deviation and were analyzed by Student t test or analysis of variance as appropriate. Statistical analysis was performed using the t-test or Mann-Whitney U test and for nonparametric samples. P < 0.05 was considered to be statistically significant. Sample size was estimated using sample size calculator software with 95% confidence interval (CI), 2 = 0.05, and a clinical difference of 20% in shivering between the 2 groups based on a pilot study. The estimated sample size was 40 patients for each group.

RESULTS
Eighty patients were enrolled in a randomized clinical trial; 40 patients received ondansetron and 40 patients received normal saline. Age, sex, and body mass index were not significantly different between the 2 groups (P > 0.05) (Table 1).

POS
POS was observed in 3 patients (7.5%) in the ondansetron group, significantly lower than in the control group (6 patients [15%]; P = 0.0048) (Figure 1).
Ondansetron decreased the relative risk of occurrence of POS after craniotomy from 4.42 (95% CI, 2.3–8.5; \( P = 0.0021 \)) in the control group to 1.05 (95% CI, 0.76–2.20; \( P = 0.674 \)). This means that the risk of shivering after craniotomy in the saline group was almost 4.42 times higher than in the ondansetron group.

**Core and Peripheral Temperature**

As shown in Figure 2, within each group, the postoperative core temperature and peripheral temperature decreased; however, there were no significant differences between the 2 groups at any time point. The mean core and peripheral temperatures were not significantly different between the ondansetron and control groups at pre-, peri-, and postoperation time points (\( P > 0.05 \)).

The core temperature preoperatively (36.6°C ± 0.66°C) was significantly higher than postoperatively (34.2°C ± 0.56°C) (\( P = 0.001 \)). In addition, the mean (± standard deviation) peripheral temperature preoperatively (36.5°C ± 0.72°C) was significantly higher than postoperatively (34.4°C ± 0.51°C) (\( P = 0.001 \)) (Figure 2).

**Table 1. Demographic Characteristics of the Patients in the 2 Groups**

<table>
<thead>
<tr>
<th></th>
<th>Ondansetron (( n = 40 ))</th>
<th>Normal Saline (( n = 40 ))</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years ± SD</td>
<td>53.4 ± 14.8</td>
<td>55.2 ± 15.6</td>
<td>0.37</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>23/17</td>
<td>25/15</td>
<td>0.22/0.26</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.4 ± 3.5</td>
<td>24.5 ± 4.2</td>
<td>0.19</td>
</tr>
<tr>
<td>Duration of surgery, hours ± SD</td>
<td>5.12 ± 3.26</td>
<td>5.13 ± 3.52</td>
<td>0.30</td>
</tr>
<tr>
<td>Bleeding, mL ± SD</td>
<td>375 ± 235</td>
<td>365 ± 250</td>
<td>0.85</td>
</tr>
<tr>
<td>Type of neurosurgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain tumor</td>
<td>24</td>
<td>22</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>11</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Brain biopsy</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Brain abscess</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Changes in systolic blood pressure were not significantly different in both groups at 2 hours (\( P = 0.12 \)), 4 hours (\( P = 0.33 \)), 6 hours (\( P = 0.26 \)), and in recovery after surgery (\( P = 0.18 \)) (Figure 3A). Heart rate was not also significantly different in the 2 groups at 2 hours (\( P = 0.20 \)), 4 hours (\( P = 0.35 \)), 6 hours (\( P = 0.44 \)), and in recovery after surgery (\( P = 0.075 \)) (Figure 3B).

**DISCUSSION**

In this study, we investigated the effect of ondansetron on POS. Our results showed that ondansetron (4 mg intravenously) given during anesthesia prevents POS without affecting the core-to-peripheral redistribution of heat during general anesthesia. This suggests that serotonergic pathways have a role in the regulation of POS, and ondansetron, a 5-HT₃ antagonist, decreases shivering after craniotomy.

In our study, POS was observed in only 3 patients (7.5%) in the ondansetron group, which was significantly lower than in the control group (15%). Ondansetron decreased the risk of shivering almost 4 times that with normal saline. Anesthesia can cause shivering due to general hypothermia and disinhibition of the shivering pathway. Propofol and isoflurane produce a marked and linear decrease in the cold-response threshold including vasoconstriction and shivering thresholds synchronously. With inhaled anesthetic agents such as desflurane, sevoflurane, and isoflurane, no significant intraoperative brain swelling, hemodynamics, and POS were noted. Bilotta et al showed that nefopam is effective in preventing POS in patients undergoing neurosurgery and in mild hypothermia and attenuates the hemodynamic effect of shivering during rewarming. As evaluated in 1995, nefopam seems to be more effective than clonidine or meperidine in quickly suppressing shivering, without producing significant adverse reactions. In 2005, the used of clonidine was recommended for neurosurgical patients to prevent POS after mild hypothermia. Another study showed that both pregabalin 300 mg/day and gabapentin 1200 mg/day significantly reduced POS. The incidence of shivering has not been determined in craniotomy, only other types of surgery. However, the incidence of shivering is less than with other surgeries as a result of
extensive preventive therapies performed for craniotomies because of fear of the hazards of shivering.17 Although the most important determinants of shivering risk are young age and low core temperature, neurosurgical procedures have not been the subject of any studies previously.18

Temperature thresholds for vasoconstriction and shivering are often higher than normal in brain-injured patients; therefore, thermoregulatory defenses may occur more vigorously and at higher temperatures in these individuals. Our results showed that the core and peripheral temperatures decreased significantly preoperatively compared with postoperatively; however, there were no significant differences in core temperature between the 2 groups in the preoperative and postoperative periods. In other words, both core and peripheral temperatures were decreased but the core-to-peripheral redistribution of body temperature during general anesthesia was not affected. This implies that ondansetron probably acts by a central inhibitory mechanism, not by changing thermoregulatory set points, and that 5-HT pathways have a role in regulating POS. Other studies have indicated similar results regarding ondansetron.19

Our results regarding the effects of ondansetron in controlling POS are comparable with other studies. Other studies have showed that ondansetron can effectively reduce POS to 25% in the control group to 5% in the ondansetron group.20 In an interesting meta-analysis, Tie et al21 showed that ondansetron has a preventive effect on POS without a parallel side effect of bradycardia. Even in patients undergoing coronary artery bypass graft, it was demonstrated that ondansetron was more effective in preventing shivering after off-pump coronary artery bypass graft than meperidine.22 Nevertheless, controversies over the effect of ondansetron on POS are still continuing. Browning et al23 showed that prophylactic ondansetron does not prevent shivering or decrease shivering severity during cesarean delivery under combined spinal epidural anesthesia. In other study,
ondansetron at a plasma concentration of ≈ 250 ng/mL did not significantly alter the core temperature thresholds triggering sweating, vasoconstriction, or shivering. In a trial, administration of 2 different doses of intravenous ondansetron, 6 mg and 12 mg, significantly attenuated spinal-induced hypotension, bradycardia, and shivering compared with the control saline group. Mahoori et al. showed that both ondansetron 8 mg intravenously and meperidine 0.4 mg/kg effectively treated patients with POS, and ondansetron 8 mg in patients with postoperative nausea, vomiting, and shivering would be an ideal choice. Others have reported the preventive effect of ondansetron in POS after general anesthesia in gynecologic surgery. Prophylactic ondansetron (4 mg) significantly decreased shivering in patients undergoing spinal anesthesia without significant side effects.

The mechanism by which ondansetron suppresses shivering is supposedly through 5-HT3 antagonism. Clinically, our results indicate that the effect of ondansetron on body temperature is similar to the control, which emphasizes its central effect on shivering instead of an effect on the thermoregulatory center or vasoconstriction threshold. μ-agonists such as meperidine are effective in treating shivering. However, the action of meperidine is in part mediated by non-μ-opioid receptors including κ activity and central anticholinergic activity. In addition, it has been shown that both ondansetron and meperidine altered the correlation between the core temperature and block level during spinal anesthesia. In other study, when postoperative hypothermia was treated by the administration of convective or conductive heat, normothermia was achieved.

In conclusion, ondansetron can effectively decrease POS after craniotomy. This effect is not mediated through maintenance of the core or peripheral temperature. Ondansetron probably acts by a central inhibitory mechanism on POS through 5-HT3 pathways, not by changing thermoregulatory set points.

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