Preoperative granisetron for shivering prophylaxis in cesarean section under spinal anesthesia

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Background
Shivering is one of the common problems during spinal anesthesia and may lead to several complications, interfere with patient monitoring, and is bothersome for the mother while holding her newborn. We performed this prospective, double-blinded, placebo-controlled study to determine the ability of preoperative intravenous (IV) granisetron to prevent or decrease shivering after spinal anesthesia during elective cesarean delivery.

Materials and methods
A total of 117 ASA I/II parturient women undergoing elective cesarean delivery were enrolled. Patients were randomly allocated into two groups: group G (n = 58) received 3 mg in 3 ml granisetron intravenously and group P (n = 59) received 3 ml intravenous normal saline before performing spinal anesthesia. Spinal anesthesia was performed in all patients using 10 mg heavy bupivacaine 0.5% and 15 μg fentanyl. Shivering was graded according to the Wrench score: 0 = no shivering; 1 = piloerection, peripheral vasoconstriction, or peripheral cyanosis without other cause; 2 = visible muscular activity confined to one muscle group; 3 = visible muscular activity in more than one muscle group; and 4 = gross muscular activity involving the entire body. Rescue medication intake, interference with neonatal holding, interference with monitoring, and maternal vomiting in 12 h postoperative as well as tympanic membrane temperature and Apgar score were recorded.

Results
The percentage of shivering and shivering score value among parturients in both groups did not show significant statistical difference during the study time periods, with a P value greater than 0.05. With respect to rescue medication intake (P = 0.086) as well as interference with monitoring (P = 0.653) and neonatal holding (P = 0.653), there was no statistically significant difference as well. In addition, tympanic membrane temperature (P = 0.48) and 1-min Apgar score (P = 0.09) did not show statistically significant difference. Granisetron significantly reduced the incidence of nausea and vomiting during the 12-h postoperative period, with only six (10.3%) mothers in group G complaining of nausea and vomiting in comparison with 16 (27.1%) mothers in group P (P = 0.036).

Conclusion
Preoperative intravenous granisetron for shivering prophylaxis in cesarean section under spinal anesthesia did not significantly reduce the incidence or severity of shivering.

Keywords:
cesarean section, granisetron, parturient, shivering, spinal

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Introduction

Central neuraxial anesthesia is considered the most commonly implemented anesthetic technique for cesarean section. Perioperative shivering is frequently encountered in the setting of neuraxial anesthesia in obstetric and nonobstetric surgeries [1]. A number of mechanisms are probably involved in the occurrence of such shivering, including reduction in body core temperature, body heat distribution, thermoregulatory threshold changes, and the temperature of fluids injected into neuraxial blocks [2]. In cesarean section, shivering is a distressing phenomenon for both anesthetist and mother, as it would interfere with ECG monitoring, measuring blood pressure, and oxygen saturation reading by pulse oximetry in the setting of sympathetic blockade and aortocaval compression. Shivering could also limit the mother's skin to skin contact with the newborn [3]. Shivering can increase the oxygen consumption by up to 400% and it increases myocardial work, which is associated with increased postoperative morbidity and mortality including increased rates of postoperative infection [4]. Preventing shivering would help in reduction in these deleterious consequences, which would have a detrimental effect on both mother and the newborn.

Meperidine (pethidine), tramadol, and clonidine are known to be useful in preventing and controlling neuraxial anesthesia-related shivering. Various adverse reactions accompany such medications, including sedation, nausea, bradycardia, and hypotension, which

limit their use in many instances. Anesthesiologists may be unwilling to administer such drugs before delivery because of the concerns about unwanted effects on the mother and fetus [5].

5-HT_3 antagonists are commonly used as antiemetics during obstetric and surgical operations. A number of studies have verified their antishivering properties, both following general anesthesia and during neuraxial anesthesia [6-9]. Granisetron is a 5-HT_3 antagonist that offers antiemetic and antipruritic activity in cesarean section under spinal anesthesia with a potential advantage of having a very low incidence of sedation, adverse cardiovascular effects, or risk to the neonate [10,11]. The administration of prophylactic intravenous granisetron to prevent shivering has not been studied previously in an obstetric population. We hypothesized that there would be a significant decrease in the incidence or severity of perioperative shivering in women given intravenous granisetron, compared with placebo, before performing spinal anesthesia for elective cesarean delivery.

Materials and methods

After obtaining approval from the ethical committee of Ain Shams University Hospitals, mothers enrolled in the study received informed consent regarding the medications to be used. A total of 120 parturients, American Society of Anesthesiologists class I or II, elected to receive spinal anesthesia for elective cesarean delivery were enrolled in the study. Exclusion criteria were age below 18 years, BMI greater than 50, contraindication for spinal anesthesia, known allergy to the studied drug, history of perioperative shivering, and failed spinal anesthesia with crossover to general anesthesia.

Mothers were allocated into two groups; this allocation was performed through a computer-generated random-number sequence. On arrival to the preinduction area, 18-G intravenous cannula was inserted; syringes containing medications were prepared and numbered 1–120 in advance by an anesthesia resident who was not involved in the evaluation of parturients; and the nature of the medication given was revealed at the end of the study during data analysis. Group G received intravenous granisetron 3 mg in 3 ml ampoule, whereas group P received 3 ml of normal saline; syringes were injected over 30 s. ECG, pulse oximetry, noninvasive blood pressure, tympanic temperature measurement were the monitors applied during the perioperative period. Parturient received 1000 ml of room temperature Ringer's solution infusion over 15 min, then spinal anesthesia was performed in the sitting position at either L3–L4 or L4–L5 interspace using 10 mg heavy bupivacaine 0.5% and 15 μg fentanyl injected through 25-G pencil-point needle with an introducer. Following spinal block, the parturient was placed in the left supine tilt; body was rapidly covered by drapes to avoid hypothermia. The occurrence of shivering in each group was assessed by an anesthesiologist who was blinded to the pretreatment drug given; shivering assessment was based on Wrench *et al.* [12] score, where 0 = no shivering; 1 = one or more of the following: piloerection, peripheral cyanosis, or peripheral vasoconstriction without muscular rigidity; 2 = visible muscular activity in one muscle group; 3 = visible muscular activity in more than one group; and 4 = gross muscular activity involving the whole body.

Score 1 and 2 are considered mild degrees of shivering, whereas 3 and 4 are severe forms of shivering. In our study, for parturients achieving a score of at least 3, the prophylactic medication was considered noneffective. Our primary outcome was the percentage and degree of shivering in both groups, percentage of parturients receiving rescue antishivering medications, interference with neonatal holding, and interference with intraoperative blood pressure, ECG, and SpO_2 readings. The assessment was at 10-min interval both in the operating room and in postanesthesia care unit. A rescue antishivering medication in the form of 0.25 mg/kg intravenous pethidine was given to the parturient who experienced discomfort as a result of her shivering or when the anesthetist observed interference with monitoring. The secondary outcome data were tympanic membrane temperature, which was recorded at 10-min interval, 1-min neonatal Apgar score, and the incidence of vomiting within 12 h postoperative.

Statistical analysis

Sample size calculation

Epi Info was used for calculation of the sample size guided by an α error of 5%, confidence level of 80%, and power of the test of 90%; the sample size of 110 patients was found to be sufficient to conduct the study. Significance level was at an α value of 0.05 (type error I).

Statistical methods

Statistical analysis was performed by computer software 'SPSS' (version 17.0; Statistical Package of Social Science). Description of quantitative (numerical) variables was expressed in the form of mean ± SD. Description of qualitative categorical data was expressed in the form of number of patients and percentage. Error bars represent 95% confidence interval. Analysis of unpaired numerical variable was

performed using the unpaired Student *t*-test, whereas analysis of paired numerical variables was performed using repeated measure general linear model. Analysis of categorical data was performed using the Fisher exact test or the χ^2-test, whenever appropriate.

The significance level was set at *P* value of 0.05 or less, and *P* value of 0.01 or less was considered highly significant.

Results

Our study included 117 parturients who completed the study; three mothers were excluded from the study, two in group G and one in group P, as they had inconsistent spinal block and were crossed over to general anesthesia before the initiation of surgery. The demographic data in both groups did not show any statistically significant difference (Table 1). The percentage of shivering and shivering score among parturients in both groups did not show statistically significant difference during the study time periods, with a *P* value greater than 0.05 (Table 2 and Fig. 1). The number of parturients who received rescue antishivering medication was comparable in both groups, with no statistically significant difference. Patients were offered pethidine according to their shivering discomfort and when shivering interfered with their monitoring and neonatal holding capabilities. Group G showed statistically significant reduction in the incidence of nausea and vomiting when compared with group P (*P* = 0.032) (Table 2). The tympanic membrane temperature, which was measured at 10-min interval, did not show a significant difference between both groups, and there was no difference with respect to the value of 1-min neonatal Apgar score between both groups (*P* > 0.05) (Table 3).

Table 1 Demographic data expressed as mean (SD)

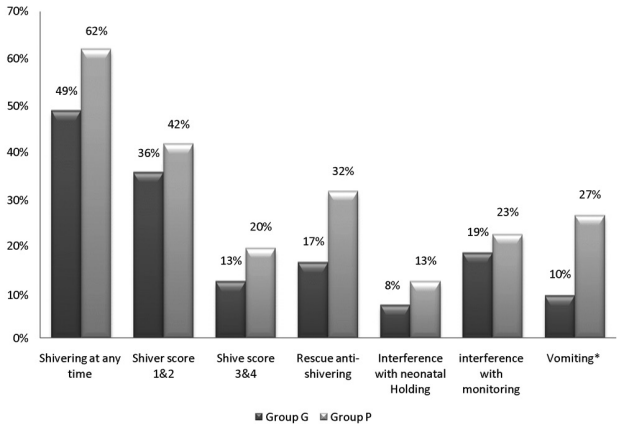
Demographic data	Groups	*n*	Mean	SD	*P* value
Age (years)	Group G	58	28.28	4.870	0.30
	Group P	59	27.32	5.127	
Height (m)	Group G	58	1.6657	0.07565	0.59
	Group P	59	1.6585	0.07085	
Weight (kg)	Group G	58	95.66	8.262	0.71
	Group P	59	96.17	7.076	
Parity	Group G	58	1.03	0.917	0.10
	Group P	59	1.29	0.767	

Discussion

Shivering is not only distressing to patients, but can lead to physiological changes such as increased tissue oxygen consumption and carbon dioxide production, resulting in raised minute ventilation and cardiac output. It also interferes with patient monitoring and with the mother's ability to hold her baby in an obstetric setting. A number of pharmacological interventions have been studied for the treatment and prophylaxis of shivering, including pethidine, ketamine, clonidine, doxapram, and tramadol [13]. The neurotransmitter serotonin ($5\text{-}HT_3$) plays a role in the control of perioperative shivering by its action in the preoptic anterior hypothalamic region [8].

Shivering can be most effectively prevented by pethidine, although its mechanism of action is not completely understood. The major concern is that, with concomitant

Figure 1



Percentage of parturients with respect to shivering endpoint variables and percentage of vomiting in 12 h postoperative. *Statistically significant difference.

Table 2 Measured outcome variables such as incidence and percentage of shivering, rescue antishivering drug intake, interference with neonatal holding and monitoring, and maternal vomiting

		Groups		
Measured variables	Calculation (%)	Group G (*n* = 58) [*n* (%)]	Group P (*n* = 59) [*n* (%)]	*P* value
Shivering at any time	Count	28 (48.3)	37 (62.7)	0.138
Shivering score 1 and 2	Count	21 (36.2)	25 (42.4)	0.571
Shivering score 3 and 4	Count	7 (13.8.5)	12 (20.3)	0.462
Rescue antishivering medication intake	Count	10 (17.2)	19 (32.2)	0.086
Interference with neonatal holding	Count	5 (8.6)	8 (13.6)	0.558
Interference with monitoring	Count	11 (19.0)	14 (23.7)	0.653
Maternal vomiting in 12 h postoperative	Count	6 (10.3)	16 (27.1)	0.032*

*Indicates that it is statistically significant.

Table 3 Maternal tympanic temperature (C) and neonatal Apgar score

Measured secondary outcome variables	Groups	*n*	Mean	SD	*P* value
Tympanic membrane temperature	Group G	58	37.021	0.2978	0.48
	Group P	59	36.980	0.3315	
Apgar score	Group G	58	8.41	0.72	0.09
	Group P	59	8.19	0.75	

use with other anesthetics, it can cause respiratory depression as well as a documented higher incidence of postoperative nausea and vomiting [14]. Ketamine is associated with a higher incidence of hallucinations. Tramadol is associated with nausea, vomiting, and dizziness [15]. Clonidine may be associated with hypotension and sedation. In contrast, 5-HT_3 antagonists appear to be relatively free of side effects, although this needs further investigations and studies.

In our study, we investigated the ability of prophylactic intravenous granisetron, a selective 5-HT_3 receptor antagonist, to prevent or decrease shivering in parturients scheduled for elective cesarean section. We found that 3 mg prophylactic intravenous granisetron did not prevent ($P = 0.138$) or decrease ($P = 0.462$) the incidence of shivering significantly in comparison with the placebo group in an obstetric setting.

Our results partially coincide with the study by Browning *et al.* [16] who evaluated the use of intravenous ondansetron 8 mg, which is another 5-HT_3 antagonist, before performing combined spinal–epidural anesthesia in women undergoing elective cesarean delivery and concluded that it does not decrease the incidence or severity of shivering.

Our results were discrepant from those found by Sagir *et al.* [9] who compared placebo, ketamine, granisetron, and a combination of ketamine and granisetron for the prevention of shivering caused by regional anesthesia in patients undergoing urological surgery. After 15 min, the number of patients with observed shivering was 22 in group P (placebo group), six in group G (the group receiving granisetron only), seven in group GK (the group receiving a combination of granisetron and ketamine), and 0 in group K (the group receiving ketamine only); thus, in their study granisetron significantly decreased shivering in comparison with placebo.

Our results also did not coincide with those of Eldaba and Amr [6] who studied the effect of pretreatment with intravenous granisetron 10 μg/kg intravenously diluted in 10 ml saline in reducing postoperative shivering after spinal anesthesia in children aged 2–5 years in comparison with placebo. They found that shivering did not occur in any patient in group G; it occurred in six patients in group P. This may be explained by the huge physiological differences between our obstetric patients and their pediatric ones, with altered pharmacological response to granisetron in both settings.

Our results also disagree with a study carried out by Sajedi and colleagues, which evaluated the efficacy of granisetron in comparison with meperidine and tramadol in preventing postanesthetic shivering in patients undergoing elective orthopedic surgery under standardized general anesthesia and found that the number of patients with observable shivering was 19 in group P (placebo), nine in group G (granisetron), seven in group T (tramadol), and six in group M (meperidine). Granisetron significantly reduced the incidence of shivering in comparison with placebo ($P = 0.013$). Although the frequency of shivering was higher with granisetron in comparison with tramadol and meperidine, it was not statistically significant ($P > 0.05$) [17]. This can be explained by the fact that their study was carried out in a different setting including male as well as female patients under general anesthesia unlike our study that was carried out only on parturients under spinal anesthesia, as the mechanism of shivering differs in general and spinal anesthesia.

Kim *et al.* [8] performed a study to evaluate the effect of ramosetron, another 5-HT_3 antagonist, on shivering during spinal anesthesia in patients who had undergone knee arthroscopy. Shivering was observed in two patients in group R (ramosetron) and nine patients in group S (saline) ($P = 0.038$). This does not coincide with our findings.

A limitation of our protocol may be that we did not include a positive control group using an agent established to have antishivering properties, such as pethidine. We believed it would be more beneficial to primarily investigate the 5-HT pathways and their role in shivering. Granisetron prophylaxis has not been studied before in an obstetric setting for prevention of shivering. Granisetron has a powerful antiemetic effect and a favorable cardiorespiratory side-effect profile, especially desirable in an obstetric setting [10].

There are a few possible explanations as to why this study did not benefit from granisetron in preventing shivering. First, our study patients included only relatively young pregnant women, who are a segment of the population with special characteristics. Another factor is that evidence shows that shivering during pregnancy differs in many ways to that in the nonpregnant population, which is mainly thermoregulatory in nature [18]. In addition, an

immunological response to fetomaternal transfusion is postulated by some researchers to be partly the cause of peripartum shivering [19]. It is also possible that, because of the physiological changes in this group of patients, such as increased blood volume and cardiac output in the third trimester, 3 mg granisetron used in our study may have been less effective and a higher dose is needed to establish the desired effect.

In our study, parturients underwent elective surgery under spinal anesthesia; therefore, our results may not apply to other settings such as emergency surgery under different types of neuraxial blocks or general anesthesia.

With respect to rescue medication intake, interference with newborn holding and monitoring as well as secondary measured variables such as tympanic membrane temperature and 1-min Apgar score, we found no significant differences between both groups. Twelve-hour postoperative maternal vomiting was significantly lower in the group of patients who received granisetron.

Conclusion

Our study found that prophylactic intravenous administration of 3 mg granisetron before spinal anesthesia in parturients undergoing elective cesarean section did not significantly decrease the incidence or severity of shivering. We think that further studies are needed on its use in different settings, with different doses as well as under different anesthetic techniques.

Acknowledgements

Conflicts of interest

The authors have no conflict of interest.

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