Brazilian Journal of Anesthesiology 2022;72(4):457–465

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

The effect of 1-mg versus 3-mg granisetron on shivering and nausea in cesarean section: a randomized, controlled, triple-blind, clinical trial

Laleh Dehghanpisheh[a], **Simin Azemati**[a,*], **Mahdi Hamedi**[b], **Zeinabsadat Fattahisaravi**[a]

[a] *Shiraz University of Medical Sciences, Shiraz Anesthesiology and Critical Care Research Center, Shiraz, Iran*
[b] *Shiraz University of Medical Sciences, Shiraz, Iran*

Received 20 May 2020; accepted 27 February 2021
Available online 2 April 2021

KEYWORDS
Shivering;
Nausea;
Vomiting;
Granisetron;
Clinical trial;
Iran

Abstract
Introduction: Intra- and postoperative nausea, vomiting and shivering are mentioned as the most common problem following spinal anesthesia. The aim of this study is to compare two different doses of granisetron to control the shivering, nausea, and vomiting caused by spinal anesthesia in women undergoing cesarean section (C/S).
Method: This study is a randomized, triple-blind clinical trial. The participants received 1-mg or 3-mg granisetron. Women who underwent elective C/S were enrolled. Inclusion criteria were ASA (American Society of Anesthesiologists) physical status grade I or II and age range of 18–40 years. Primary outcome was changes in the score of shivering, and nausea and vomiting. Secondary outcomes were Apgar score, mean arterial pressure, systolic blood pressure, diastolic blood pressure, temperature and heart rate.
Results: According to binary logistic regression, the incidence of shivering (6.9% vs. 1.5%; *p*-value = 0.049), and nausea and vomiting (19.2% vs. 9.2%; *p*-value = 0.024) was significantly higher in patients received 1-mg granisetron in comparison with 3-mg granisetron. Multinomial logistic regression showed that the occurrence of shivering, and nausea and vomiting were not associated with the dose of granisetron. There was no significant difference between the age and Apgar score of 1 ($p = 0.908$) and 5 ($p = 0.843$) minute(s) between the two groups.
Conclusion: This study showed that although 3-mg of granisetron reduces the incidence of intra- and postoperative shivering, nausea and vomiting after spinal anesthesia in comparison with 1-mg of granisetron, the difference was not statistically significant.

* Corresponding author.
E-mails: azamatis@yahoo.com, azemati@sums.ac.ir (S. Azemati).

https://doi.org/10.1016/j.bjane.2021.02.049

Introduction

Cesarean Section (C/S) is one of the most common surgeries among women. The incidence of C/S has been increased in the past years.[1] Spinal anesthesia has been used widely due to its better postoperative pain control, short onset of action, lower dose of drug, and also maternal awakening at birth. Postoperative hypotension and nausea are mentioned as common problems following spinal anesthesia.[2,3]

Shivering is one of the mechanisms of protection in healthy human body to maintain the core temperature in normal range.[4] Adverse effects of shivering including tachycardia, increased cardiac output, raised body oxygen consumption, and meddling with mother-infant skin to skin contact are annoying for the mother and her fetus during delivery process.[5] The effectiveness of non-pharmacological interventions like warmed intravenous (IV) fluid injection or forced air warming on post-C/S shivering is controversial. Therefore, the role of medications has become more significant for controlling shivering after C/S.[6]

Several medications are used for decreasing the frequency and severity of shivering.[7] Previous studies have demonstrated that disturbance in the serotogenic system is one of the main causes of postoperative shivering.[6,8] The uptake of serotonin is inhibited by 5-HT_3 receptor antagonists in the preoptic anterior region of hypothalamus, which is responsible for adjusting the body temperature.[6]

The possible maternal and fetal adverse effects (such as nausea, vomiting, hemodynamic effects, and depression of respiratory system) have limited the use of many drugs (for example meperidine, tramadol, dexmedetomidine, or clonidine) which is used extensively as prophylaxis of shivering in non-pregnant patients.[9]

Serotonin antagonists decrease body's set-range temperature, thereby reducing the defense mechanism and discomfort caused by postoperative hypothermia. These indicate that serotogenic systems are effective in controlling shivering after anesthesia.[8]

Granisetron, a selective serotonin 5-HT_3 receptor antagonist, has been used to prevent shivering during spinal anesthesia. Previous studies have showed the effectiveness of granisetron with a dose of 3 mg and 1 mg for prevention of shivering after spinal anesthesia.[10] Granisetron has fewer side effects, including extrapyramidal effects and sedation, in comparison with other antiemetic drugs.[11]

At present, few studies have been conducted to find a dose for granisetron in patients undergoing C/S under spinal anesthesia.[8]

Objectives

We hypothesized that 3-mg granisetron would be more effective than 1-mg granisetron at preventing post-spinal shivering, nausea, and vomiting caused by spinal anesthesia in women undergoing C/S in the first 80 minutes after study.

Methods

Trial design

This study is an unicentric, randomized, triple-blind (participants, investigator, and statistician) clinical trial with parallel design. The participants were randomly divided into two groups (1:1 allocation ratio) to receive 1-mg granisetron or 3-mg granisetron.

Study participants

Women who underwent elective C/S in operation rooms of Hafez hospital, a tertiary hospital affiliated to Shiraz University of Medical Sciences, Shiraz, Iran from 1-July 2019 to 31-December 2019 were studied.

Inclusion criterion was grade I or II of physical status classification system according to American Society of Anesthesiologists[12] (ASA) guideline and age between 18–40 years. The exclusion criteria were (1) dissatisfaction to participate in research; (2) history of smoking and IV drug abuse; (3) history of neuromuscular diseases; (4) preeclampsia; (5) spinal anesthesia contraindications such as infection at the site of injection, unknown neurologic disease, hypovolemia, severe bleeding tendency, and high intracranial pressure; (6) past history of hypertension or cardiovascular disease; (7) body temperature below 36.5 or above 38 degrees before C/S; (8) past history of hypo- or hyperthyroidism; (9) blood transfusion during C/S and medications (for example misoprostol) that cause changes in the body temperature or nausea and vomiting; (10) history of shivering before C/S; and (11) history of allergy to granisetron or ondansetron.

Intervention

All drug solutions were prepared in equal syringes of the same size and shape by one nurse who knows the study group and gave them to the anesthesiologist for sterile injection. The nurse was staff of operation room and all syringes were prepared by her. One-miligram or 3-mg granisetron (Caspian Tamin pharmaceutical company, Iran) was injected intravenously 10 minutes before spinal anesthesia at the same volume (3 mL) and the similar syringes in size and shape.

After each patient was assigned in the study groups, pulse oximetry, Electrocardiogram (ECG), and blood pressure and temperature monitoring were done for her. An intravenous line was inserted by an angiocath 18G and 5-cc.kg^{-1} ringer's lactate solution infused at 37 °C 15 min before spinal anesthesia. The temperature of the operating room was kept at 24 ± 0.6 °C during the surgery. Patients did not receive any medication before C/S.

Spinal anesthesia was performed in both groups in sitting position using spinal needle 25G at L3–L4 or L4–L5 level. After ensuring that the needle is in the correct place, blocking was done by injection of 10 mg bupivacaine 0.5% and the patient immediately placed in supine position. Then, all patients were covered with a layer of surgical drape and a blanket was placed on the chest and arms. No heater was used in the operation room. Age, length of anesthe-

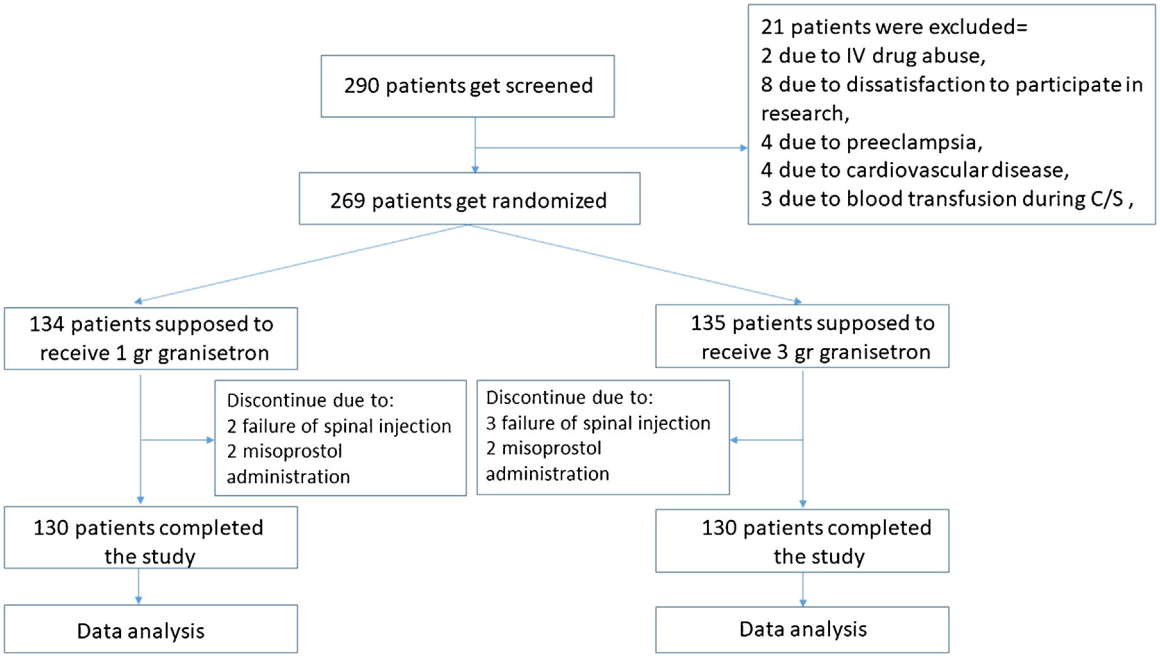

Figure 1 CONSORT flow diagram of the study.

sia and surgery, body temperature, shivering score, nausea and vomiting, Apgar score of 1 and 5 minutes were recorded for each patient. Before injection of the drugs and every 10 minutes during surgery, the body temperature was measured using infrared ear thermometer (Braun ThermoScan IRT 450, Braun GmbH, Germany).

Shivering was evaluated every 10 minutes during the operation and after recovery and according to the Tsai and Chu study.[13] Shivering was graded according to following categories: 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, 4 = shivering involving the whole body.[13] Patients with shivering score of 1–2 were considered as moderate shivering and those with degrees of 3–4 as severe shivering. Pethidine was administered intravenously 0.25 $mg.kg^{-1}$ to patients with shivering of grade 3 or higher.

The patients' blood pressure and pulse rate were measured every 10 minutes, and if systolic blood pressure was lower than 100 mmHg or 20% of the baseline, 5 mg ephedrine was administered intravenously. If the heart rate was less than 50 per minute, 0.5 mg intravenous atropine was administered. Nausea and vomiting were assessed every 10-minutes during C/S till 80 minutes postoperatively and recorded by a physician blinded to the group allocation. Base on the Bellville scoring score, grading was as below: without nausea = 0, nausea = 1, retching = 2, and vomiting = 3.[14]

If nausea and vomiting were observed, 10 mg metoclopramide was given intravenously.

Outcomes

Primary outcome was changes in shivering, and nausea and vomiting. Secondary outcomes were Apgar score, mean arterial pressure, systolic blood pressure, diastolic blood pressure, temperature, and heart rate.

Sample size

Based on the results of study by Abdel-Ghaffar and Moeen[9] ($p1$ = 0.159 and $p2$ = 0.292), and considering α = 0.05 and 1-β = 0.7 and 1:1 allocation ratio between the control and treatment groups, the minimum sample size was 122 in each group (244 in total).

Randomization

Patients were randomly assigned to two groups to receive 1-mg granisetron (Group I) or 3-mg granisetron (Group II). Randomization was performed using online random generator website ''www.randomizer.org'' which uses the ''Math.random'' method within the JavaScript programming language to generate its random numbers.[15] Randomization was performed by a statistician who worked in Shiraz anesthesiology and critical care research center, Shiraz University of Medical Sciences, Shiraz, Iran. He was blinded to patients' group.

Blinding

The researcher (anesthesiologist who injected the drug and measured the response), patients, and statistician were blinded to the patient's group assignment and allocations of the treatment.

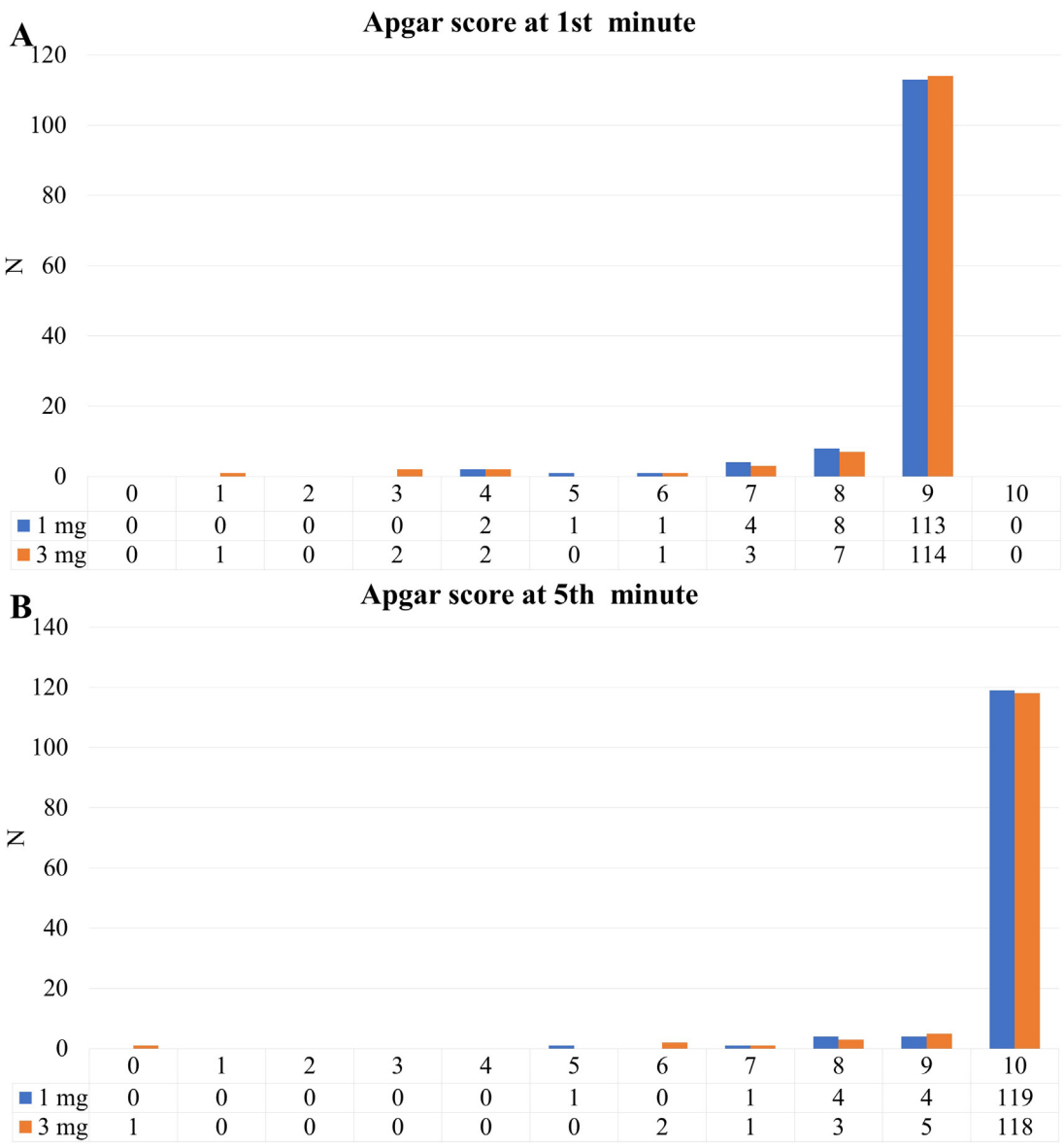

Figure 2 The children's Apgar scores.

Ethical approval

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (Ethic code: IR.SUMS.MED.REC.1396.113), and all the patients signed the written informed consent form before their participation in this study. The study protocol was registered in www.irct.ir website (IRCT20141009019470N81; https://en.irct.ir/trial/28145).

Statistical analysis

Results are reported as descriptive statistics including Mean (±SD) or frequency (%). Independent sample *t*-test and Chi-Square were used where appropriate. Two-way repeated measure ANOVA was used to determine any statistically significant change in the trend of systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, heart rate, and temperature. Greenhouse-Geisser correction was reported if assumption of sphericity was violated. Because of low incidence of shivering and nausea/vomiting, these variables were converted to binary variable, and binary and multinomial logistic regression analysis were conducted. Analyses were performed using SPSS version 21 (Chicago, USA) software; *p*-value less than 0.05 was considered as statistically significant.

Results

After screening 290 patients, 269 of them were enrolled in the study (Fig. 1).

The mean (±SD) age of patients in 1-mg and 3-mg granisetron were 29.83 ± 5.81 and 29.88 ± 5.53, respectively. The mean (±SD) weight of patients was

Table 1 The nausea and shivering scores.

Variable	Group	Grade	Baseline	10 minutes n (%)	20 minutes n (%)	30 minutes n (%)	40 minutes n (%)	50 minutes n (%)	60 minutes n (%)	70 minutes n (%)	80 minutes n (%)
Nausea and vomiting	1 mg (n = 130)	Without nausea	130 (100)	122 (93.8)	120 (92.3)	121 (93.1)	126 (96.9)	126 (96.9)	128 (98.5)	130 (100)	126 (97.0)
		Nausea	0	4 (3.1)	1 (3.1)	1 (1.5)	3 (2.3)	1 (0.8)	0	0	2 (1.5)
		Retching	0	1 (0.8)	2 (1.5)	6 (4.6)	1 (0.8)	0	1 (0.8)	0	0
		Vomiting	0	3 (2.3)	4 (3.1)	1 (0.8)	0	3 (2.3)	1 (0.8)	0	2 (1.5)
	3 mg (n = 130)	Without nausea	130 (100)	125 (96.2)	126 (96.9)	128 (98.5)	129 (99.2)	128 (98.5)	130 (100)	129 (99.2)	129 (99.2)
		Nausea	0	3 (2.3)	3 (2.3)	0	0	2 (1.5)	0	0	0
		Retching	0	1 (0.8)	0	2 (1.5)	0	0	0	1(0.8)	0
		Vomiting	0	1 (0.8)	1 (0.8)	0	1 (0.8)	0	0	0	1 (0.8)
	p-value[a]		1.000	0.825	0.244	0.091	0.184	1.000	0.498	1.000	0.433
Shivering	1 mg (n = 130)	0	129 (99.2)	130 (100)	129 (99.2)	129 (99.2)	128 (98.5)	128 (98.5)	126 (96.9)	125 (96.2)	129 (99.2)
		1	0	0	0	0	0	0	0	0	0
		2	1 (0.8)	0	0	1 (0.8)	0	0	1 (0.8)	0	0
		3	0	0	0	0	0	3 (2.3)	0	1 (0.8)	0
		4	0	0	1 (0.8)	0	2 (1.5)	2 (1.5)	3 (2.3)	4 (3.1)	1 (0.8)
	3 mg (n = 130)	0	130 (100)	130 (100)	130 (100)	130 (100)	129 (99.2)	130 (100)	130 (100)	130 (100)	129 (99.2)
		1	0	0	0	0	0	0	0	0	0
		2	0	0	0	0	0	0	0	0	0
		3	0	0	0	0	1 (0.8)	0	0	0	0
	p-value[a]	4	0	0	0	0	0	0	0	0	1 (0.8)
			1.000	1.000	1.000	1.000	0.498	0.498	0.122	0.060	1.000

[a] Fisher's exact test.

Figure 3 Trend of maternal blood pressure, heart rate and temperature.

79.20 ± 12.01 in 1-mg group and 81.98 ± 9.06 in 3-mg group.

Although the incidence of nausea was lower in the group that received 3-mg granisetron in almost all times, the difference was not statistically significant. Overall, 12 patients had reported grade 1 nausea in the group with 1 mg of granisetron, while 8 patients with 3 mg of granisetron reported this. Eleven patients in the group with 1 mg of granisetron had grade 2 (nausea with retching), whereas only four in the group with patients who received 3 mg of granisetron had the same grade; also, in patients who received 1 mg of granisetron, 14 had grade 3 nausea, whereas only 4 in the group with 3 mg of granisetron had the same grade (Table 1).

Shivering was graded into 5 levels. The difference between the two groups was not statistically significant in all episodes. At the end of the study, a total of 19 shivering cases were reported in the group with 1 mg of granisetron, of which 13 had shivering grade 4, 4 had grade 3, and the two others were grade 2. In the group with 3 mg of granisetron, only two patients (one grade 4 and one grade 3) stated shivering (Table 1).

Table 2 Binary logistic regression.

Variables	Group				*p*-value	Exp (B)	95% Confidence Interval for Exp (B)	
	1 mg (n = 130)		3 mg (n = 130)					
	Count	%	Count	%			Lower	Upper
Shivering								
No	121	93.1%	128	98.5%	0.049	4.760	1.008	22.477
Yes	9	6.9%	2	1.5%				
Nausea and vomiting								
No	105	80.8%	118	90.8%	0.024	2.341	1.121	4.892
Yes	25	19.2%	12	9.2%				

Table 3 Multinomial regression of parameters associated with shivering and nausea and vomiting.

Variables	Factors	*p*-value	Exp (B)	95% Confidence Interval for Exp (B)	
				Lower	Upper
Shivering	Mean arterial blood pressure	0.926	0.995	0.887	1.115
	Temperature	0.890	0.919	0.278	3.042
	Heart rate	0.209	1.034	0.982	1.088
	Granisetron (1-mg is reference)	0.067	4.457	0.901	22.048
Nausea and vomiting	Mean arterial blood pressure	0.020[a]	0.921	0.859	0.987
	Temperature	0.245	1.588	0.728	3.460
	Heart rate	0.192	1.022	0.989	1.057
	Granisetron (1-mg is reference)	0.057	2.132	0.977	4.650

[a] Statistically significant.

Binary logistic regression showed significant increase in shivering (Exp (B) = 4.760; *p*-value = 0.049) and nausea and vomiting (Exp (B) = 2.341; *p*-value = 0.024) (Table 2).

Multinomial regression of parameters associated with shivering, and nausea and vomiting is shown in Table 3. Mean arterial blood pressure, temperature, heart rate and dose of granisetron were not associated with shivering. Occurrence of nausea and vomiting was associated with mean arterial blood pressure, but temperature, heart rate and dose of granisetron did not affect nausea and vomiting.

Apgar scores of infants at first and fifth minutes are reported in Figure 2. There was no significant difference in Apgar 1 (p = 0.908) and 5 (p = 0.843) between the two groups.

There was significant difference in trend of systolic blood pressure (p = 0.014), diastolic blood pressure (p = 0.042), and mean arterial blood pressure (p = 0.010) over time. The change in trend of heart rate (p = 0.072) and body temperature (p = 0.067) were not statistically significant (Fig. 3).

Discussion

In this clinical trial, we compared the effects of two different intravenous doses of granisetron on prevention of shivering, nausea and vomiting following spinal anesthesia in C/S. The results showed that the two different doses of 1 mg and 3 mg did not differ significantly in the control of intra- and postoperative shivering. However, given the incidence of shivering in 19 patients in the 1-mg granisetron group versus 2 patients in the 3-mg granisetron group, the results could be clinically significant. The difference in the heart rate and body temperature was not significant between the two groups. There was significant difference in trend of systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure over time.

The relation between hypothermia and shivering was documented in previous studies.[16] Vasoconstriction is the main mechanisms against hypothermia. Second-line thermoregulatory mechanism is shivering. It can increase core body temperature in hypothermic patients.[17] Bameri et al., studied the effects of a hypothermia prevention program on the shivering after C/S. They concluded that prevention of hypothermia can significantly prevent the decrease in central body temperature and thus shivering after C/S.[18]

Many medications including non-opioid and opioid drugs are usually administered to prevent and subside postoperative shivering. Some potential side effects include decrease or increase in blood pressure, respiratory system depression, nausea and vomiting, and sedation. 5-HT_3 receptor antagonists have recently been used to prevent postoperative shivering.[6]

Previous studies showed that 5-HT_3 receptor antagonists could prevent postoperative shivering, which is comparable to the efficacy of meperidine. The 5-HT_3 is released from the preoptic area of the hypothalamus and increase the body temperature by initiating heat production pathways. Preventing 5-HT reuptake in the preoptic area is the possible cause of decrease in postoperative shivering by 5-HT_3 antagonists after general or spinal anesthesia.[8]

A meta-analysis study reviewed 14 randomized clinical trials that included 980 patients. They reported that the rate of shivering was significantly lower in the 5-HT3 groups in comparison to the placebo ones. On the other hand, no significant difference was observed in the frequency of shivering between the 5-HT_3 and meperidine groups.[8]

Another meta-analysis investigated the efficacy of intravenous infusion of granisetron for prevention of shivering after the operation. Researchers included 8 clinical trials with 839 patients. They concluded that granisetron had anti-shivering effects in both general and spinal anesthesia and also laparoscopic and laparotomic surgery. They concluded 40 $\mu g.kg^{-1}$ and 2 mg of granisetron diminished the rate of shivering, postoperative nausea, vomiting, and pruritus compared with placebo.[19]

A clinical trial by Abdel-Ghaffar and Moeen compared the efficacy of 0.9% saline, 1-mg granisetron, or 0.7-mg granisetron. Patients received medications before spinal anesthesia. Shivering was noted in 77.5% of patients who received 0.9% saline, 15.9% in 1-mg granisetron and 29.2% in 0.7-mg granisetron. The severity of shivering mean intraoperative arterial pressure and heart rate was significantly lower in patients who received 1 mg of granisetron compared with other groups. Pruritus was reported by 22.5% of patients in the saline group. No patients in granisetron groups noted pruritus. Incidence of nausea was 11.3, 14.5 and 5.6 in 0.9% saline, 1-mg granisetron and 0.7-mg granisetron groups, respectively. 22.5%, 11.6 and 8.3% of patients vomited in the 0.9% saline, 1-mg granisetron and 0.7-mg granisetron groups, respectively. The patient satisfaction scores were higher in the 1-mg granisetron group.[9]

Another study evaluated the effects of granisetron, ketamine and pethidine on prevention of shivering following spinal anesthesia. This study reported intravenous administration of 3 mg of granisetron, 25 mg of ketamine, or 25 mg of pethidine before spinal anesthesia can reduce the intensity of shivering significantly. Furthermore, prophylactic administration of granisetron decreases nausea and vomiting and the need of antiemetics.[20]

A study by Sharma and Singh investigated the effect of Granisetron on prevention of nausea and vomiting after C/S. Patients received either 40 $\mu g.kg^{-1}$ of granisetron or 0.9% saline intravenously. The rate of early (between 0 to 6 hours) and late (between 6 to 24 hours) postoperative nausea and vomiting after administration of granisetron was 18.0% and 14.0%, respectively. There was 56.0% and 48.0% for the 0.9% saline group. They stated granisetron had preventive effects on the prevalence of post-operative nausea and vomiting following spinal anesthesia.[21]

A clinical trial was conducted on patients undergoing lower abdominal surgery following spinal anesthesia. The researcher investigated the efficacy of granisetron in decreasing postoperative shivering, nausea, and vomiting. The study showed that a high dose of granisetron (40 $\mu g.kg^{-1}$) significantly decreased the rate and severity of postoperative shivering, nausea and vomiting compared to placebo. Low dose granisetron (10 $\mu g.kg^{-1}$) did not show any beneficial effects on shivering, nausea, and vomiting.[22]

Our study had some strength. We conducted this study on a large group of patients. The other strength was recording blood pressure, Apgar score, heart rate, and temperature in several times in addition to the incidence and severity of nausea and vomiting and shivering. This gives valuable data about systemic effects of granisetron in different doses.

We recommend that further studies gather data about the volume of bleeding loss, so that we can discuss about blood pressure according to it. In addition, the follow-up time could have been longer.

This study showed that although 3 mg of granisetron reduces the incidence of intra- and postoperative shivering, nausea and vomiting after spinal anesthesia in comparison with 1 mg of granisetron, but the difference was not statistically significant.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgment

This article was extracted from the residency thesis written by Dr. Mahdi Hamedi and supported by the Vice Chancellor for Research of Shiraz University of Medical Sciences (grant number: 95-01-01-12667).

References

1. Uppal V, Retter S, Casey M, Sancheti S, Matheson K, McKeen DM. Efficacy of intrathecal fentanyl for cesarean delivery: a systematic review and meta-analysis of randomized controlled trials with trial sequential analysis. Anesth Analg. 2020;130:111–25.
2. Miao S, Shi M, Zou L, Wang G. Effect of intrathecal dexmedetomidine on preventing shivering in cesarean section after spinal anesthesia: a meta-analysis and trial sequential analysis. Drug Des Devel Ther [Internet]. 2018;12:3775–83.
3. Weigl W, Bieryło A, Wielgus M, Krzemień-Wiczyńska Ś, Kołacz M, Dąbrowski MJ. Perioperative analgesia after intrathecal fentanyl and morphine or morphine alone for cesarean section: A randomized controlled study. Medicine (Baltimore). 2017;96, e8892-e.
4. Lomo T, Eken T, Bekkestad Rein E, Nja A. Body temperature control in rats by muscle tone during rest or sleep. Acta Physiol (Oxf). 2019:e13348.
5. Majd MN, Tazeh-kand NF, Hoseini L, Sepidarkish M. Pre-Delivery conscious sedation with intravenous low dose thiopental na bolus during spinal anesthesia for cesarean section. Arch Anesth Crit Care. 2020;6:8–15.
6. Lopez MB. Postanaesthetic shivering - from pathophysiology to prevention. Rom J Anaesth Intensive Care. 2018;25:73–81.
7. Liu J, Wang Y, Ma W. Shivering prevention and treatment during cesarean delivery under neuraxial anesthesia: a systematic review. Minerva Anestesiologica. 2018;84:1393–405.
8. Zhou C, Zhu Y, Liu Z, Ruan L. 5-HT3 receptor antagonists for the prevention of postoperative shivering: a meta-analysis. J Int Med Res. 2016;44:1174–81.
9. Abdel-Ghaffar HS, Moeen SM. Prophylactic granisetron for post-spinal anesthesia shivering in cesarean section: A randomized controlled clinical study. Acta Anaesthesiol Scand. 2019;63:381–8.
10. Ngo AL, Orhurhu V, Urits I, Delfin EO, Sharma M, Jones MR, et al. Extended release granisetron: Review of pharmacologic considerations and clinical role in the perioperative setting. Saudi J Anaesth. 2019;13:231–6.
11. Spartinou A, Nyktari V, Papaioannou A. Granisetron: a review of pharmacokinetics and clinical experience in chemotherapy

induced – nausea and vomiting. Expert Opin Drug Metab Toxicol. 2017;13:1289–97.
12. Doyle DJ, Garmon EH. American Society of Anesthesiologists Classification (ASA Class). StatPearls Publishing: Treasure Island (FL); 2019.
13. Tsai YC, Chu KS. A comparison of tramadol, amitriptyline, and meperidine for postepidural anesthetic shivering in parturients. Anesth Analg. 2001;93:1288–92.
14. Bellville JW, Bross ID, Howland WS. A method for the clinical evaluation of antiemetic agents. Anesthesiology. 1959;20:753–60.
15. Urbaniak G, Plous S, Available from: Research Randomizer (Version 4.0) [Compute software]; 2013 http://www.randomizer.org/
16. Dendis M, Hooven K. Preventing hypothermia during cesarean birth: an integrative review. MCN The American journal of maternal child nursing. 2020;45:102–8.
17. Lenhardt R. Body temperature regulation and anesthesia. Handbook Clin Neurology. 2018;157:635–44.
18. Bameri F, Navidian A, Shakeri A, Pishkarmofrad Z. The effects of a hypothermia prevention program on the body temperature and shivering in women undergoing cesarean section. World Family Med J: Incorporating Middle East J Family Med. 2018;99:1–7.
19. Ma J, Si B, Liang X, Cui D, Pan D, Wang Z. Prophylactic granisetron for prevention of postoperative shivering: a meta-analysis of randomized controlled trials. Int J Clin Exp Med. 2019;12:11027–36.
20. Sayed AE-DM. Studying the effects of granisetron, ketamine, and pethidine on prevention of shivering induced by spinal anesthesia. Al-Azhar Assiut Medical J. 2018;16:176.
21. Sharma S, Singh M. Efficacy of granisetron for prevention of nausea and vomiting in patients undergoing cesarean section under spinal anesthesia: A randomized double blind placebo-controlled study. J Advanced Med Dental Sciences Res. 2019;7:152–5.
22. Dehghani A, Anvari HMP. High dose but not low dose granisetron decreases incidence and severity of post anesthesia shivering (PAS) and postoperative nausea and vomiting (PONV) following lower abdominal surgeries under spinal anesthesia. Archives Anesthesiol Crit Care. 2017;3:304–7.