Efficacy of granisetron on prevention of shivering, nausea and vomiting during cesarean delivery under spinal anesthesia: A randomized double-blinded clinical trial

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ABSTRACT

Background: Hypothermia, shivering, nausea and vomiting are frequent perioperative events in patients undergoing cesarean delivery under spinal anesthesia. Apart from physical warming for shivering many drugs have also been used for prevention of these events.

Objectives: We conducted a randomized double-blinded clinical trial to evaluate the effect of a single drug, granisetron on prevention of shivering, nausea and vomiting during cesarean section performed under spinal anesthesia.

Materials and Methods: One hundred American Society of Anesthesiologists I-II patients undergoing elective cesarean section under spinal anesthesia were randomly allocated into two groups, control saline ($n = 50$) or granisetron groups ($n = 50$). Warmed (37°C) lactated ringer’s solution was infused over 15 min before anesthesia. Spinal block was performed with the same technique in both groups. In the saline group 3 ml of 0.9% saline and in granisetron 3 mg (3 ml) granisetron was injected intravenously after intrathecal injection at identical times. Shivering, maximum and minimum level of spinal block, core body temperature, nausea and vomiting and need to treat shivering with intravenous pethidine and neonates APGAR scores were all recorded.

Results: Demographic data, median of sensory block level and mean core body temperature were not statistically different in groups. Eight percent (4/50) of patients in granisetron and 54% (27/50) of patients in the saline group had shivering during the perioperative period that was treated with pethidine ($P = 0.001$). Ten patients (20%) in granisetron and 30 patients (60%) in saline group had nausea ($P = 0.002$). No patients in both groups needed rescue medication. 1st and 5th minutes APGAR scores of neonates were not statistically different in the groups. Ten patients (20%) in granisetron and 30 patients (60%) in saline group had nausea ($P = 0.002$).

Conclusions: Granisetron is an effective way to prevent shivering, nausea and vomiting during cesarean delivery under spinal anesthesia with no effect on APGAR score.

Key words: Granisetron, nausea and vomiting, shivering, spinal anesthesia, thermoregulation

INTRODUCTION

Maintaining core temperature of patients during anesthesia is difficult due to rapid heat loss and core-to-peripheral redistribution of body heat. Regional anesthesia significantly impairs the thermoregulation and predisposes patients to hypothermia, which reduces the threshold for vasoconstriction and shivering.\[1,2\]
The incidence of shivering is up to 40-60% even in regional anesthesia that is distressing for the patients.[6-9] Shivering causes increased metabolic activity, oxygen consumption, intracranial and intraocular pressure. The other effects are increased in cardiac output, peripheral resistance, carbon dioxide production, and lactic acidosis. Moreover, it also interferes with electrocardiogram (ECG) and oxygen saturation monitoring (pulse oximetry).[10]

The mechanisms chiefly responsible for shivering in patients undergoing surgery are intraoperative temperature loss, increased sympathetic tone, pain, and systemic release of pyrogens. The best way to avoid the intraoperative and postoperative shivering-induced complications is to prevent shivering.[5]

Perioperative hypothermia and shivering are usually prevented by physical methods like surface warming and pharmacologically by drugs such as pethidine, tramadol, clonidine, and ketamine.[6-9]

Serotonin (5-hydroxytryptamine [5-HT3]), a biologic amine found in the brain and spinal cord, plays a part in neurotransmission; studies suggest that the serotonergic system plays a role in controlling perioperative shivering. A serotonin 5-HT3 receptor antagonist inhibits the uptake of serotonin in the preoptic anterior hypothalamic region, which influences both heat production and heat loss.[10]

In some studies ramosetron, a selective serotonin 5-HT3 receptor antagonist, has been shown to be effective in the prevention of shivering during spinal anesthesia.[10]

On the other hand, nausea and vomiting during spinal anesthesia for cesarean section are common and unpleasant complications. During regional anesthesia, granisetron has been shown to be effective in the prevention of emetic symptoms.[11-15]

The hypothesis of the present study was that granisetron can reduce intra-operative shivering in pregnant patients who go under spinal anesthesia for cesarean delivery.

The primary aim of our study is to evaluate the efficacy of granisetron (a 5-HT3 receptor antagonist) on the spinal-induced shivering during cesarean section. The secondary aim is to evaluate the efficacy of granisetron on reducing intraoperative nausea and vomiting in this group of patients.

**MATERIALS AND METHODS**

This randomized double-blinded controlled trial was performed in Dr. Shariati Hospital of Tehran University of Medical Sciences since March to September of 2013. The study protocol conformed to the ethical guidelines of the 1989 Declaration of Helsinki and ethical approval was provided by the Ethical Committee of Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran, protocol number 110 on 20 January 2013.

A total of 100 pregnant women aged 18-42 years, who were scheduled for elective cesarean section under spinal anesthesia were included and oral informed consent was obtained separately before surgery. Patients were randomly allocated into two equal groups. Randomization was done by means of computer-generated codes and was concealed until interactions were assigned. Patients with contraindications to spinal anesthesia, history of hypertension or other cardiovascular disease, preoperative fever or hypothermia (temperature >38°C or below 36.5°C), hypo or hyperthyroidism, a requirement for blood transfusion during surgery and medications likely to alter thermoregulation or nausea and vomiting, were excluded.

On arrival to the operating room, standard monitoring was applied to all patients including pulse oximeter, ECG, noninvasive arterial blood pressure and tympanic thermometer for controlling core temperature. An 18 gauge intravenous catheter was placed on the dorsum of the nondominant hand of the patients and 5 ml/kg lactated ringer’s solution warmed to 37°C was infused over 15 min before spinal anesthesia. All warmed solutions were prepared by nursing staffs who were not involved in patient’s management or data collection. Temperature of the operating room was maintained about 24°C ± 0.6°C during the perioperative period.

Patients received no premedication. All patients were blocked in the lateral position in which a 25-gauge Quincke needle was inserted by midline approach into the L3-L4 or L4-L5 interspaces and after ensuring the correct position of the needle, 12 mg of hypertonic 0.5% bupivacaine was injected. Patients were immediately placed in the supine position after the block. Study drugs were prepared, according to the randomization code, by one of anesthesia staff who was not involved in the study and envelopes containing the information of the randomization were sealed and kept in the patient’s folder until the end of the study period. Then prepared solution (Granisetron [Kytril, Roche, Germany] 3 mg or saline) with the same volume (3 ml) was given to the blinded anesthesiologist who injected drug intravenously to patient who was also blinded to allocation immediately after performing spinal anesthesia. All patients were covered with one layer of paper surgical drapes and one layer of a cotton blanket positioned over the thighs and calves. In addition, one layer of a cotton blanket was placed over the chest and arms. No other warming device was used. The upper and lower level of sensory block, age,
weight, duration of anesthesia and surgery, core temperature, shivering score and presence or absence of nausea and vomiting during perioperative period, 1st and 5th min neonates APGAR scores were all recorded. Before intrathecal injection and 5-min intervals during the perioperative period, body temperatures were monitored with an ear thermometer (Thermoscan IRT 3020; Braun, Kronberg, Germany).

Shivering was graded, by following scale: Grade 0 = no shivering, Grade I = piloerection or peripheral vasoconstriction but no visible shivering, Grade II = muscular activity in only one muscle group, Grade III = muscular activity in more than one muscle group but not generalized, Grade IV = shivering involving the whole body. Patients in Grade 0-II assumed have no shivering and patients in Grade III, and IV assumed as have shivering.

If, during spinal anesthesia the patients shivered continuously according to at least Grade III, the prophylaxis was regarded as ineffective and intravenous pethidine 25 mg was administered. In cases that mean arterial pressure drop <100 mmHg or more than >20% decrease in it, 50 µg intravenous phenylephrine administered. In cases of heart rate <50 beat/min, 0.5 mg IV atropine was administrated. Patients with refractory nausea or vomiting were received 10 mg intravenous metoclopramide as a rescue medication.

**Statistical analysis**

A sample size of 50 patients in each group will be sufficient to detect a difference of 50% in shivering between the study-groups assuming a power of 85% and a significance level 0.05. Statistical analysis was performed using SPSS package (version 19, SPSS, Chicago, IL, USA). Normality of distribution of data was tested by the Kolmogorov-Simirnov test. Data were analyzed with independent sample t-test, Chi-square and Mann-Whitney U-test when appropriate. Two-tailed $P < 0.05$ was considered significant.

**RESULTS**

A total of 110 pregnant women who were scheduled for elective cesarean section under spinal anesthesia were included in the study. Finally, 100 patients were analyzed [CONSORT flow chart, Figure 1].

Demographic data and median of sensory block level were not statistically different between the study groups [Table 1].

Duration of surgery and anesthesia were $56.7 \pm 9.7$ and $116.1 \pm 26.6$ min in granisetron and $57.7 \pm 13$ and $111.2 \pm 18$ min in control saline group, respectively ($P = 0.6$ and $P = 0.2$).

There was no difference in mean core body temperature in groups ($P = 0.4$, Figure 2).

Shivering at Grade IV was not observed in any patient. Eight percent (4/50) of patients in granisetron and 54% (27/50) of patients in saline group had Grade III of shivering
during perioperative period that was treated with pethidine [P = 0.001, Table 2].

Ten patients (20%) in granisetron and 30 patients (60%) in saline group had nausea (P = 0.002). No patients in both groups needed rescue medication.

None of the patients in both group received atropine. Four patients in the saline and 3 patients in the granisetron group received the phenylephrine for hypotension (P = 0.16).

First minute APGAR scores were 10 ± 3 and 10 ± 2 and 5th min APGAR scores were 10 ± 1 and 10 ± 1 in granisetron and saline group, respectively (P = 0.17, P = 0.16). There were no adverse effects of granisetron on fetuses after delivery compared to the saline group regarding the APGAR scores.

**DISCUSSION**

This study showed that granisetron 3 mg intravenously is an effective method for prevention of spinal anesthesia induced shivering during cesarean section compared to saline control group. Nausea and vomiting were also reduced in this group of patients.

It has been reported that shivering develops in up to 40-60% of regional anesthesia; in our study the incidence of shivering was similar (54% [27/50]) in the control group.

Shivering is a response to hypothermia, body temperature should be maintained within limits of 36.5-37.5°C, however, shivering may be seen even in normothermic patients undergoing regional anesthesia. A number of factors including age, level of sensory block, temperature of the operating room and infusion solution are risk factors for developing hypothermia in regional anesthesia.

In our study, patients’ ages were between 18 and 42 years (pregnant patients), the temperature of the operating room was maintained about 24°C ± 0.6°C during the perioperative period and infusions of cold crystalloid solutions were avoided. However, it is not always possible to keep the body temperature within normal limits (36.5-37.5°C).

Ondansetron, dolasetron, and granisetron, which are all 5-HT3-receptor antagonists, have been used effectively to decrease postoperative shivering. The mechanism for 5-HT3-receptor antagonists is still unclear but is thought to be related to inhibition of serotonin reuptake on the preoptic anterior hypothalamic region.

In a study by Kim et al. on 52 patients who had undergone knee arthroscopy under spinal anesthesia, romasetron, a selective serotonin 5-HT3 receptor antagonist effectively prevent shivering during spinal anesthesia that was correlated with our study.

In a study by Sagir et al. on 160 patients undergoing urological surgery under spinal anesthesia with bupivacaine, the patients were randomly allocated to receive saline (Group P, n = 40), ketamine 0.5 mg (Group K, n = 40), granisetron 3 mg (Group G, n = 40) or ketamine 0.25 mg + granisetron 1.5 mg (Group KG, n = 40). The number of patients with observed shivering was 22 in Group P, 6 in Group G, 7 in Group KG and 0 in Group K. The number of patients with a shivering score of 3 was statistically significantly higher in Group P.
compared with the other groups. They study showed that prophylactic use of ketamine and granisetron separately and in combination was effective in preventing shivering developed during regional anesthesia that emphasize the effect of a serotonin 5-HT3 receptor antagonist on the prevention of shivering.[7b]

In a prospective double-blinded study by Sajedi et al. on 132 American Society of Anesthesiologists I-II patients undergoing elective orthopedic surgery under standardized general anesthesia patients were randomly assigned to one of the four equal groups. Group T received 1 mg/kg tramadol; Group G received 40 µg/kg granisetron, Group M received 0.4 mg/kg meperidine, and Group P received saline 0.9% as placebo. They found that prophylactic use of granisetron 40 µg/kg is as effective as meperidine (0.4 mg/kg) and tramadol (0.1 mg/kg) in preventing postanesthetic shivering without prolonging the emergence time from anesthesia. Although they used four different drugs in patients undergoing general anesthesia, they also found that granisetron was an effective drug as pethidine in preventing postanesthetic shivering compared to our study.[12]

Recent studies showed that serotonin receptor antagonists (ondansetron, granisetron) are highly effective for nausea, retching, and vomiting during regional anesthesia for cesarean delivery in parturients and correlated with our results.[13]

The distinctive feature of this study is that we assessed the effectiveness of one drug for prevention of both shivering, nausea and vomiting at the same time during neuroaxial block.

The limitations of our study are that we did not include a positive control group using an established agent such as meperidine. Because meperidine are already established and also the Grade I and II shivering was ignored. Only Grade III and IV were taken as significant.

More clinical studies are needed to compare the efficacy of granisetron to other drugs that can be used to prevent shivering and nausea and vomiting at the same time, in pregnant patients undergoing spinal anesthesia.

CONCLUSION

We found that granisetron 3 mg intravenously is an effective method for prevention of spinal anesthesia induced shivering during cesarean delivery; it also reduced nausea and vomiting.

REFERENCES