Original Article

Comparison of the efficacy of ondansetron and ketamine as premedication in reducing shivering after cesarean section under spinal anesthesia

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ABSTRACT

Introduction: Postoperative shivering not only can create an undesirable feeling in the patient but may also be associated with serious and dangerous complications. Therefore, this study was aimed to examine the efficacy of ondansetron and ketamine as premedication in reducing shivering after cesarean section (CS) under spinal anesthesia. Methods: This randomized-controlled clinical trial was performed on 150 patients scheduled for elective CS, who were randomly assigned to three groups according to the block model. Spinal anesthesia was performed by the anesthesiologist for all patients with a 25-G spinal needle to inject 2 ml of 5% Xylocaine with epinephrine. Then, according to their groups, the corresponding drug was injected intravenously to patients in the supine position at doses of 20 mg for the ketamine group, 4 mg for the ondansetron group and 2 cc of normal saline for the placebo group. After arrival in the recovery room, the patient's intensity of shivering was measured by the project executive, according to Wrench's Criterion. Results: The placebo group had the greatest score of shivering among the three groups. This indicated a significant difference with regard to the intensity of postoperative shivering. Both ketamine and ondansetron were more effective than the placebo in reducing shivering. There was no significant difference between ketamine and ondansetron groups in this regard. Conclusion: The results of this study indicate that ketamine and ondansetron compared to placebo can contribute to the meaningful reduction of postoperative shivering after cesarean section under spinal anesthesia.

Keywords: Ketamine, ondansetron, postoperative shivering, spinal anesthesia

Introduction

Postoperative shivering is a common complication with a prevalence of 50-65% [1] after general or regional anesthesia, which can be caused by thermoregulatory mechanisms in response to core hypothermia (a decrease of 0.5-1.5°C in the core temperature following anesthesia) and/or the release of cytokines by the surgical procedure. In addition to creating an undesirable feeling in patients, postoperative shivering can be associated with deleterious complications such as raised oxygen consumption (by 600 percent), release of catecholamines, increased cardiac output, raised carbon dioxide production, and increased intracranial and intraocular pressures [1]. Hypothalamus, along with the autonomic nervous system, is responsible for keeping the body's core temperature constant at 37°C. Reduction of core temperature can activate defensive mechanisms such as vasoconstriction (to reduce heat loss from the skin), reduced sweating, shivering (to generate heat in the muscles), and release of thyroxine and catecholamines to increase basal metabolism. Shivering not only can increase the rate of metabolism but may also cause lactic acidosis in some cases. In addition, it can interfere with postoperative monitoring, including EKG, blood pressure and pulse oximetry [2].

The effects of ketamine, at sub-anesthetic doses have been examined in several studies for the treatment of refractory chronic pain, neuropathies, refractory depression, postoperative pain, and postoperative shivering. The blockade of N-methyl D-aspartate receptors probably inhibits thermoregulatory centers, which in turn prevents from postoperative shivering [3].

Use of ketamine has been shown, in limited studies, to have impact on control and reduction of postoperative shivering at doses of 0.5 to 0.75 $mg.kg^{-1}$ [4-6].

Some studies have demonstrated limited anti-shivering effects from ondansetron. Ondansetron is a serotonin antagonist with antiemetic properties. Its anti-shivering mechanism is thought to be through serotonin reuptake inhibition in the anterior hypothalamic area. Ondansetron is currently used routinely as a drug of choice at doses of 4 mg in the prophylactic treatment of

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chemotherapy-induced nausea and vomiting, although in one study, it could contribute to the reduction of shivering at doses of 8 mg [7].

Pazoki *et al.* in a study on 189 patients undergoing CS, indicated that the frequency and severity of shivering was less in the pethidine group than the two ketamine groups. Also ketamine at 0.5 $mg.kg^{-1}$ dosage was more effective in controlling shivering than 0.3 $mg.kg^{-1}$ dose [8]. Asefzadeh *et al.* showed that diclofenac sodium as 100 mg suppository 10 minutes before induction of anesthesia, can effectively decrease postoperative shivering in patients undergoing Cesarean delivery [9].

A study[1] by Oshvandi *et al.* showed that the infusion of pre-warmed lactated ringer's solution immediately before anesthesia could prevent core hypothermia as well as the incidence of shivering after general anesthesia among mothers undergoing CS and thus was recommended as a preventive measure [10]. In a study to evaluate the efficacy of different classes of drugs (i.e. ketamine, tramadol, magnesium sulfate, hydrocortisone and pethidine) in prevention of post-anesthesia shivering, Modir *et al.* found that pethidine was more effective than other drugs used in the study [11].

In a study[2] to compare the efficacy of intramuscular ketamine with pethidine and normal saline in 120 children, Fouad A Zahra *et al.* found the incidence of postoperative shivering to be lower in the ketamine group compared to the placebo group. The pethidine group had the lowest rate of shivering in Fouad's study [12].

In a study by Ayatollahi *et al.* a reduction in shivering was observed in 3 patient groups receiving meperidine 0.4 mg/kg, ketamine 0.3 mg/kg and ketamine 0.5 mg/kg, compared to normal saline. Differences between meperidine group and two ketamine groups were not statistically significant [13].

Since ondansetron is commonly used as an antiemetic agent that its effectiveness against shivering is not known exactly, this study was aimed to examine the pretreatment effect of ondansetron in the control of shivering, comparing it with that of ketamine.

Materials and Methods

This study was designed as a randomized, controlled, double-blind clinical trial. The study population consisted of 150 first time mothers who were scheduled to undergo cesarean delivery under spinal anesthesia. The study's inclusion criteria were ASA[3] class I or II, age between 18-40 years, 38-40 weeks of gestation and completion of written consent forms.

Patients with histories of previous cesarean section, coronary artery diseases, mental illness, convulsions, allergy to anesthetic agents, body mass index of greater than 30, use of narcotics or NSAIDs in the past 24 hours, and addiction to alcohol and narcotics were not included in the study. Patients with bleeding volumes of more than 2 liters, or receiving blood or blood products during surgery, and patients experiencing surgery times exceeding 1.5 hours, were excluded from the study.

To comply with randomization, patients were divided into three groups according to the last two digits of their file numbers. Spinal anesthesia was performed by the anesthesiologist for all patients with a 25-G spinal needle to inject 2 ml of 5% Xylocaine with epinephrine. Then, according to their groups, corresponding drugs were immediately injected intravenously to patients in the supine position (right side of the hip slightly higher) at doses of 20 mg for the ketamine group, 4 mg for the ondansetron group and 2 cc of normal saline for the placebo group. The volume of injected solution was equal to 2 cc in all three groups. Neither the person responsible for drug administration nor the patients did know about the syringes' contents. Also the person assessing the patients for shivering in the post anesthesia care unit, was unaware to their grouping. Patients received approximately 1 to 1.5 liters of Ringer's solution during the surgery. The operating room's temperature was kept constant at 22-23 °C and no methods of active patient warming were used. Blood pressure, heart rate and arterial oxygen saturation (SPO2) were continuously monitored (BP every 5 minutes). Five minutes after arrival in the recovery room, the patient's intensity of shivering was measured according to the Wrench's Criteria, which included:

1) Narrowing of peripheral arteries without a visible shivering
2) Muscular activity only in one muscle group
3) Muscular activity in more than one muscle group
4) whole-body shivering

The patients' information were confidential. The study was fully explained to patients prior to obtaining the written consent. The principles of the Helsinki Declaration and the Ethics Committee of Arak University of Medical Sciences were met at all stages of the research.

For statistical analysis, the data were first analyzed by descriptive statistics. Central indices, dispersion indices and the quantitative data were evaluated by One-way ANOVA and Fisher's post hoc test. Independent groups and qualitative data were analyzed by chi-square test. SPSS software version 21 was used for all these operations.

Results

This study included a total of 150 elective cesarean patients, who were between 17 and 41 years old (a mean age of 26.25 ± 4.8 years). The participants were divided into three groups of 50 people receiving ondansetron, ketamine or saline, with an average weight of 74.3±5.8 kg, 74.8±6.5 kg and 73.6±6.3 kg, respectively. There was no statistically significant difference in weight between the three groups.

After injection of the drug, mean systolic blood pressure was 114.38±5.73 in the ondansetron group, 115.84±5.2 in the ketamine group and 116.18±51.5 in the placebo group. Mean diastolic blood pressures were 66.52±5.36, 66.22±6.75, and 66.10±6.82 in the three groups respectively (all figures in mmHg). There was no significant difference in mean systolic and mean diastolic blood pressures after drug injection between the three groups.

In addition, on arrival to the recovery room, mean systolic blood pressure was equal to 112.94±7.96 in the ondansetron group, 112.72±0.45 in the ketamine group, and 113.88±8.23 in the placebo group. Mean diastolic blood pressures were 63.9±7.3, 64.52±7.57 and 64.76±7.48 in the three groups respectively. There was again no significant difference in both mean systolic and mean diastolic blood pressures on arrival to the recovery room between the three groups.

Average heart rate after injection of the drug was 85.86±6.02 in the ondansetron group, 86.8±5.71 in the ketamine group, and 88.58±6.60 in the placebo group (showing no significant

[1] "the Effect of Pre-warmed Intravenous Fluids on Prevention of Intraoperative Hypothermia in Cesarean Section"

[2] "Intramuscular Ketamine for Prevention of Post anesthesia Shivering in Children"

[3] American Society of Anesthesiologist

difference between the three groups). Average heart rate on arrival to the recovery room was 86.36±8.63, 86.02±8.27 and 84.18±9.01 in the three groups respectively. There was no significant difference in average heart rate between the three groups on arrival to the recovery room.

With regard to the shivering intensity, in the ondansetron group, 36 people had grade 1, 5 patients had grade 2, 5 patients had grade 3 and 4 patients had grade 4 shivering (according to Wrench's Criteria). In the ketamine group, there were 36 people in grade 1, 6 patients in grade 2, 6 patients in the grade 3, and 2 patients in the grade 4. The placebo group consisted of 20 people in the grade 1, 11 patients in the grade 2, 9 patients in the grade 3, and 10 patients in the grade 4 (Table 1).

There was no significant difference with regard to the intensity of shivering between the ondansetron and the ketamine groups (P=0.12). There was a significant difference between the ondansetron and the placebo groups (the latter group shivered more intensely, P=0.002). There was also a significant difference regarding the shivering intensity between the ketamine and the placebo groups (which was higher in the placebo group, P=0.012) in (Figure 1).

Table 1: Comparison of the shivering intensity, 5 minutes after arrival in the recovery room (according (to Wrench's Criterion

	Grade 1	Grade 2	Grade 3	Grade 4
Ondansetron	36	5	5	4
Ketamine	36	6	6	2
Placebo	20	11	9	10

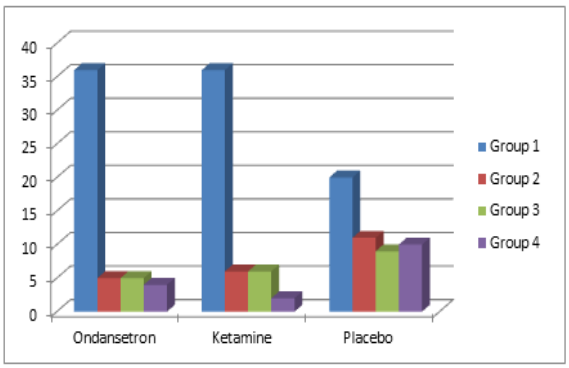

Figure 1: The diagram of shivering intensity, 5 minutes after arrival in the recovery room (according to Wrench's Criterion)

Discussion and Conclusion

As the results show, the placebo group had more intensity of shivering than the ketamine and ondansetron groups (statistically significant), while there was no significant difference between ketamine and ondansetron groups. In a study by Dal D (2005) to evaluate the efficacy of prophylactic ketamine in preventing postoperative shivering, patients received ketamine (0.5 mg kg^{-1}) or pethidine (20 mg) or saline, 20 minutes before completion of surgery. The number of patients shivering on arrival to the recovery room, and at 10 and 20 minutes after completion of surgery were significantly less in ketamine and pethidine groups than in the saline group [1].

In their study[4] on 189 patients undergoing CS, Shirin Pazoki *et al.* (2009) found that five minutes after injection, the frequency and intensity of shivering in the pethidine group were less than the two ketamine groups and that ketamine, at a dose of 0.5 mg/kg, was more effective in controlling shivering than a dose of 0.3 mg/kg [8]. It is consistent with our study where, compared to the placebo group, ketamine significantly reduced the frequency of postoperative shivering. In a study[5] to evaluate the effect of intramuscular ketamine (1 mg kg^{-1} in 120 children), Fouad A. Zahra *et al.* (2008) showed that the ketamine group shivered less than the placebo group postoperatively. This is also consistent with our study where ketamine was more effective than the placebo in reducing shivering.

Vida Ayatollahi et al (2011) in their study[6] on 120 patients undergoing endoscopic sinus surgery found that, compared to the placebo group, meperidine and 2 different doses of ketamine (0.3 mg/kg and 0.5 mg/kg) significantly reduced shivering compared to the normal saline group. It is also consistent with our study, regarding the comparison between ketamine and placebo.

We did not record baseline blood pressure and heart rate of the patients, which of course could be used to measure the rate of changes.

The results of this study and similar studies indicate that ketamine and ondansetron can be recommended in patients scheduled for cesarean section because they can significantly contribute to the reduction of shivering after the operation. However, there are more than one reason why further studies with more samples at different doses may be recommended, including the similar results of the ketamine and ondansetron groups, and the very different effects and complications of ketamine at different doses.

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