The Effect of Prophylactic Administration of Intravenous Ondansetron for Control of Shivering during and after Spinal Anesthesia for Cesarean Section

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A B S T R A C T

Nowadays, spinal anesthesia is the selected anesthesia technique for elective cesarean section and emergency cases because of the low incidence of maternal mortality and morbidity and less infant depression in this method compared to general anesthesia. Unavoidable Hypothermia refers to the reduction of the core temperature below 36°C. Hypothermia and shivering during and after anesthesia has adverse results and complications which lead to dysfunction of monitoring of electrocardiogram, blood pressure and arterial oxygen saturation, in addition to incidence of discomfort and bad feelings in patients. The aim of this study is to evaluate the influence of prophylactic administration of intravenous Ondansetron in controlling shivering during and after spinal anesthesia for caesarean section. In a double-blind clinical trial, 40 patients were randomly divided into two groups of 20 people. After recording vital signs and basal body core temperature of patients undergoing spinal anesthesia, and after birth, the case group received about 8 mg (2 ml) Ondansetron drug and the control group received the same amount of normal saline. The score of shivering, blood pressure, core body temperature, need for medical treatment of shivering and existence of any possible side effect during surgery and recovery were measured and recorded. Demographic findings did not show significant differences except for weight. The mean score of shivering in the operating room was about 0.30±0.57 in patients in the case group and 1.35±1.25 in patients in the control group. The mean score of shivering in the recovery ward was about 1.45±1.09 in patients in the case group and 2.25±1.37 in patients in the control group, which represents a decreased incidence score of shivering in the control group (p =0.02), however patients in both groups showed no significant difference in terms of severity of shivering and thus the need for Pethidine analgesic drug (p = 0.049). Significantly low mean score of shivering in the operating room and in recovery in patients in the case group compared to that in patients in the control group (P<0.001 and P<0.001) represents the effective role of Ondansetron in reduction of the level of shivering in patients, however this drug does not reduce the intensity of shivering.

KEYWORDS
Cesarean Section, Spinal Anesthesia, Ondansetron, Shivering.
Introduction

Today, Spinal anesthesia is the adopted method of anesthesia for elective C-section and emergency, which is due to the lower incidence of maternal mortality and morbidity and less fetal depression in this method compared to general anesthesia [1, 2]. Unavoidable hypothermia, i.e. decrease of core temperature below 36°C, commonly occurs in patients during (general and regional) anesthesia for various reasons, such as direct restraint of temperature control by anesthetic drugs, decreased metabolism, exposure of patient to cold environment of operation room, and loss of body warmth from the place under surgery. During regional anesthesia, autonomic thermoregulation gets impaired, and thereby core temperature decreases during procedure. It is remarkable that the patient cannot consciously perceive this hypothermia, nonetheless, starts to shiver, which often leads to a dangerous clinical paradox as a hypothermic disease that does not feel cold [1].

Epidural and Spinal anesthesia both reduce vasoconstriction and shivering threshold above block level by 0.6°C, which indicates a change in central control towards environmental control. This reduction is proportional to the number of the spinal segments blocked in spinal anesthesia. Afferent signals from legs, which are mostly signals of cold, are disrupted under the blocked region and brain interprets it as a sign of warming up in legs. Since the dermal temperature is an important input signal to the thermoregulation system, warming the legs up continually reduces shivering and vasoconstriction threshold. Other reasons of thermoregulation disorder during regional anesthesia are application of accompanying sedative drugs, reduction in the rate and maximum intensity of response of shivering towards the normal people, dysfunction in temperature behavioral adjustment and starting to defend against cold in lower temperatures with less efficiency. The major result of these disorders is shivering and hypothermia during and after anesthesia and surgery [1-3]. Shivering is one of the most prevalent complications and problems during and after anesthesia with a reported incidence rate of 20-60% (meanly about 55-56.7%) [4, 6]. Several reports indicate that hypothermia and shivering during and after anesthesia have adverse results and complications which lead to dysfunction of monitoring of electrocardiogram, blood pressure and arterial oxygen saturation, in addition to causing discomfort and bad feelings in patients. They also increase oxygen consumption and production of CO₂ [2 and 6]. Studies have shown that hypothermia and shivering during and after surgery increased pressure inside eye and cranium and increased rates of wound infection, higher intraoperative hemorrhage, higher adregeneric activity, and, according to some reports, increased the rate of ischemic cardiac events [10-6]. Several methods and drugs have been used to prevent and cure shivering during and after surgery. One of these methods is to warm up the body surface, since by high dermal temperature, the core thermoregulation system can tolerate high central hypothermia. However, dermal temperature is only 20% involved in controlling shivering [1]. Various drugs such as fentanyl or intrathecal sufentanil [2 and 3], midazolam, ketamine, intravenous meperidine, and recently, serotonin receptor blockers such as ondansetron and granisetron have been used and compared in prevention of shivering during and after surgery [5, 6 and 8-11]. Serotonin (5-hydroxytryptamine (5-HT)) is a thermoregulatory neurotransmitter. Receptors with 5-HT₁A subtypes are highly concerned in the hypothermia caused by 5-
HT and findings indicate 5-hydroxytryptamine as ligands. Also, studies have shown that 5-HT$_3$ agonists cause hypothermia in rats; therefore, it can be expected that 5-HT$_3$ antagonists, such as Ondansetron, can prevent incidence of shivering by reducing vasoconstriction and shivering threshold [11]. Several studies have been conducted in this field, but results have been inconsistent.

According to these studies and different results from evaluating the effect of 5-HT$_3$ antagonists in preventing shivering during and after the surgery, and bearing in mind that most studies have been about the antiemetic effect of Ondansetron in the population of pregnant patients undergoing C-section [14-16], and not enough studies has been conducted about its effect on preventing shivering during C-section, therefore, this study is planned accordingly to examine the effect of Ondansetron on preventing shivering during and after spinal anesthesia for C-section, which is, in addition to the aforementioned complications, an often inconvenient problem for mothers undergoing C-section. The assumption is that administration of this drug can prevent shivering during and after operation or reduce its intensity in case of incidence. It should be noted that according to several studies on the antiemetic effect of Ondansetron on nausea and vomiting during and after operation with no reports mentioning its adverse effect on the newborn infant, we also used the drug at the same dose applied in other studies and injected after clamping the umbilical cord to ensure full safety.

The aim of this study was to evaluate the effect of prophylactic administration of intravenous Ondansetron in controlling shivering during and after spinal anesthesia for C-section.

**Methods and Materials**

In a double-blind randomized clinical trial in Al-Zahra educational and medical center, Tabriz University of Medical Sciences, conducted on patients undergoing spinal anesthesia for C-section, the effect of prophylactic administration of intravenous Ondansetron in controlling shivering during and after spinal anesthesia for C-section was examined.

Sample size: 40 patients with physical status of ASA I or II candidate for C-section were selected and enrolled into the study.

Sampling was performed by easy burst consecutive method and based on the order of patients’ reference. Randomization was performed by online randomization software as Randomly Permuted Blocks.

After obtaining the prior written permission for the study from the ethics committee of Tabriz University of Medical Sciences, 40 pregnant women candidate for elective C-section, who have given informed consent to participate in this study and lacked any of exclusion criteria, were select and enrolled into the study.

Study population consisted of women aged 16-45 years and physical status of class I and II based on ASA standard that termination of pregnancy was performed by C-section.

Patients with ASA class III or higher, patients with any type of cardiovascular, respiratory, pre-eclampsia diseases or any type of hypertension during pregnancy, fever and patients with any contraindications of spinal anesthesia did not participate in the study. Patients who had failed spinal anesthesia or had block level lower than that required for spinal anesthesia and those who
had any unexpected accident during the operation were excluded from the study.

By RPB (Randomly Permutated Blocks) method and using online randomization software, Patients were randomly assigned to either the intervention group or the control group.

Before entering the operating room, basic vital signs including blood pressure, heartbeat rate and the percentage of arterial oxygen saturation were recorded for all patients. Basic core temperatures of all patients were also measured and recorded by specialized tympanic membrane probes. Temperature of operation room was preserved between 22ºc - 24ºc and patients’ coating consisted of two layers of surgical prep and drep coatings in addition to the operation room clothes. Fluids prescribed for the patients were kept in the same room temperature. After recording the basic vital signs, Ringer’s solution 10ml/kg was infused to all patients and then, spinal anesthesia was performed by injecting 2.5-3 cc Bupivacaine 0.5% by no. 25G needle through the mid-vertebral space between L3-L4 or L4-L5 vertebras in sitting position. The intervention group, i.e. Ondansetron group, received 8mg of Ondansetron immediately after birth and clamping the umbilical cord and the control group received the same volume (2cc) of normal saline in numbered syringes. Regarding the coded injection syringes, the person in charge of injections was unaware of the type of the mixture (Ondansetron or placebo) administered into the patient; and finally, the person who filled out the questionnaire during surgery and in recovery was also unaware of prescribed medications. The vital signs were checked and recorded every 2 minutes until the childbirth and afterwards, every 5 minutes until the end of surgery; and in case of a drop in blood pressure more than 20% of the baseline, 5-10mg dose of intravenous ephedrine vasopressor drug injected and repeated with the same dosage if necessary. The core body temperature was also recorded by specialized tympanic membrane probe every 15 minutes during surgery and immediately after arrival in the recovery room and then every 15 minutes until leaving the recovery room.

Patients were examined in terms of shivering according to Crossley and Mahjon criteria during operation and after it in recovery room and shivering scores were recorded as described below:

0 = no shivering

1 = existence of one or more of these symptoms including raised hair of the body, vasoconstriction of peripheral vessels, peripheral cyanosis without specific cause but no muscle movement.

2 = muscle movements in a muscle group

3 = muscle movements in more than one muscle group

4 = severe muscle movements throughout the body

If the intensity of shivering score was 3 or 4, a 0.5mg/kg dose of meperidine was administered for treatment of shivering.

Spinal anesthesia and drug administration was performed by an anesthesia resident or specialist and another person unaware of the medications prescribed was in charge of monitoring patient’s vital signs, body temperature and shivering.

Data obtained from patients, including demographic info, vital signs during
surgery, incidence and intensity of shivering, the need for medicinal treatment of shivering in case of high intensity (grade 3 or 4), the number of injections (once or more than once), total dosage of meperidine injections and incidence of any potential complications were recorded in a questionnaire and the data obtained from the study were evaluated and statistically analyzed using descriptive statistical methods, repeated measures design test, t-test for independent groups or Mann-Whitney’s U-test and chi square test or Fisher’s exact test if needed and calculation of RR with confidence interval of 95 percent and using SPSS v.17 statistical software. In this study, p<0.05 was considered statistically significant.

Ethical Considerations

Ondansetron is a known drug in the treatment of nausea-vomiting and routinely used as a safe drug around the time of surgery.

In this study, patients’ information remained confidential and written informed consent was obtained from all patients at the beginning of the trial; In addition, patients kept the right to exit from the study at any stage.

Results and Discussion

In this study, 40 patients were studied in two groups of 20 people and the effect of prophylactic administration of intravenous Ondansetron was examined in controlling shivering during and after spinal anesthesia for C-section.

The mean shivering score in the operating room was 0.30±0.57 in case group and 1.35±1.08 in control group (P=0.002).

The mean shivering score in the recovery room was 1.45±1.09 in case group and 2.25±1.37 in control group (P=0.049).

No significant difference was observed among patients in both groups in terms of systolic blood pressure and diastolic blood pressure during the study.

Except the basic body temperature, which was significantly less in patients in ondansetron group than the control group, in other times during the study, no significant difference was observed between the two groups.

Shivering is the instinctive shaking of the body due to reasons like the cold and hypothermia [17]. Prevalence of shivering in the recovery room is 60% after general anesthesia and 30% following epidural anesthesia [18]. Postoperative shivering usually lasts 2-60 minutes and its pathogenesis is not clear exactly [19]. Many different causes have been suggested for postoperative shivering including spinal reflexes, reduced sympathetic activity, suppression of the adrenal gland, respiratory alkalosis and response to hypothermia [20]. Generally, thermoregulation is implemented by triggering the core temperature, followed by altering vascular tone through autonomic systems (vasoconstriction, vasodilatation); and that's why raising the temperature of the surface of the skin is the fastest way to raise the shivering threshold [21].

Shivering is a lifting agent of postoperative complications by increasing the body's oxygen consumption, particularly myocardial which increases the risk of cardiac ischemia as well as increased intraocular and intracranial pressure and will cause postoperative problems and increased costs [22]. Postoperative shivering increases oxygen consumption up to 500%. It also

increases the production of carbon dioxide, metabolic rate and sympathetic tone as well. Thus, increases the need for cardiac output and minutely ventilation. The incidence of myocardial ischemia increases myocardial infarction [21].

Drinking warm fluids is very effective in maintaining body temperature during and after operation [23]. Several drugs have been introduced for prevention and treatment of postoperative shivering, such as morphine and meperidine which have anti-shivering effect, and as estimated, this effect will apply through............ [21]. Fentanyl is used with bupivacaine μ receptor............... in spinal anesthesia that prevents shivering after C-section [24]. Ketamine at doses of 0.5mg/kg has been found effective in reducing shivering even in major cardiac operations [25]. 2-3mg/kg dose of Tramadol and 0.4mg / kg dose of pethidine have the ability to prevent shivering [26].

Ondansetron is a serotonin antagonist with anti-shivering mechanism of action through inhibition of serotonin reuptake on the anterior hypothalamic area.

At the moment, Ondansetron in 4mg doses is the drug of choice as the routine drug in the prophylaxis of nausea and vomiting after chemotherapy [27] and its 8mg doses has been effective in reducing shivering in the study conducted [28]. Prevention and treatment of postoperative shivering is an important part of patient care after surgery, as it may cause severe damages to the patients by sympathetic stimulation, or increased oxygen consumption and carbon dioxide emissions [29].

Kelsaka et al., in a study compared the effect of prophylactic administration of 0.4mg/kg Ondansetron and 8mg/kg meperidine on reduction of shivering after spinal anesthesia conducted on three groups of 25 patients. In their study, shivering rate had decreased from 36% in the control group to 8% in the meperidine group and 8% in the Ondansetron group, and there was no significant difference between the two groups of meperidine and Ondansetron [29].

Paul et al., also compared the effect of prophylactic administration of 4mg and 8mg Ondansetron and normal saline on postoperative shivering in three groups of patients (n=27 per group). Based on the results of their study, the incidence rate of postoperative shivering in the normal saline group was 57% which reduced to 33% by 4mg Ondansetron and to 15% by 8mh Ondansetron [29].

In the present study, the mean score of shivering in the operating room in patients in case group was significantly less than that in patients in the control group (P=0.002) and the mean score of shivering in recovery room in patients in case group was significantly less than that in patients in the control group (P=0.049), which represents an effective role of ondansetron in reducing shivering rate in patients. However, patients in both groups showed no significant difference in the intensity of shivering, which can be determined by comparing the difference in need of pethidine to treat severe cases of shivering, i.e. grades 3 or 4; So that there was no significant difference between the two groups in terms of the need to anti-shivering treatment; that is to say although patients experiencing shivering in the ondansetron group were fewer in number, their shivering intensity was similar to the patients who did not receive any medication.

Another study by Piper et al., conducted on three groups of 30 patients, showed that the prophylactic administration of 12.5mg Dolasetron (another serotonin antagonist)
before the start of anesthesia does not make such a big change in the incidence rate of postoperative shivering compared to control group [28], which was likely due to the low dosage of the drug [30].

In similar studies, other drugs are used to reduce postoperative shivering, the majority of which are causing several problems for patients. Despite the decline in the incidence of postoperative shivering, clonidine can be associated with evident hypotension and drowsiness [31].

Tramadol, as a non-opioid analgesic, in spite of inhibition of postoperative shivering, can cause decreased sweating, vasoconstriction and lower shivering threshold [32].

Doxapram, as a brain stimulant, suppresses postoperative shivering, but has significant hemodynamic effects on patients [33]. Physostigmine, as an anti-cholinesterase drug despite its significant effect in reducing postoperative shivering, causes decreased heartbeat rate and hypotension, which can be dangerous especially to patients with coronary artery deficiency. It also increases the incidence of nausea and vomiting after surgery [34].

The study of Powell RM et al., on the role of ondansetron in reducing shivering after general anesthesia shows that administration of 8mg Ondansetron the immediately before induction of anesthesia reduces incidence of postoperative shivering [12].

Kelsaka et al., in their study compared the effects of meperidine and ondansetron in the prevention of shivering during spinal anesthesia and concluded that anti-shivering effect of ondansetron is just the same as meperidine and both of them change the relationship between the core temperature and sensory block level during spinal anesthesia [9].

Asif Igbal et al., conducted a study on prevention of postoperative shivering after general anesthesia during laparoscopic surgery with pethidine and granisetron (a 5-HT₃ antagonist receptor) and concluded that prophylactic administration of granisetron is effective in the prevention of shivering after general anesthesia [13].

**Table.1** Demographic Finding of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Case</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>28.30±5.34</td>
<td>28.75±7.17</td>
<td>0.823</td>
</tr>
<tr>
<td>weight</td>
<td>82.70±10.27</td>
<td>75.63±14.94</td>
<td>0.089</td>
</tr>
<tr>
<td>ASA</td>
<td>1.20±.41</td>
<td>1.25±.44</td>
<td>0.714</td>
</tr>
<tr>
<td>Gestational Age</td>
<td>37.45±1.85</td>
<td>37.45±2.33</td>
<td>1</td>
</tr>
<tr>
<td>During Surgery</td>
<td>48.75±8.41</td>
<td>50.20±6.57</td>
<td>0.547</td>
</tr>
</tbody>
</table>

**Table.2** Systolic Blood Pressure in patients of two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>Control</td>
</tr>
<tr>
<td>Base</td>
<td>121.20±9.92</td>
</tr>
<tr>
<td>Login Recovery</td>
<td>111.09±9.37</td>
</tr>
</tbody>
</table>
Table 3: Diastolic Blood Pressure in patients of two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Case</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>73.98±15.39</td>
<td>75.87±12.33</td>
<td>0.477</td>
</tr>
<tr>
<td>Login Recovery</td>
<td>64.85±10.86</td>
<td>64.71±11.20</td>
<td>0.945</td>
</tr>
</tbody>
</table>

Table 4: Body temperature in patients of two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Case</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>35.81±0.74</td>
<td>36.13±0.57</td>
<td>0.011</td>
</tr>
<tr>
<td>Login Recovery</td>
<td>34.57±4.74</td>
<td>35.33±0.56</td>
<td>0.240</td>
</tr>
<tr>
<td>Exit recovery</td>
<td>35.00±0.72</td>
<td>35.14±0.53</td>
<td>0.249</td>
</tr>
</tbody>
</table>

However, Komastu et al., in a study examined the effect of ondansetron on controlling the core temperature and preventing the shivering after incidence of therapeutic hypothermia and showed that ondansetron with a dosage equal to that required for prevention of nausea-vomiting has no effect on shivering and vasoconstriction threshold [11].

O. Sagirr et al., in their study compared the prophylactic effects of ketamine and granisetron on controlling shivering during spinal anesthesia, and showed that granisetron is effective on controlling shivering during spinal anesthesia, however, its effect is less than ketamine and unlike the study by Asif Igbal which has shown its significant effect on the prevention of shivering, this study indicates that its effect on the prevention of shivering during spinal anesthesia is less and even lesser than a low dose 0.5mg/kg ketamine, so that O. Sagirr et al., in their study, patients who received ketamine during urologic surgery with spinal anesthesia had significantly lower shivering during surgery compared to patients who received granisetron or were in the placebo group [10].

Conclusion

Similar to above-mentioned studies, the results of the present study show that the use of ondansetron in C-section with spinal anesthesia reduces the incidence of postoperative shivering in patients, however, has no effect on the intensity of shivering and thus, on the need for Pethidine for the treatment of severe cases (higher scores of shivering). Also, use of Ondansetron is not associated with increased complications in patients and furthermore, in addition to reducing the incidence of shivering, draws on utmost relief and comfort of patients by reducing the incidence of postoperative nausea and vomiting.

Recommendation

According to the results of the present study, the use of Ondansetron is recommended in patients undergoing C-section with spinal anesthesia as well as its comparison in patients under general anesthesia and conduction of further studies is also recommended with larger sample size. Also, the comparison of this drug with other drugs in controlling postoperative shivering can be examined.
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