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Research article

The role of ondansetron in prevention of post-spinal shivering (PSS) in obstetric patients: A double-blind randomized controlled trial

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ABSTRACT

Background: Elective cesarean delivery (C/D) under neuraxial anesthesia is commonly associated with shivering. Ondansetron is a widely used antiemetic during both pregnancy and surgery. Few controversial studies investigated its anti-shivering effect in C/D under spinal anesthesia.
Objectives: To study the efficacy of ondansetron to prevent post-spinal shivering in parturients underwent cesarean delivery under spinal Anesthesia.
Methods: This double-blinded, prospective, randomized, trial included 80 parturients underwent C/D under spinal anesthesia, randomized into two equal groups [40 patients each]; group **O** [Ondansetron]: received 8 mg/4 ml ondansetron and group **S** [Saline] received 4 ml normal saline as placebo. Post-spinal shivering and maximum shivering at any time were recorded on a (0–4) scale and total meperidine dose required to treat shivering at score ⩾ 3, was calculated. Maternal MAP assessed before spinal anesthesia (**T_0**), just after spinal and lateral tilt positioning (**T_1**), 2 min after positioning (**T_2**), 5 min after positioning (**T_3**), Just after delivery of the baby (**T_4**), at the end of surgery (**T_5**), together with total ephedrine *(required to treat any hypotension)* were recorded**.** Incidence of nausea and vomiting at any time during surgery was also recorded.
Results: Incidence of shivering, maximum shivering, total meperidine dose and incidence of nausea were lower in ondansetron group compared to saline group. Maternal MAP was lower at (**T_3**) in placebo group, without difference in the total ephedrine dose between the two study groups.
Conclusion: Ondansetron (8 mg) was effective in reducing post-spinal shivering in parturients underwent elective cesarean delivery and decreasing the requirement to meperidine together with lower incidence of post-spinal hypotension and nausea when compared to placebo (saline).

1. Introduction

Elective cesarean delivery (C/D) is most commonly carried on under neuraxial anesthesia, which is commonly associated with shivering, both intra- and postoperatively. The etiology of shivering is not clearly understood, it may involve a combination of mechanisms, including modulation of thermoregulatory thresholds, changes in body heat distribution, reduction in body core temperature, and the cooling effect of the fluids injected into the neuraxis [1].

Severe shivering interferes with electrocardiogram (ECG), pulse oximetry, and monitoring of blood pressure during the critical period of sympathetic block and aortocaval compression, when hypotension is more likely. It may also cause maternal irritability and interfere with her ability to hold her baby [2].

Several drugs are effective in treating or preventing post-spinal shivering (PSS) [1], including meperidine, tramadol, and clonidine. These drugs have adverse effects on the mother and fetus, including sedation, nausea, vomiting, bradycardia, and hypotension. These unwanted effects limit the use of such drugs before delivery, because of concerns about on the mother and the fetus [3].

Ondansetron, a 5-HT_3 antagonists, is a widely used antiemetic during both pregnancy and surgery. Some studies showed its anti-shivering effect following both general and neuraxial anesthesia [4–8]. It has a potential advantage in the obstetric anesthesia, because of its very low incidence of sedation, hypotension, bradycardia, or risk to the neonate [9]. The mechanism of action of Ondansetron as anti-shivering is not clear and it is proposed to act centrally at the level of the pre-optic anterior hypothalamic region by inhibition of serotonin reuptake [5].

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The prophylactic use of ondansetron to prevent PSS in obstetric patients was investigated by few studies; however, the results were disappointing [10,11]. The work done by Browning et al. [10] was criticised by Wan-Jie and Jing-Chen [12] for considering score 1 of shivering on a scale (0–4) to be positive and then concluded that prophylactic ondansetron does not prevent shivering. This criticism encouraged us to repeat the work with some modulation of shivering scoring.

The aim of this work was to assess the prophylactic effect of a single intravenous dose of ondansetron (8 mg), compared with placebo, on the prevention of post-spinal shivering during elective cesarean delivery. It also aimed to detect the possible preventive effect of ondansetron on other adverse effects of spinal anesthesia, as hypotension, nausea, and vomiting.

2. Patient and methods

After approval of our institutional ethics committee and obtaining written informed consents, 80 American Society of Anesthesiologists (ASA) physical status I or II full term parturients, 20–38 years old, scheduled for elective cesarean delivery (C/D) surgery under spinal anesthesia were enrolled in this double-blind, placebo-controlled, randomized study. The study carried out in *Kasr Al Ainy University* hospital from August to November 2016. This study was registered in *Pan African Clinical Trial Registry* with unique identification number for the registry is **PACTR201612001896411.**

Demographic data of all participants were collected preoperatively included age, height, weight, history of shivering during previous C/D. Exclusion criteria included complicated pregnancy, preoperative use of ondansetron or meperidine, known allergy to the tested drug, preoperative shivering, preoperative fever (>38 °C), hypo- or hyperthyroidism, Parkinson's disease or any extrapyramidal disease, Raynaud's syndrome, intraoperative blood transfusion; or administration of opioids, clonidine, or vasodilator drugs. Exclusion criteria also included any contraindication (absolute or relative) to spinal anesthesia.

Patients were randomly allocated into two equal groups using a computer generated random sequence and sealed envelope technique. All patients received an intravenous (IV) bolus of the tested drug in 4 mL volume, immediately before induction of spinal anesthesia; group (O) *[40 patients]* received ondansetron (8 mg) while group (S) *[40 patients]* received normal saline 0.9%. These doses were prepared in a masked 5-mL syringe by an independent anesthesiologist not involved in the rest of the study.

In the operating room, standard monitors (electrocardiogram, noninvasive blood pressure, and pulse oximetry) were attached to the parturient. Tympanic membrane temperature was monitored with an ear thermometer pre- an intraoperatively. A wide bore (18 gauge) IV cannula was established and a Ringer's solution (15 ml/kg) warmed to 37 °C was infused over 30 min before spinal anesthesia. The warmed infusion rate was then reduced to 2 mL/kg/h. Spinal anesthesia was then performed using a 27-gauge pencil point spinal needle at L3/4 or L4/5 level in the lateral decubitus position, and 2.5 mL of hyperbaric bupivacaine (0.5%) was administered. The parturient was then immediately placed supine in a left tilt position, spinal block level was assessed by loss of pinprick sensation, and level of block was recorded. The administration of pre- or intraoperative opioids was not permitted except as described below. Supplemental oxygen (3 L/min) was applied via a nasal cannula till the end of the operation. All patients were covered with two layers of surgical drapes all over the body intraoperatively, and with one cotton blanket postoperatively. The ambient temperature was maintained at 21–22 °C with room humidity around 60%.

Shivering *(as a primary outcome)* was graded by a blinded observer during the intraoperative and postoperative period using the scale validated by Crossley and Mahajan [13] and Tsai and Chu [14]: [***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*]. Grades **3**, and **4** shivering for at least 3 min were considered positive, and maximum shivering was considered if generalized shivering interfering with ECG monitoring or ability of the mother to hold the baby. Positive shivering or lower grade shivering but described as distressful by the patient were treated with an IV bolus of meperidine (0.5 mg/kg) [15]. Hypotension, nausea and vomiting *(as secondary outcomes)* were recorded. Hypotension was defined as more than 20% drop in mean arterial blood pressure (MAP) compared to baseline reading, and treated with repeated IV boluses of ephedrine (10 mg/bolus), as required. Total dose of administered ephedrine was recorded. Bradycardia (heart rate < 50 beat/min) was treated with IV atropine (0.5 mg) repeated as required.

In a study conducted on 2006 by Kelsaka et al. [5], they have shown that ondansetron can reduce the incidence of postspinal shivering (PSS) to 8% compared with 36% in the control group. A sample size was calculated based on these findings, with an α value of 0.05 and a power (1-β) of 0.80. It was calculated that 36 subjects were required per group. We enrolled 80 patients (40/-group) to allow for drop-outs.

Statistical analysis was performed using the SPSS (version 16.0; SPSS Inc, Chicago, IL). According to the type of data it was represented as mean and standard deviation or frequencies and percentages. Comparisons of the two studied groups were performed using either Student *t*-test or Chi-Square test as appropriate. In all tests results were considered statistically significant if *p* value was less than 0.5 (see Fig. 1).

3. Results

The results of the present study showed no statistical difference between the two studied groups as regards the demographic data of the patients, the level of sensory block, the operative duration or the tympanic temperature all through the procedure.

Also, the results of the present study showed no statistical difference in the total ephedrine administration although the mean arterial blood pressure (MAP) was statistically significant lower in the control group (S) when recorded 5 min after positioning (MAP3) which was not clinically significant on the need for ephedrine compared to ondansetron group (O) (Tables 1 and 2).

The total intraoperative meperidine requirement was statistically significant higher in the control *(Saline)* group (S) compared to the ondansetron group (O), being [14.4 ± 15.5 mg and 7.2 ± 13.1 mg], respectively, (*p* value = *0.01*) (Table 1).

The significant difference of meperidine requirement was a in harmony with the statistically significant higher incidence of shivering in group (S), [19/37 (51%)] compared to group (O), [10/38 (26%)], (*p* value = *0.007*) and the statistically significant higher incidence of maximum shivering scoring in group (S) compared to group (O), being [8/37 (22%) and 3/38 (7.8%)], respectively, (*p* value = *0.004*). The median range of shivering score in group (S) was [2 (1–4)] which was statistically significant higher than group (O) [1 (0–4)], (*p* value = *0.005*) (Table 3).

Although there was no statistical difference between the two groups as regards the incidence of vomiting, still, the incidence of nausea was statistically significant higher in group (S) [11/37 (29.7%)], compared to group (O) [2/38 (5.2%)], (*p* value = *0.002*) (Table 3).

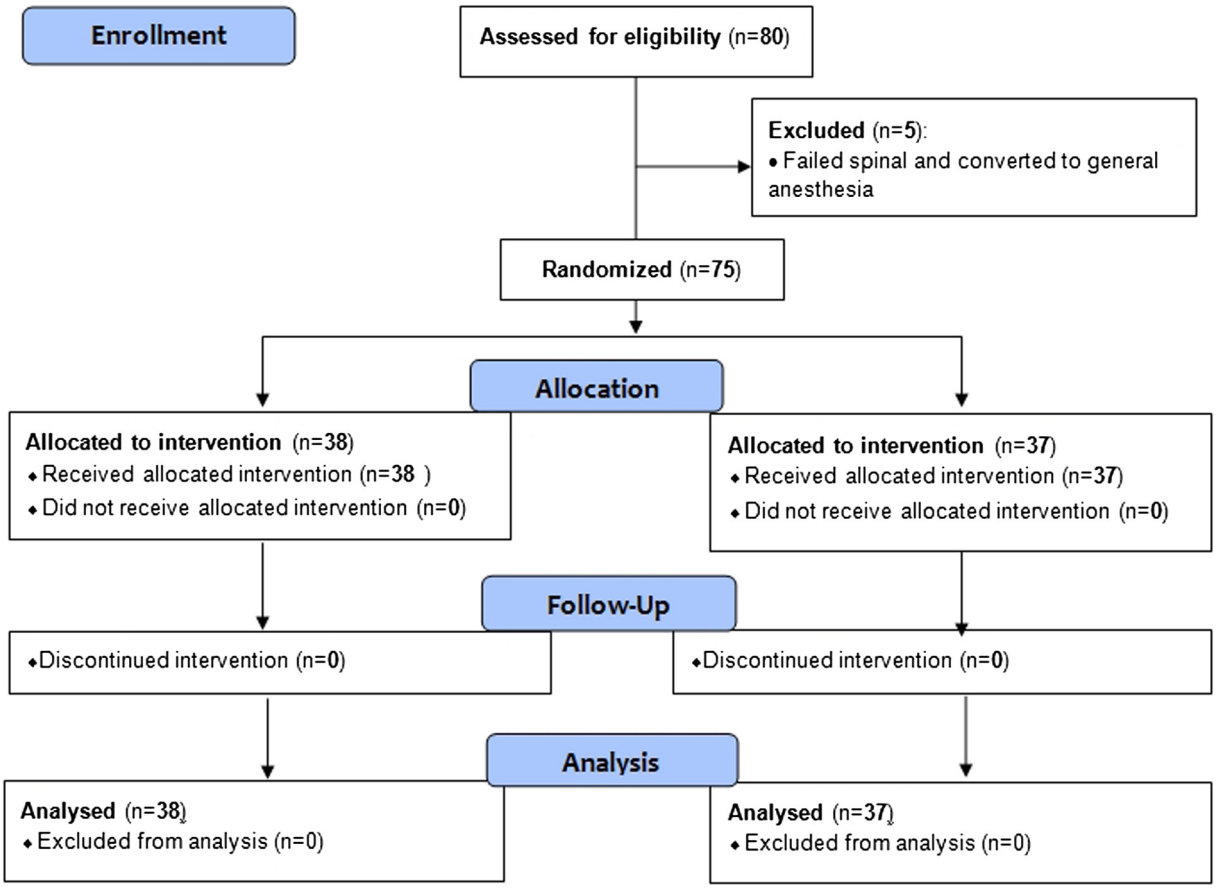

Fig. 1. Flow diagram of the study.

Table 1
Demographic and operative data in the two studied groups.

	Group (O) (n = 38)	Group (S) (n = 37)	P value
Age (year)	31 ± 5	30 ± 6	<0.44
Height (cm)	158 ± 3	157 ± 4	<0.055
Weight (kg)	72 ± 7	69 ± 8	<0.11
Body Mass Index (BMI)	33 ± 5	31 ± 6	<0.11
Block level (Thoracic segment = T)	6 (4–6)	6 (4–6)	<0.51
Operative duration (min)	52 ± 8	50 ± 9	<0.22
Total ephedrine dose (mg)	6.1 ± 7.6	7.6 ± 8.8	<0.24
Total meperidine dose (mg)	7.2 ± 13.1	14.4 ± 15.5[a]	<0.01

Data represented as (Mean ± SD) or [median (range)].
Group (O) = Ondansetron group; Group (S) = Normal saline group.
[a] Statistically significant difference between groups; (p < 0.05).

Table 2
Vital signs and clinical data in the two studied groups.

	Group **(O)** (n = 38)	Group **(S)** (n = 37)	P value
MAP0 (mmHg) [Just before induction of spinal anesthesia]	95 ± 11	98 ± 9	<0.15
MAP1 (mmHg) [Just after induction and lateral tilt position]	91 ± 10	91 ± 9	<0.46
MAP2 (mmHg) [2 min after positioning]	86 ± 10	85 ± 8	<0.29
MAP3 (mmHg) [5 min after positioning]	83 ± 9	78 ± 8*	<0.03
MAP4 (mmHg) [(Just after delivery of the baby]	86 ± 8	83 ± 6	<0.12
MAP5 (mmHg) [At the end of the surgery]	89 ± 12	88 ± 9	<0.23
$\mathbf{T_0}$ °C (Just before induction of spinal anesthesia)	36.7 ± 0	37 ± 0	<0.31
$\mathbf{T_1}$ °C (Just after delivery of the baby)	36.5 ± 0.3	36.5 ± 0.5	<0.25
$\mathbf{T_2}$ °C (At the end of the surgery)	36.4 ± 0.5	36.3 ± 0.5	<0.56

Data represented as (mean ± SD) or numbers and percentages (%).
Group (O) = Ondansetron group; Group (S) = Normal saline group, MAP = Mean Arterial Blood Pressure, T = Tympanic temperature.
* Statistically significant difference between groups; (p < 0.05).

4. Discussion

The results of the present study showed statistically significant higher incidence of shivering, incidence of maximum shivering scoring and total intraoperative meperidine requirement in group (S) compared to group (O). Also, the incidence of nausea was statistically significant higher in group (S) compared to group (O). Mean arterial blood pressure (MAP) was statistically significant lower in the control group (S) compared to group (O), when recorded 5 min after positioning (MAP3) without concomitant increase in the total ephedrine requirement between the two groups.

To our knowledge, few studies investigated the prophylactic preventive effect of Ondansetron on post-spinal shivering (PSS) in obstetric parturients underwent cesarean delivery (C/D) under spinal anesthesia.

One of our motives to design and carry out the present study was the disappointing results of the study done by Browning et al. [10] *(published in Jan.- Feb.2013)*, which was criticised by Wan-Jie and Jing-Chen [12].

The results of the present study showed significant reduction in the incidence of the positive shivering (score ⩾ 3) in ondansetron group comparison with the control group. These results were in

Table 3
Incidence of shivering, nausea and vomiting in the two studied groups.

	Group **(O)** (n = 38)	Group **(S)** (n = 37)	P value
Incidence of **shivering** at any time (%)	10/38 (26%)	19/37 (51%)*	<0.007
Incidence of **maximum shivering** at any time (%)	3/38 (7.8%)	8/37 (22%)*	<0.004
Median and range of **shivering**	1 (0–4)	2 (1–4)*	<0.005
Incidence of **nausea** (%)	2/38 (5.2%)	11/37 (29.7%)*	<0.002
Incidence of **vomiting** (%)	0/38	0/37	

Data represented as [median (range)] or numbers and percentages (%).
Group (O) = Ondansetron group; Group (S) = Normal saline group.
* Statistically significant difference between groups; (p < 0.05).

disagreement with the results of the study done by Browning et al. [10], who found no significant difference in the incidence of post-spinal shivering, between ondansetron 8 mg or saline administered before establishing combined spinal/epidural anesthesia in parturients underwent cesarean section. Wan-Jie and Jing-Chen [12] in a letter to editor criticised these results and attributed them to the point of scoring system *(1 = piloerection and vasoconstriction without visible muscle activity)* at which the investigators considered shivering to be positive, while it may be a physiological response above the level of block in compensation to the vasodilating effect of the neuroaxial blockade below the level of the block.

Also, Browning et al. [10] administered intrathecal fentanyl in his both groups which is associated with decreased incidence and severity of shivering [16,17], so that, it presumably interfered with their results.

Again, the results of Browning et al. [10] showed that ondansetron did not reduce nausea and vomiting without data supporting these results [12].

Meanwhile, the results of the present study were in accordance with the results of the study done by Shakya et al. [18], who compared both ketamine and ondansetron to placebo in lower abdominal surgeries under spinal anesthesia and found that incidence of shivering was (42.5%) in saline group compared to only (10%) in ondansetron group.

Also, the results of the present study *(as regards reduction in the incidence of shivering)* was in agreement with those of the work done by Kelsaka et al. [5], who compared ondansetron and meperidine to saline as a preventive measure of shivering under spinal anesthesia and showed that both ondansetron and meperidine reduced shivering to (8%) compared to the control group (38%). The difference in the degree of reduction in the incidence of shivering between this study (8%) and the present study (26%) may be rationalized by the facts that, Kelsaka et al. [5], studied a different group of patients (mostly males) underwent orthopaedic surgeries, with the median and range of sensory block in ondansetron group [T9 (T4-T12)], compared to higher level [T6 (T4-T6)] in the present study and also, they pre-medicated their patients with diazepam 10 mg 45 min before anesthesia.

Again, the results of the present study were matched with those of the study done by Marashi et al. [7], who studied two different doses of ondansetron (6 mg) and (12 mg) compared to normal saline to attenuate spinal induced hypotension and shivering and showed that (17%) of the control group patients experienced hypotension (MAP <80 mmHg) which was statistically higher than the ondansetron groups (p value = *0.04*). Also, the incidence of shivering was statistically higher in the control group (45%) compared to the ondansetron two groups (p value = *0.04*). but still these results showed more reduction in the incidence of shivering in ondansetron (6 mg) group [4%] and (12 mg) group [2%] compared to the present study which showed [26%] incidence of shivering. These differences may be attributed to the different shivering scoring system used by Marashi et al. [7], which consisted of 4 grades only and considered Grade (II): [fasciculation in the head and neck just visible as artefact of ECG] as negative. Also, the gender of the patients of the present study (female only) and the physiological changes of pregnancy with volume overload may affect the pharmacokinetics and pharmacodynamics of the studied drug.

Still, the results of the present study as regards the lower incidence of hypotension in ondansetron group compared to the control group were supported by the results of the recently published work of Melissa Dawn Hudson et al. [19], who retrospectively analyzed the charts of 46 parturients underwent cesarean section under spinal anesthesia and found that, prophylactic ondansetron was concomitant with more hemodynamic stability and reduced the incidence of vasopressor administration to 35.7% compared to 46.9% in those patients did not receive ondansetron.

Finally, the results of the present study were in partial agreement with those of the study done by Meng Wang et al. [20], who compared the prophylactic efficacy of different doses of ondansetron (2, 4, 6 and 8 mg) to placebo (normal saline) to prevent hypotension in parturients underwent cesarean section under spinal anesthesia. The results of their study showed that the incidence of hypotension was 60% in the saline group compared to 48.3%, 30%, 31% and 40% in (2, 4, 6 and 8 mg) ondansetron, respectively. According to their results, the authors assumed that the 4 and 6 mg doses of ondansetron were optimal doses to prevent maternal hypotension, but their methodology was different from ours as they defined hypotension as >20% reduction in systolic blood pressure, while we defined it as >20% reduction in mean arterial blood pressure. Still, the results of that study showed similarity to the present study as regards the incidence of nausea (10%) in the 8 mg ondansetron group which was statistically significant compared with the control group (33%).

4.1. Limitations of this study

One of the limitations of the present study was the economic cost of ondansetron which limits its use to the therapeutic role rather than routine premedication, (metoclopramide is still used as the first line) in our university hospital. Another imitation was that we did not use a standard anti-shivering drug like meperidine as a control group as we considered it the rescue medication for all patients if the ondansetron failed to prevent distressing shivering.

5. Conclusion

Ondansetron (8 mg) was effective in reducing post-spinal shivering (PSS) in parturients underwent elective cesarean delivery (C/D) and decrease the requirement to meperidine together with lower incidence of post-spinal hypotension and nausea when compared to placebo (saline).

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