

## Comparison of High Dose Ondansetron versus Low Dose Ondansetron for Prevention from Postanesthesia Shivering

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### ABSTRACT

**Background:** Postanesthesia shivering (PAS) is a very common anesthesia-related complication the not only is a discomfortable phenomenon for that patients, but can cause undesirable events and affect the patient's prognosis negatively. This study compares the high dose ondansetron versus low dose of this agent for PAS control.

**Methods:** In this clinical trial 101 patients under general anesthesia for elective surgeries in three groups of premedication with high dose ondansetron (8mg) (n=33), low dose ondansetron (4mg) (n=34) and placebo (normal saline) (n=34) were evaluated. The agents were injected immediately before anesthesia induction, and hemodynamic data, nausea and vomiting incidence and shivering severity were compared.

**Results:** Mean arterial pressure and pulse rate significantly decreased within the time (P-value<0.05), while oxygen saturation, peripheral and central body temperature did not have statistically significant alterations (P-value>0.05). The duration of recovery room stays and use of meperidine for shivering control were not different in the three groups (P-value>0.05), while incidence of nausea and vomiting and shivering intensity in placebo treated group was worse than ondansetron treated groups regardless of the dose (P-value<0.05). Comparison of two ondansetron treated groups represented insignificant difference considering nausea and vomiting and shivering intensity (P-value>0.05).

**Conclusion:** Ondansetron use regardless of the dose was superior to placebo in terms of PAS intensity and nausea and vomiting prevention. Low dose of ondansetron (4mg) was superior to high dose (8 mg) considering the hemodynamic stability, while the two doses were similar in terms of PAS intensity, nausea and vomiting occurrence, duration of recovery room stay and meperidine requirement for shivering control.

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Shivering is a common postoperative complication, particularly following general anesthesia, found in 6.3-66% of the cases. [1]. The etiology of this phenomenon is not well-elucidated, but the impairment of central thermoregulation control may be responsible for post-anesthesia shivering. Therefore, shivering may occur as a response to hypothermia during anesthesia [2-3].

Postanesthesia shivering (PAS) is not only a discomfortable condition that exacerbates the patient's pain, but causes significant complications including cardiopulmonary system implications, a remarkable

increase in cardiac output, oxygen consumption, dioxide carbon production, intraocular pressure, peripheral vascular resistance, intracranial pressure, and eventually lactic acidosis. [4-6] Besides, PAS affects surgical care in a negative manner, for cases that require postoperative immobilization such as vascular anastomosis [7]. Mentioned factors shows that PAS prevention is not merely beneficial for patients, but also positively affects the prognosis of surgical procedures [8].

In a complex neuraxial system, neurotransmitters and receptors play a role in the central thermoregulation [9]. Therefore, scientists have investigated the action of

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various pharmacological agents on the pathways affecting central thermoregulation such as the  $\alpha$ -2 adrenergic agonist clonidine, the opioid meperidine, and the anticholinergic agent physostigmine [10-12].

One such study was large in terms of the number of patients with 5 different drugs being used in 2003 with 5354 patients who had been candidates for elective surgery. In this study 1767 (31%) of patients suffered from shivering of which 160 patients had grades 3 and 4 shivering and were randomly treated with alfentanil, fentanyl, sufentanil, pethidine and tramadol with no difference noticed between these drugs [13].

Recently, attention has been turned to the use of ondansetron, a specific antagonist of the 5-HT<sub>3</sub> receptors that in addition to its widespread postoperative use as an antiemetic agent, may have preventive effects on PAS, as well [14-15]. Despite the results in favor of sole ondansetron use or in combination with other agents, we have aimed to compare the efficacy of high dose ondansetron versus low dose or placebo for shivering after general anesthesia.

## Methods

This The current double-blinded study is a randomized clinical trial (RCT) conducted on 101 patients under general anesthesia for elective surgeries referred to hospitals affiliated to the Isfahan University of Medical Sciences from April 2016 to June 2017.

After approval by the ethics committee of Isfahan University of Medical Sciences (IR.MUI.MED.REV.1396.3.0484), the study process was explained to the patient (if possible) and their legal guardian, and they were asked to sign an informed consent form to participate in the study.

Patients with body mass index (BMI) of less than 30 kg/m<sup>2</sup> and age range of 20-80 years old who had American Society Anesthesiology (ASA) status of I-II, had tympanic temperature of 36.5 -38° centigrade, and who were candidates for any elective surgery requiring general anesthesia were included.

Emergent operation requirement, ASA status of III-IV, Parkinson disease and any neuromuscular disorder, the presence of wax in the ear making it impossible to measure the tympanic temperature, poorly controlled diabetes mellitus, medical history of seizure or drug abuse, and recent medical history of corticosteroid therapy for over three months, use of vasodilator agents and administration of any agent affecting thermoregulation were considered as unmet criteria.

Alteration in the technique of anesthesia, bleeding to the extends that required blood transfusion, allergy to the administered anesthetic agents or ondansetron, and significant change in the hemodynamic or instability of hemodynamic were considered as the exclusion criteria.

The Isfahan University of Medical Sciences Ethics Committee approved the study protocol. After that, the study protocol was entirely explained for the patients or their legal guardians and written consent for participation in the study was obtained.

The patients who met the inclusion criteria were non-randomly entered in the study through convenience sampling until achieving the required number of study population. Eventually the included patients were randomly divided into three subgroups of A (high dose ondansetron), B (low dose ondansetron) and control group (placebo) using Random Allocation software. Therefore, each of the patients was provided with a particular number that was allocated him/her for each of the groups. In the current double-blinded study, the patients and the nurses who collected the data in the study checklists were blinded to the type of the medicine used as premedication.

For the blinding of the patients and the nurses all of the agents were injected using 2 ml syringes similar in shape. The content of the syringes was written on them as 1 or 2, to which only the anesthesiologist was aware of the codes allocated to normal saline or ondansetron.

All of the patients were fasted for 8 hours before the surgical procedure, and hydration was performed for them. The height, weight, and BMI of the patients were measured before the operation. Besides, both of ear tympanic membranes were examined and the tympanic temperature was measured. After that, premedication agent was administered for the patients as follows; the patients allocated to the group A were treated with 8 mg of ondansetron divided into two equal syringes as the premedication. The group 2 underwent premedication with 4 mg of ondansetron, as one of the syringes was filled with 4 mg of ondansetron and the other one with 2 ml of normal saline; and the group C as the control group were treated with normal saline divided into two separate 2 ml doses.

The data including age, ASA physical status, duration of the surgical procedure (from the first incision to the time of suturing), duration of stay in recovery room, the used dose of narcotic analgesia and incidence of nausea and vomiting were recorded in the study checklist.

Besides, the central body temperature was measured through tympanic membrane immediately following the anesthesia induction, and then every 15 minutes until the patients were discharged from the recovery room. The mean arterial pressure (MAP), oxygen saturation and pulse rate were measured every 15 minutes as well.

The primary study measurement was assessment of post-operative shivering and the intensity done immediately following the anesthesia induction, and then every 15 minutes until discharge from the recovery room. The intensity of nausea and vomiting was assessed using four-point scale of crossly and Mahajan as follows [16]:

- 0: No shivering;  
 1: No visible muscle activity, but one or more of piloerection, peripheral vasoconstriction or peripheral cyanosis (other causes excluded);  
 2: Muscular activity in only one muscle group;  
 3: Moderate muscular activity in more than one muscle group, but not generalised shaking and,  
 4: Violent muscular activity that involves the entire body.

In cases with grade 1 and 2 of shivering, heat lamp and blanket were used while for those with grades 3 and 4, 0.4 mg/kg of meperidine was administered.

The recruited data were entered into the Statistical Package for the Social Sciences version 23 (SPSS-23) and analyzed. Descriptive data were presented in mean, standard deviation, percentages and absolute numbers. For analytics Chi-Square test, one-way ANOVA, Kruskal-Wallis, and Repeated measure ANOVA were utilized. P-value of less than 0.05 considered as the level of significance.

## Results

### Characteristics of the patients

In the current study, premedication using ondansetron on anesthesia-related shivering was assessed on 101 patients allocated to three groups of high dose ondansetron (n=33), low dose ondansetron (n=34) and placebo (n=34). The three groups of the study were similar in terms of age, weight, height, BMI, and gender distribution. Table 1 represents the study population demographics in detail (Table 1).

### Hemodynamic changes

The comparison of hemodynamic variables including MAP, oxygen saturation, pulse rate, and peripheral and

central temperatures have been demonstrated in (Table 2). The pulse rate alterations showed significant changes within time, as the pulse rate significantly decreased with time (P-value=0.02). Besides, the trend of reduction in the pulse rate was remarkably higher in the high dose ondansetron treated group (P-value=0.04). Further evaluations showed a statistical MAP change within the time (P-value=0.03) but the group assessments revealed insignificant alterations (P-value=0.62) (Table 2).

In Table 3. Oxygen saturation of the patients revealed insignificant changes within the time (P-value>0.05). Repeated measure ANOVA showed insignificant differences among the three groups in terms of peripheral and central temperatures, neither by time consideration nor by group consideration (P-value>0.05) (Table 3).

### Shivering variables

According Further evaluations included the comparison of duration of surgical procedure, length of recovery room stay, meperidine injection requirements for the control of shivering (P-value>0.05). A significant difference was found among the three groups in terms of nausea and vomiting occurrence (P-value=0.01). The Mann-Whitney test revealed statistically higher rate of nausea and vomiting in placebo treated group than high dose (P-value=0.04) and low dose (P-value=0.006) ondansetron treated groups, while comparison of two ondansetron treated groups showed insignificant difference (P-value=0.15).

The main assessment of this study represented significant difference among the three assessed groups in terms of shivering intensity (P-value<0.001); where the shivering intensity was more severe in the placebo treated group than the other two others (P-value<0.001 for both groups), comparison of high dose versus low dose ondansetron showed non-statistical difference among the two groups (P-value=0.29) (Table 4).

**Table 1- Comparison of demographic data in the three assessed groups of the study**

Variables	High dose ondansetron (n=33) Mean±SD	Low dose ondansetron (n=34) Mean±SD	Placebo (n=34) Mean±SD	P-value
Age (y),	47.7±14.2	44.9±14.8	50±15.1	0.39
Weight (kg)	74.3±14.1	77.1±11.2	72.4±8.9	0.25
Height (cm)	165.5±9.3	169.2±8.1	166.4±9.7	0.22
BMI (kg/m <sup>2</sup> )	27.04±3.9	26.7±3.5	26.3±4.5	0.75
Gender	Male	16 (48.5%)	19 (55.9%)	0.78
	Female	17 (51.5%)	15 (44.1%)	

Y, year; Kg, kilogram; CM, centimeter; SD, standard deviation.

**Table 2- Comparison of MAP and HR in the three assessed groups**

Variables	HD ODT (n=33)	LD ODT (n=34)	Placebo (n=34)	P Time	P groups			
	Mean	St.	Mean			St.		
		Mean	Arterial					
Baseline	107.5	15.5	103.6	18.9	101.7	14.1	0.03	0.62
IFAI	92.1	17.9	97.7	23.3	87.4	15.6		
15 min	91.3	15.1	88.8	16.5	93.5	19.1		
30 min	85.1	16.3	92.6	15.5	89.6	17.6		
45 min	90.4	16.02	92.9	14.1	88.1	20.9		
60 min	86.2	15.6	90.3	12.3	82.2	14.7		
75 min	85.4	12.1	88	15.	82.4	15.8		
90 min	87.6	13.5	96.2	13.6	88.7	15.02		
105 min	93.1	12.6	96.2	13.6	88.7	15.02		
			Pulse	Rate				
Baseline	92.1	16.6	84.2	15.2	87.6	16.6	0.02	0.04
IFAI	92.1	19.7	82.1	15.8	86.9	15.6		
15 min	85.1	17.3	77.8	14.9	86.4	17.5		
30 min	78.2	17.1	75.4	12.3	83.5	16.1		
45 min	73.1	11.9	77	12.01	83.4	16.3		
60 min	74.8	11.5	77.8	13.7	79.8	15.9		
75 min	77.3	10.3	75.9	13.6	78.7	15.8		
90 min	75.8	10.4	83.2	12.2	77.5	15.2		
105 min	78.5	6.6	85.5	12.6	79.9	16.7		

HD, High dose; LD, Low dose; ODT, ondansetron; IFAI, immediately following anesthesia induction; Min, minutes.

**Table 3- Comparison of SpO2 and temperature in the three assessed groups**

Variables	HD ODT (n=33)	LD ODT (n=34)	Placebo (n=34)	P Time	P groups			
	Mean	St.	Mean			St.		
			SpO <sub>2</sub>					
10 min	94.9	2.6	94.8	2.6	95.1	2.3	0.15	0.58
20 min	94.03	4.2	94.1	2.4	94.8	2.1		
45 min	94.2	1.6	94.1	2.1	94.6	2.3		
			Peri	Temp				
IFAI	36.9	0.4	36.9	0.3	36.7	0.3	0.10	0.18
15 min	36.6	0.2	36.7	0.3	36.8	0.3		
30 min	36.6	0.2	36.7	0.3	36.7	0.3		
45 min	36.6	0.2	36.7	0.3	36.5	0.4		
60 min	36.7	0.2	36.7	0.3	36.5	0.4		
75 min	36.6	0.2	36.7	0.3	36.6	0.4		
90 min	36.8	0.3	36.9	0.2	36.8	0.5		
105 min	36.8	0.6	37	0.3	36.9	0.3		
			Core	Temp				
15 min	36.01	0.2	36.1	0.2	36.1	0.3	0.13	0.36
30 min	36	0.2	36.1	0.3	36.02	0.3		
45 min	36.01	0.2	36	0.3	35.9	0.4		
60 min	36.1	0.3	36.02	0.3	35.9	0.5		
75 min	36.1	0.2	36.1	0.3	35.9	0.4		
90 min	36.2	0.3	36.2	0.2	36.1	0.4		
105 min	36.3	0.3	36.1	0.4	36.3	0.3		

HD, High dose; LD, Low dose; ODT, ondansetron; IFAI, immediately following anesthesia induction;

**Table 4- Comparison of shivering intensity in the three assessed groups of the study**

Variable	HD ODT N (%)	LD ODT N (%)	Placebo N (%)	P-value
Grade I	0(%0)	0(%0)	0(%0)	<0.001
Grade II	0(%0)	0(%0)	0(%0)	
Grade III	5(%15.2)	2(%5.9)	8(%23.5)	
Grade IV	2(%6.7)	8(%23.5)	15(%44.1)	

HD, High dose; LD, Low dose; ODT, ondansetron.

## Discussion

In the current study, we evaluated different doses of ondansetron versus placebo for the prevention of PAS. The members of the three assessed groups of the study included high dose ondansetron, low dose ondansetron and placebo that were similar in terms of age, BMI, gender distribution and duration of the surgical procedure. Therefore, the variables that probably could affect the study outcomes were eliminated, as various factors such as duration of surgical procedure and patient's age have been demonstrated to a play role in PAS incidence [17]. In general, findings of our study are in favor of low dose ondansetron use (4 mg) compared to high dose ondansetron and placebo, because low dose of ondansetron was not only accompanied with less shivering intensity and remarkably fewer rates of nausea and vomiting but led to less hemodynamic changes. Another advantage of low dose ondansetron was fewer alterations in pulse rate, where bradycardia did not occur in any of the three assessed groups. Besides, the two doses of ondansetron were similar in terms of length of recovery stay and additional meperidine requirement for the control of shivering.

Numerous studies in the literature have assessed the use of ondansetron, alone or in combination with other agents, and also in different doses for the prevention of PAS following both general and spinal anesthesia. To the best of our knowledge, the current study is one of the limited studies evaluating different doses of ondansetron for PAS prevention. In accordance with our study, several studies in the literature have shown notable superiority of ondansetron to placebo for PAS prevention. In addition, these studies have shown that the preventive preoperative use of ondansetron is statistically associated with lower risk of postanesthesia hypotension, although not significantly related to bradycardia [1, 9, 15]. The Browning et al. study is one of the rare reports representing that prophylactic ondansetron does not prevent PAS and even affect its intensity. This conclusion may have occurred due to their study design as they assessed ondansetron efficacy for combined spinal epidural anesthesia; therefore in addition to impairing central thermoregulation, neuraxial pathway was affected

as well [18], while ondansetron may not have had any effect on neuraxial thermoregulation pathway [19].

Other investigations that compared ondansetron with meperidine presented comparable outcomes. Noaman et al. compared prophylactic 4 mg of ondansetron with 0.5 mg/kg of meperidine, and showed that although the two regimens were similar in terms of post anesthesia shivering prevention and its intensity, postoperative nausea, vomiting occurrence and sedation requirement were considerably higher in the meperidine treated group [2]. Mahoori et al. conducted another similar study and declared that ondansetron had favorable antishivering effects as meperidine. They used 8 mg of prophylactic ondansetron and even concluded that the dose of 8 mg is the choice [20]. In confirmation of the previous reports, Kelsaka et al. compared three regimens of ondansetron, meperidine and placebo. The declared similar efficacy of meperidine and ondansetron, while both were superior to placebo [21].

Shakya et al. evaluated the efficacy of 4 mg ondansetron in combination with 0.25 mg/kg of ketamine, and achieved compatible outcomes as compared to placebo. [22] Chowdhury et al. represented the superiority of tramadol to ondansetron for PAS control because of its delayed action onset, despite prevention effects. They concluded that ondansetron is not only an effective agent for PAS prevention but is superior to tramadol in terms of hemodynamic stability, nausea and vomiting incidence [23]. The other confirmatory report by Chagalety et al. declared insignificant superiority of tramadol than ondansetron for PAS prevention [24].

Limited studies in the literature have compared different doses of ondansetron for PAS prevention. Powell et al. conducted a study on 82 patients randomly divided into three groups of prophylactic 8 mg ondansetron, 4 mg ondansetron or placebo. They injected the agents 2-3 minutes before the anesthesia induction and found insignificance difference in terms of hemodynamic change among the assessed groups, while contrary to our findings PAS prevention was better in the 8 mg treated group than the two others [11]. The other investigation by Marashi et al. represented similar outcomes by the use of either 6 mg or 12 mg of intravenous ondansetron for the prevention of PAS

following spinal anesthesia. Besides, they presented considerable superiority of ondansetron regardless of its dose than placebo in terms of hemodynamic stability, bradycardia improvement and shivering following spinal anesthesia [25].

## Conclusion

Based on our findings, ondansetron use regardless of its dose was superior to placebo in terms of PAS intensity and nausea and vomiting prevention. Besides, low dose ondansetron (4 mg) was better than high dose (8 mg) because of fewer hemodynamic alterations, while similar regarding PAS intensity, nausea and vomiting occurrence, duration of recovery stays and additional meperidine requirement.

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