



## Acceptance Letter

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### **Use of Ondansetron, Ketamine or Their Combination for Prevention of Post-Anesthetic Shivering**

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Date of acceptance: 6 /2014

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**Running title:** Abdelhalim, *et al*: Post-Anesthetic Shivering - Ondansetron vs. Ketamine

**ORIGINAL ARTICLE**

## **Use of Ondansetron, Ketamine or Their Combination for Prevention of Post-Anesthetic Shivering**

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**ABSTRACT**

**Background:** Postanesthetic shivering (PAS) is relatively common side-effect of general anesthesia. We examined the preventive effects of ondansetron, ketamine or both on postanesthetic shivering.

**Patients and Methods:** In this prospective, randomized, double-blind controlled trial, 120 ASA I-II, patients, undergoing ENT surgery under general anesthesia were randomly assigned to one of four equal groups receiving either a combination of ondansetron 4mg plus ketamine 0.25 mg/kg (Group OK), ondansetron 8mg (Group O), ketamine 0.5 mg/kg (Group K), normal saline as the control group (Group C), intravenously 20 minutes before the end of surgery. Tympanic temperature and time to extubation were measured. Postanesthetic shivering was graded upon patient's arrival to the PACU. Sedation and adverse reactions were evaluated.

**Results:** Shivering was observed in 12 patients (40%) in Group C, 3 patients (10%) in group OK, 4 patients (13.3%) in groups O and 3 patients (10%) in group K, however, the difference between group C and all other groups was statistically significant ( $P < 0.001$ ). The number of patients with a shivering grade of 3 was significantly higher in Group C compared with other groups ( $P=0.001$ ). The sedation score was significantly higher in group K than the other groups ( $P = 0.021$ ). The incidence of nausea or vomiting in the ondansetron group (8mg) was 6.7%, which was significantly less compared to other groups ( $P = 0.0162$ ).

**Conclusion:** a combination of intravenous ondansetron 4mg plus ketamine 0.25 mg/kg is comparable to either ondansetron 8mg IV or ketamine 0.5 mg/kg IV in preventing post-anesthetic shivering in pre-medicated patients undergoing ENT surgery under general anesthesia.

**Key words:** *Ondansetron, Ketamine, Prevention, Post-Anesthetic, Shivering*

## INTRODUCTION

Postanesthetic shivering (PAS) is very unpleasant, and it may be harmful for the patient undergoing surgery. [1] The incidence of postanesthetic shivering was described to be as high as 60% in patients recovering from general anesthesia. [2] It causes physiological stress resulting in increased oxygen consumption, carbon dioxide production, lactic acidosis, and increased cardiac output. It also increases intracranial and intraocular pressure, moreover, severe shivering interferes with electrocardiogram and pulse oximetry monitoring so that it is important to provide effective prevention of this clinical dilemma allowing early ambulation. [2, 3]

A variety of physical and pharmacological methods have been used to prevent hypothermia and decrease the incidence of PAS. Physical methods include radiant heat warmers, warming of the operative theatre, blankets and using IV fluids at body temperature .[1,3] A various pharmacological strategies including IV administration of alfentanil [4], tramadol[5], magnesium sulphate [6], physostigmine [7] and meperidine[4,8] have been used to treat or prevent postanesthetic shivering.

Ketamine, a competitive N-methyl-d-aspartate (NMDA) receptor antagonist, has a role in thermoregulation. NMDA receptor modulates noradrenergic and serotonergic neurons in locus coeruleus; moreover, the direct central sympathetic stimulation and inhibition of norepinephrine uptake into postganglionic sympathetic nerve endings may decrease core-to-peripheral redistribution of heat. [8, 9] Its antishivering effect has been reported in many studies, but it may cause side effects such as drowsiness, hallucination and nystagmus [8-11]. Ondansetron, a 5-hydroxytryptamine (5-HT<sub>3</sub>) antagonist, primarily used to treat postoperative nausea and vomiting, has also been tried as antishivering with good results, both following general anesthesia and during neuraxial anesthesia [12-14]. This prospective, randomized, double-blind, placebo controlled study was performed to compare IV ondansetron (4 mg) and ketamine (0.25 mg/ kg) in combination, IV ondansetron (8 mg) or IV ketamine (0. 5 mg/ kg) , and placebo (saline) for prevention of postanesthetic shivering (PAS) in patients who underwent ENT surgery under general anesthesia.

## **PATIENTS AND METHODS**

After obtaining Institutional Review Board approval ( No.E-14-1073) and written informed consent, this prospective, randomized, double-blind and placebo-controlled study was conducted at King Abdul-Aziz University Hospital, Riyadh, Saudi Arabia including 120 patients of ASA physical status I&II, of both sexes, aged 18 to 45 years, who had undergone ENT surgery under general anesthesia.

Patients with hypo- or hyperthyroidism, hypertension, severe cardiopulmonary disease, hypersensitivity to one of the studied drugs, neuromuscular pathology, a psychological disorder, pregnancy, history of convulsions or addictions ,duration of anesthesia < 1 hour or >3 hours, those with a known history of alcohol or drug abuse, those receiving vasodilators or other medications likely to alter thermoregulation were excluded. Patients whose an initial body temperature reading intraoperatively of >37.5 °C or < 36.5 °C were also excluded from the study.

The selected patients were randomly assigned to one of the four equal groups by using sealed, opaque envelopes to receive a combination of intravenous ondansetron 4mg plus ketamine 0.25 mg/kg (Group OK, n=30), ondansetron 8mg and normal saline (Group O, n=30), ketamine 0.5 mg/kg and normal saline (Group K, n=30), or normal saline together with another normal saline as the control group (Group C, n=30), intravenously approximately 20 min before the completion of the surgery.

All test drugs and placebo were prepared, diluted to a volume of 5 ml in a 5 ml syringes and presented as covered, coded syringes by an anesthesiologist who was not participating in the study or in grading of the patients' shivering. The attending anesthesiologists and data collectors were all unaware to the content of each syringe, and the master codes were held by a person who did not participate in data collection.

All patients were subjected to a standard pre-operative evaluation and they were premedicated with lorazepam 2mg administered orally 2hours before surgery. The visual analogue scale (VAS) was explained to all patients before the operation. On arrival at the operating theatre, routine standard monitoring was used for all patients, including noninvasive blood pressure monitoring, a three-leads ECG, bispectral index of the electroencephalogram (BIS monitoring; Aspect A-2000, Aspect Medical Systems Inc., Natick, Massachusetts, USA), peripheral oxygen saturation (SpO<sub>2</sub>), capnogram and train-of-four monitoring. Also, body temperature (tympanic temperature) was monitored using a digital ear thermometer (an aural canal thermometer, OMRON 510, Germany).

After preoxygenation using 100% Oxygen for 3 minutes, all patients received standard anesthetic techniques; anesthesia was induced by IV fentanyl 2 µg/kg and IV propofol 2-2.5mg/kg in 20 mg increment titrated to loss of eyelash reflex, followed by the administration of rocuronium 0.6 mg/kg to facilitate orotracheal intubation. Anesthesia was maintained with sevoflurane 1-3% in combination with nitrous oxide 60% in oxygen. Sevoflurane concentration was titrated on the basis of BIS changes to achieve a target value between 40 and 50 and patients received repeated doses rocuronium (0.2 mg/kg) as needed to maintain muscle relaxation based on neuromuscular stimulation. An increase in blood pressure or heart rate by more than 15% from the pre-operative value was defined as insufficient analgesia and was treated with intermittent doses of fentanyl 0.5 ug/kg IV as needed. Ventilation was controlled mechanically (Datex- OhmedaR, Helsinki, Finland) to maintain an end tidal carbon dioxide tension at 30–35 mmHg and an oxygen saturation of  $\geq 98$  per cent with 40 per cent oxygen in air. During surgery, patients were positioned in the 20 ° reverse Trendelenburg and a standardized protocol of local anesthetic administration to infiltrate the surgical site by 1% lidocaine with epinephrine (1:100,000) was used for control of bleeding and pain. All the procedures were performed by the same two surgeons, all with a clinical experience of more than 5 years using the same surgical technique for each type of surgery.

The ambient temperature of the operating room was measured by a wall thermometer and maintained between 21-23 °C with constant humidity. Intraoperative fluid was adequately compensated with an infusion of lactated Ringer's solution during surgery according to standard guideline. All fluids therapy and drugs used were at room temperature. In the operating room, all the patients were only covered with similar cotton blanket but were not actively heated. Approximately 20 min before the anticipated end of surgery, patients were randomly allocated to receive the study drugs, the attending anesthesiologist who was blinded to the drug and group allocation administered the study drug over 10 minutes.

At the end of surgery, sevoflurane and nitrous oxide were switched off and 100% oxygen was administered. The oral cavity was inspected under direct vision, throat pack was removed and then the secretions and blood clots were aspirated. The residual neuromuscular block was reversed with neostigmine 0.04 mg/kg i.v and atropine 0.02 mg/kg i.v, Tracheal extubation was done when the train-of-four response was 90%, and the patient demonstrated facial grimace, adequate tidal volume and respiratory rate, coughed with open mouth, or opened their eyes spontaneously. Then, patients were transferred to Post- Anesthesia Care Unit (PACU). Extubation time (from termination of sevoflurane until extubation), duration of the surgery, and duration of anesthesia were recorded.

In both groups, tympanic temperature was measured and recorded at 8 predetermined measurement points ( $T_0$ – $T_7$ ), as follows:  $T_0$ , before anesthetic induction as the baseline;  $T_1$ , immediately after induction;  $T_2$ , 30 minutes after induction ;  $T_3$ , before administration of the study drugs;  $T_4$ , on admission to PACU;  $T_5$ , 10 min postoperatively;  $T_6$ , 20 min postoperatively and  $T_7$ , 30 min postoperatively and if tympanic temperature was  $<36^{\circ}\text{C}$  , active warming using a forced-air warmer (Warm Touch; Mallinckrodt Medical, St Louis, MO, USA) was applied to patients.

In post anesthesia care unit (PACU), the patients were monitored and covered with standard cotton blanket over the entire body without active warming and all patients received oxygen 4 liter/min via a facemask. Temperature in PACU was kept between 22-23 °C. PACU nurse blinded to the study drugs assessed the patients for postanesthetic shivering (PAS), pain, nausea and vomiting for 30 minutes after admission to PACU. The nursing staff judged PAS using a 5-

point rating scale similar to that validated by Wrench et al. [4] (0 = no shivering, 1 = peripheral vasoconstriction without visible muscular activity, 2 = visible muscular activity confined to 1 muscle group, 3 = visible muscular activity in >1 muscle group, and 4 = gross muscular activity involving the entire body). If shivering grade was 3 or 4, the prophylaxis was regarded as ineffective and meperidine 0.5 mg/kg IV was administered to patients.

Postoperative pain was measured using a 0–10 cm visual analogue scale (VAS) 30 min after admission to the recovery room, where 0=no pain and 10=worst pain imaginable; and all those patients who suffered from pain  $\geq 3$  VAS were treated with boluses of intravenous fentanyl 0.5- 1  $\mu\text{g}/\text{kg}$ . Postoperative analgesia required and times to first analgesia required were recorded. Moreover, the degree of sedation was assessed at 20 and 30 minutes after PACU entrance using the following a 5-point scale [15]: 1, fully awake and oriented; 2, drowsy; 3, eyes closed but rousable to command; 4, eyes closed but rousable to mild physical stimulation; and 5, eyes closed but unrousable to mild physical stimulation.

Patients were considered ready for discharge from the PACU when the modified Aldrete post-anesthesia score was  $\geq 9$ , [16] and all the patients stayed for at least 30 min observation in the PACU independent of whether or not they attained discharge criteria earlier.

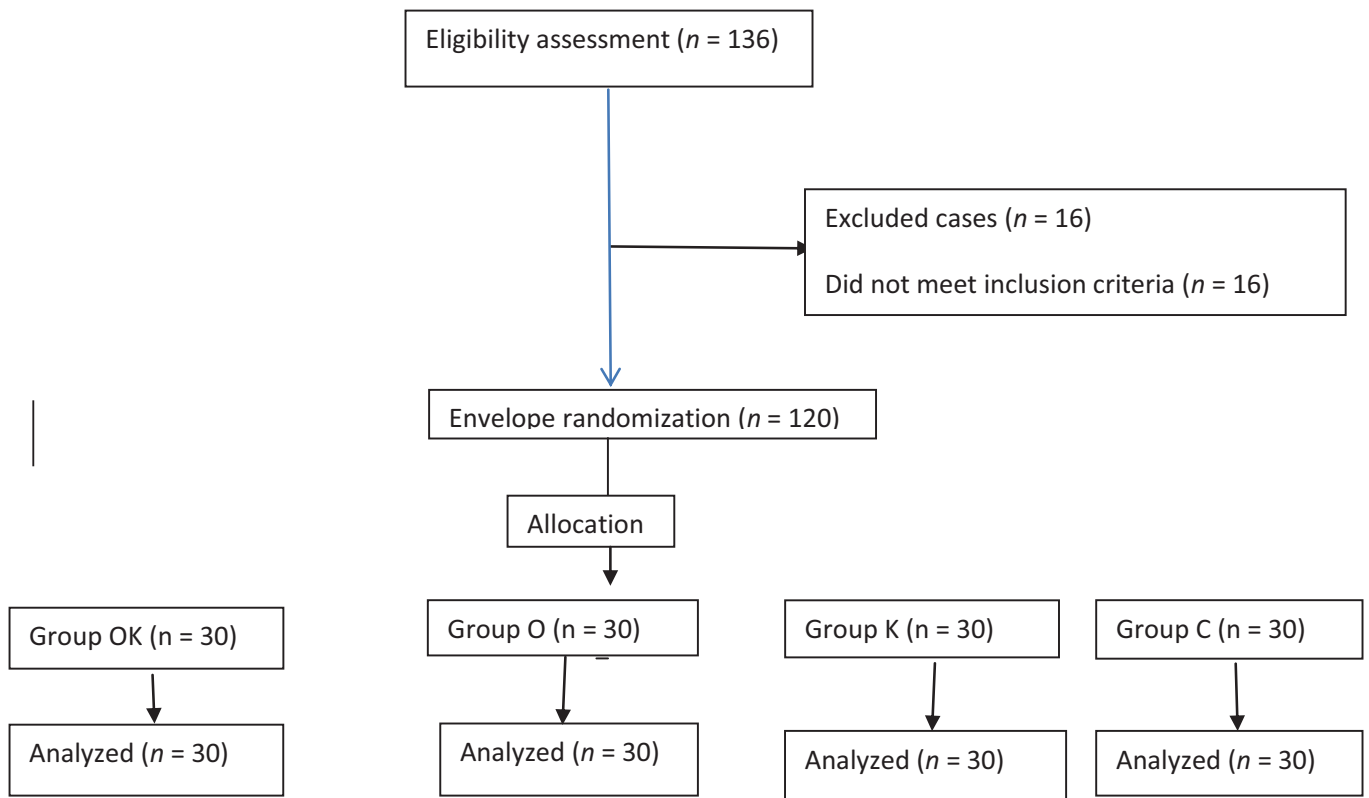
The possible side-effects that might be related to the study drugs including nausea, vomiting, hypertension ( $> 30\%$  baseline), tachycardia, respiratory depression, apnea, oxygen desaturation, nystagmus and hallucination were recorded and patients who complained of postoperative nausea and vomiting were given 10 mg IV metoclopramide.



## STATISTICAL ANALYSIS

Incidence of postanesthetic shivering was estimated to be around 40-65% [8]. We anticipated an incidence of 45% in the control group so that the sample size of 30 patients in each group would be necessary to detect a 40% reduction in the incidence of shivering with a power of 80% and an  $\alpha$  of 0.05.

Statistical analysis was performed using the SPSS statistical package (version14.0; SPSS Inc., Chicago, IL, USA). Continuous variables were analyzed using repeated measures analysis of variance (ANOVA) followed by Bonferroni's post hoc testing. Statistical comparisons among the groups were performed using two-way ANOVA, followed by unpaired t-tests with Bonferroni's correction. Nominal or categorical data were analyzed using Chi-square ( $\chi^2$ ) test or Fisher's exact test as appropriate. Data are presented as mean  $\pm$  standard deviation, median (range) or numbers and percentages. P value of  $<0.05$  was considered statistically significant.



**Figure 1:** Flow chart of the study

## RESULTS

All four groups were comparable with respect to age, sex, weight, height, ASA class, duration of anesthesia, duration of operation, and temperatures of operating and recovery rooms ( $P > 0.05$ , Table 1).

Although, the decreases in the tympanic temperatures at  $T_3$ ,  $T_4$ ,  $T_5$ ,  $T_6$  and  $T_7$  were statistically significant in all groups when compared with the baseline level values ( $P < 0.05$ , Figure 2), there were no significant temperature differences among the groups at any time interval ( $P > 0.05$ , Figure 2).

The number of patients experiencing shivering was the highest in group C where 12 out of 30(40%) patients shivered. On the other hand, 3 (10%), 4 (13.3%) and 3 (10%) patients shivered in groups OK, O and K respectively, however, the difference between group C and all the other groups was statistically significant ( $P < 0.001$ ). The number of patients with a shivering at grade 3 was statistically significantly higher in group C compared with the other groups ( $P=0.001$ , Table 2). These patients were subsequently treated with meperidine 0.5 mg/kg IV as rescue antishivering agent, shivering ceased in all patients after the first dose of meperidine. None of patients among groups experienced shivering at grade 4.

Visual analog pain scores was significantly lower in groups K than in other groups ( $P = 0.0365$ ) with no significant difference between the other groups ( $P > 0.05$ , Table 3). There were no significant differences in the extubation time and PACU stay among groups ( $P > 0.05$ , Table 3). Fewer patients required rescue analgesia in groups K than in other groups ( $P = 0.0348$ ), moreover, the time to rescue analgesia was longer in group K than in other groups ( $P = 0.001$ ).

The sedation score was significantly higher in group K (median 2) than the other groups ( $P = 0.021$ , Table 3) with no significant difference between the other groups ( $P > 0.05$ , Table 3). Only one patient experienced hallucination and another two patients developed nystagmus in group K, but the result was not statistically significant ( $P > 0.05$ , Table 3). The incidence of nausea or vomiting and number of patients required rescue antiemetic in group O was 6.7%, which was significantly less than that of other three groups; ( $P = 0.0162$ , Table 3) with no significant difference between the other groups ( $P > 0.05$ , Table 3).

None of the patients in groups demonstrated respiratory depression, apnea, oxygen desaturation, tachycardia, or hypertension episodes after study drug administration or during the postoperative stay in the recovery room.

Table 1: Patients Characteristics.

Parameters	Group OK	Group O	Group K	Group C	<i>P</i>
Number ( <i>n</i> )	30	30	30	30	-
Age (years)	38.70 ± 8.51	37.27 ± 9.00	37.67 ± 7.80	36.23 ± 10.02	0.562
Sex (M:F)	20/10	19/11	21/9	18/12	0.485
Weight (kg)	68.33 ± 8.98	67.93 ± 8.68	67.13 ± 10.46	67.50 ± 9.34	0.798
Height (cm)	169.00 ± 4.84	167.50 ± 6.39	169.10 ± 6.25	168.23 ± 5.96	0.541
ASA (I:II)	23/7	23/7	22/8	21/9	0.743
Duration of surgery (min)	119.80± 11.63	123.20± 11.17	121.17± 10.38	119.40 ± 12.30	0.365
Duration of anesthesia (min)	127.47± 14.52	131.09± 13.66	128.38± 12.89	127.58 ± 12.57	0.420
Operation room temperature (°C)	23.00 ± 1.49	22.00 ± 0.87	22.77 ± 1.52	22.03 ± 1.16	0.622
PACU temperature (°C)	22.47 ± 0.51	22.60 ± 0.50	22.53 ± 0.51	22.50 ± 0.51	0.704
Surgery type, n (%)					
Septoplasty	16 (53.3)	15 (50)	15 (50)	17 (56.7)	0.591
Septorhinoplasty	8 (26.7)	9 (30)	8 (26.7)	7 (23.3)	0.643
FESS	6 (20)	6 (20)	7 (23.3)	6 (20)	0.487

ASA = American Society of Anesthesiologists. FESS (functional endoscopic sinus surgery). Values are presented as means (SD), or number of patients (*n*) and percentages (%).

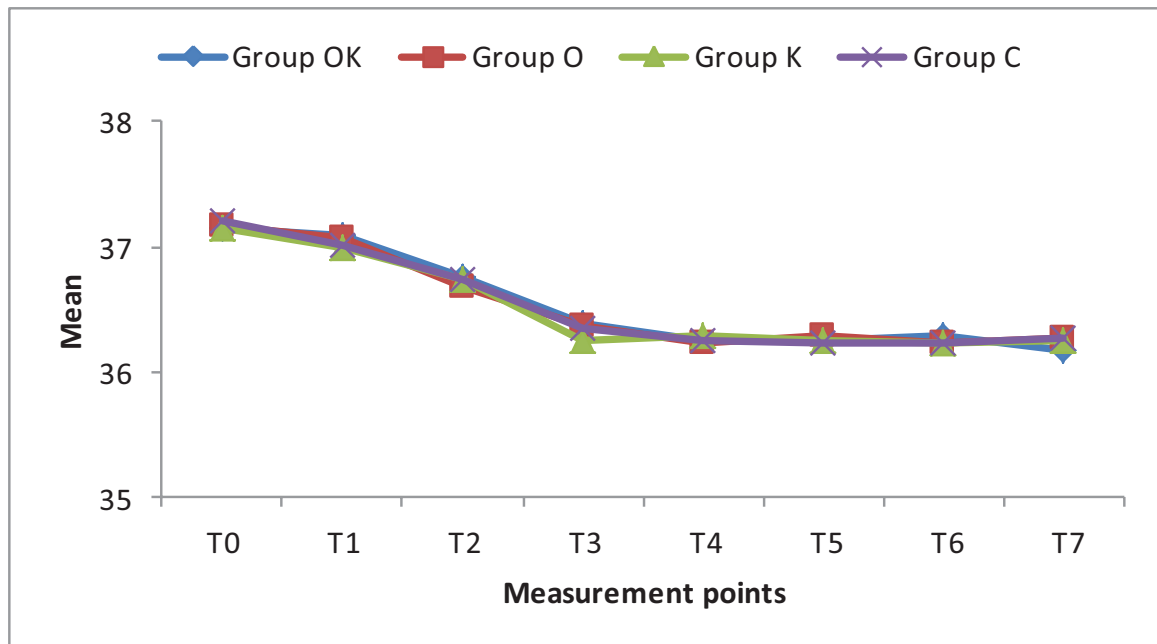


Figure 2: Tympanic temperature ( $^{\circ}\text{C}$ ) at predetermined measurement points. ( $T_0$ , before anesthetic induction as the baseline;  $T_1$ , immediately after induction;  $T_2$ , 30 minutes after induction ;  $T_3$ , before administration of the study drugs;  $T_4$ , on admission to PACU;  $T_5$ , 10 min postoperatively;  $T_6$ , 20 min postoperatively and  $T_7$ , 30 min postoperatively) .

Table 2: Number of patients with different grades of shivering in the four study groups, 30 minute after admission in PACU.

Shivering grades	<b>OK (n=30)</b>	<b>O(n=30)</b>	<b>K (n=30)</b>	<b>C (n=30)</b>
Grade 0	27	26	27	18*
Grade 1	1	1	0	5†
Grade 2	1	1	2	1
Grade 3	1	2	1	6‡
Grade 4	-	-	-	-

\* P<0.05 significant compared with the other groups. † P<0.05 significant compared with the other groups. ‡ P<0.05 significant compared with the other groups.

Table 3: Post-operative profiles and incidence of adverse effects among groups

Parameters	OK (n=30)	O (n=30)	K (n=30)	C (n=30)	P
Extubation time (min)	4.73 ± 1.08	4.57 ± 1.17	4.80 ± 1.16	4.60 ± 1.16	0.336
PACU stay	43.43 ± 3.50	41.03 ± 4.01	43.13 ± 3.91	42.90 ± 3.59	0.498
Postoperative pain (VAS)	2.67 ± 0.88	2.70 ± 0.88	1.73 ± 0.64*	2.53 ± 0.82	0.0365
Postoperative analgesia required(n)	13 (43.3)	14 (46.7)	7 (23.3) *	14 (46.7)	0.0348
Intraoperative Fentanyl dose (µg/kg)	2.80 ± 0.53	2.88 ± 0.55	2.77 ± 0.57	2.60 ± 0.64	0.688
Fentanyl dose at PACU (µg/kg)	0.47 ± 0.41	0.57 ± 0.39	0.30 ± 0.26*	0.47 ± 0.39	0.027
Time to first analgesia required (min)	15.73 ± 3.11	14.40 ± 3.43	27.90 ± 4.43*	14.20 ± 2.89	0.001
Sedation score	1 (1–3)	1(1–3)	2 (1–3) *	1(1–3)	0.021
Nausea and vomiting (n)	10(33.3)	2(6.7) *	11(36.7%)	12(40%)	0.0162
Hallucination(n)	-	-	1(3.3)	-	0.265
Nystagmus(n)	1 (3.3%)	-	2 (6.7)	-	0.652
Metoclopramide use (n)	8 (26.7)	2 (6.7) *	8(26.7)	9 (30)	0.041

Values are presented as mean ±SD, median (range) and number of patients (n) or percentages (%). \*Significantly different compared to other groups ( $P < 0.05$ ). PACU = Post-anesthesia care unit, VAS =visual analogue scale

## DISCUSSION

This prospective, randomized, double-blinded placebo-controlled study revealed that prophylactic administration of a combination of intravenous ondansetron 4mg plus ketamine 0.25 mg/kg is comparable to either ondansetron 8mg IV or ketamine 0.5 mg/kg IV in preventing post-anesthetic shivering in pre-medicated patients undergoing ENT surgery under general anesthesia with no delay in recovery or discharge from PACU.

Ketamine probably controls shivering by non-shivering thermogenesis either influencing the hypothalamus or by the beta adrenergic effect of norepinephrine. [17] The results of the current study supported the findings reached by Norouzi *et al.* [18] who compared IV ketamine 0.25 mg/kg and 0.5 mg/kg and found that both doses are effective in prevention of postanesthetic shivering with no significant difference in their hemodynamic parameters, however, recovery, extubation time and hallucination was observed to be less with 0.25 mg/kg dosage in their study. Similarly, a study by Gecaj- Gashi *et al.* [19] reported that prophylactic low-dose of an IV injection of ketamine 0.5 mg/kg was effective in preventing postoperative shivering, and no hallucinations, hypertension, tachycardia, and nystagmus were noticed in their study. Kose *et al.* [10] demonstrated that ketamine 0.5 and 0.75 mg/kg to be effective and more rapid than meperidine 25 mg for the treatment of postanesthetic shivering after general anesthesia but the side effect profile including nystagmus and feeling like "walking in space" were noted with both doses of ketamine.

Ondansetron (4 and 8 mg), a specific 5-HT<sub>3</sub> receptor antagonists, have been effectively used in the prevention of PAS. Powell and Buggy. [12] have shown that the incidence of shivering was 33% of patients received 4mg Ondansetron IV and 15% with 8 mg Ondansetron IV compared to 57% in placebo group, given immediately before the anesthetic induction accordingly, ondansetron could produce a dose-dependent reduction in PAS, furthermore, they clearly reported reduced incidence of PAS without affecting the core-to-peripheral redistribution of heat during general anesthesia, highlighting that serotonergic pathways have a role in the regulation of PAS and the anti-shivering effect of ondansetron is independent of intraoperative hypothermia.

In another study, Asl *et al.* [20] argued that, the use of ondansetron 4 mg immediately before the induction of general anesthesia effectively reduced the incidence of postoperative shivering to 13.3% of patients in comparison to 50% in control group. Kelsaka *et al.* [13] compared ondansetron (8mg) with meperidine (0.4mg /kg) for prevention of shivering during and after spinal anaesthesia and found that, the incidence of shivering was significantly decreased to 8% in ondansetron group. The antishivering effect of ondansetron could be related to central inhibitory mechanism of the shivering response through inhibition of serotonin reuptake in the preoptic anterior hypothalamic region, 5-HT<sub>3</sub> receptors may also influence both heat production and heat loss pathways. [13] However, Shakya *et al.* [14] reported that low doses ketamine 0.25mg/kg and ondansetron 4mg significantly decreased the incidence of shivering to 2.5 % and 10% respectively in patients undergoing spinal anesthesia, the difference in the mean weight of patients in Kelsaka and shakya studies (76 vs. 52.80 kg, respectively). Hence, the dose requirement of ondansetron would be less in shakya's group of population [14].

Conflicting results have been reported by Browning *et al.* [21] who demonstrated that intravenous ondansetron 8 mg before performing combined spinal epidural anesthesia in obstetric patients undergoing cesarean section was not effective in decreasing the incidence or severity of shivering and this could be partially attributed to many factors, including variations in the study subjects as they were all female, pregnant, and relatively young, and so such patient factors modified the antishivering effect of ondansetron, additionally, ondansetron (8 mg) may have been less effective in their patients because of physiological changes, such as the increased blood volume and cardiac output seen in late pregnancy. Our study is not quite similar with previous studies because of the variations in study design; patient characteristics, premedication given, type of surgical procedures, the route and timing of administration of the studied agents lastly the scale used to assess incidence of postanesthetic shivering.



In the current study, a combination of ondansetron 4mg with very low dose of Ketamine 0.25/kg was advantageous as it showed almost same result in term of incidence of shivering compared ondansetron 8mg or Ketamine 0.5mg/kg with minimal possible side effects, the efficacy of this combination may be attributed to synergistic effect of both drugs by dual mechanisms of action when given prophylactically for prevention of PAS.

Undesirable side effects like sedation and hallucinations, limits the clinical usage of ketamine; not surprisingly, we reported one case of post-operative hallucinations in patients receiving ketamine 0.5 mg/kg, and non in patients receiving ketamine 0.25 mg/kg supporting the findings reached by Dich-Nielsen *et al.* [22] who demonstrated that the incidence of such adverse effects is lower with administration of small doses of ketamine (<1 mg/kg).

In the current study, although, patients received ketamine 0.5 mg/kg IV had higher postoperative sedation grades in the immediate recovery period; we did not observe deep sedation, fortunately, there was obvious finding that no delay in recovery and the time to reach discharge criteria was unchanged by the addition of small dose of ketamine during general anesthesia. We noticed that, pain scores were significantly lower in patients received ketamine 0.5 mg/kg IV, with consequent reduction in the postoperative analgesic requirements; accordingly, this analgesic effect might have contributed to the reduction of PAS as postoperative surgical pain facilitates non-thermoregulatory shivering. [23] Additionally, similar to findings of other studies in the literature [8, 18], a low dose of Ketamine have been used successfully to reduce the incidence of PAS in patients receiving general anesthesia without producing significant hemodynamic changes.

Considering the potential respiratory depressant effect of meperidine especially if used during the surgery with other opioids, [4, 20] the findings of this study demonstrated the safety and efficacy of using ondansetron and ketamine as an alternative antishivering agents, however, ondansetron is more expensive.

There are certain limitations of our study: Firstly, the current study assessed the incidence of post-anesthetic shivering subjectively within short duration of observation (only 30 minutes postoperatively) in PACU, so that we cannot exclude the possibility of occurrence of additional shivering after transfer to the ward. Secondly, we did not include a positive control group using a standard agent such as meperidine.

**In conclusion,** we found that prophylactic IV administration of a combination of ondansetron 4mg plus ketamine 0.25 mg/kg is comparable to either ondansetron 8mg IV or ketamine 0.5 mg/kg IV in preventing post-anesthetic shivering in pre-medicated patients undergoing ENT surgery under general anesthesia with no delay in recovery or discharge from PACU, however, administration of low dose of ketamine 0.25 mg/kg combined with ondansetron 4mg resulted in lower chance of possible sedative effect or hallucination compared with 0.5 mg/kg ketamine, additionally, ondansetron as antishivering agent has advantages, because of reduced incidence of post-operative nausea and vomiting (PONV) .

### **Acknowledgement**

The authors are grateful to the staff members of otolaryngology operating room, King Abdulaziz University Hospital, College of Medicine, King Saud University, Riyadh, Saudi Arabia

**Source of Support:** Nil.

**Conflict of Interest:** None declared.

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