

COMPARISON OF ONDANSETRON IN TWO DIFFERENT DOSES IN THE REDUCTION OF POST ANESTHETIC SHIVERING AFTER GENERAL ANESTHESIAUmar Qadir Bacha¹, Rafia Hassan²**HOW TO CITE THIS ARTICLE:**

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ABSTRACT: GOALS OF STUDY: Ondansetron, a specific 5-HT₃ antagonist, conventionally used as an antiemetic may also affect perioperative thermoregulation and Post Anesthetic Shivering (PAS). Therefore, we decided to compare the effect of Ondansetron in 2 different doses (4mg and 8 mg) given just before the induction of general anesthesia on the incidence of PAS. **METHODS:** A double blind, placebo-controlled study was adopted to study 90 patients divided into 3 equal groups receiving general anesthesia for elective general surgeries. Groups-A, B and C received Ondansetron 4 mg, 8mg and Normal Saline 4 ml I/V respectively immediately before anesthetic induction. Core and peripheral temperatures were documented every 10 minutes from baseline to recovery from anaesthesia. After recovery from anaesthesia the occurrence of shivering was documented. Data was entered in excel and statistically important tests were done. P <0.05 was considered as significant. **RESULTS:** The incidence of PAS was 60% in the Group-C compared with 16.7% in Group-B, and 36.7% in Group-A. PAS was significantly low in the group receiving 8 mg ondansetron. **CONCLUSIONS:** Ondansetron 8 mg when compared with Ondansetron 4 mg given before the induction of anesthesia, reduces the incidence of PAS in adults significantly, without affecting the core-to-peripheral redistribution of temperature. The incidence of shivering was highest in the control group (60%) with an intermediate incidence in the group receiving 4mg Ondansetron (36.7%) and a lowest incidence in the group receiving 8mg Ondansetron (16.7%). **CONTEXT:** Different observations suggest that the serotonergic system has a role in the control of postanesthetic shivering. Ondansetron is a specific 5-HT₃ antagonist that may affect perioperative thermoregulation and PAS. Therefore, we decided to compare the effect of Ondansetron, in 2 different doses (4mg and 8 mg) given just before the induction of general anesthesia, on the incidence of PAS. **AIMS:** To compare the effect of Ondansetron in 2 different doses (4mg and 8 mg) given just before the induction of general anesthesia on the incidence of PAS. **METHODS AND MATERIAL:** A double blind, placebo-controlled study was adopted to study 90 patients divided into 3 equal groups receiving general anesthesia for elective general surgeries. Groups-A, B and C received Ondansetron 4 mg, 8mg and Normal Saline 4 ml I/V respectively immediately before anesthetic induction. Core and peripheral temperatures were documented every 10 minutes from baseline to recovery from anaesthesia. After recovery from anaesthesia the occurrence of shivering was documented. **STATISTICAL ANALYSIS USED:** Data was entered in excel and later on analysed using SPSS 14.0. Chi-square tests were applied. Differences from baseline within groups and between groups were evaluated using ANOVA (Analysis Of Variance). P < 0.05 was considered as significant. **RESULTS:** The incidence of PAS was 60% in the Group-C compared with 16.7% in Group-B, and 36.7% in Group-A. PAS was significantly low in the group receiving 8 mg ondansetron. **CONCLUSIONS:** Ondansetron 8 mg when compared with Ondansetron 4 mg given before the induction of anesthesia, reduces the incidence of PAS in adults

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significantly, without affecting the core –to -peripheral redistribution of temperature. The incidence of shivering was highest in the control group (60%) with an intermediate incidence in the group receiving 4mg Ondansetron (36.7%) and a lowest incidence in the group receiving 8mg Ondansetron (16.7%).

KEYWORDS: Ondansetron; Shivering; General Anesthesia; Serotonergic pathway; Core Temperature.

INTRODUCTION: In man, the core temperature is normally maintained within narrow limits of 36.5-37.5°C even in presence of an adverse environmental temperature by a combination of behavioral a physiological response.¹ Reduction in core body temperature may lead to shivering which is basically a protective mechanism to increase the body temperature. The occurrence of shivering during and after anesthesia is well recognized since long and described by various authors as ‘pentothal shakes’, ‘halothane shakes’, ‘shivering’, ‘post-operative spasticity’ and ‘spontaneous post anesthesia tremors’² Apart from the distress it cause to the patients, shivering produces undesirable physiological consequences such as raised oxygen consumption & hypoxemia, increased cardiac work, raised carbon dioxide production, lactic acidosis and lower mixed venous O₂ saturation.² A wide range of drugs include pethidine, fentanyl, alfentanil, sufentanil, tramadol, buprenorphine, doxapram, clonidine & ketanserin etc. have all been reported to be effective in suppressing shivering.^{3,4,5}

The neurotransmitter pathways involved in the mechanism of PAS are poorly understood. Meperidine, clonidine & physostigmine are all effective treatments indicating that opioid, alpha-adrenergic and anticholinergic systems are probably involved,⁶ Ondansetron is a specific 5HT₃ antagonist that may affect thermoregulation & PAS. Studies done in this regard have shown that serotonergic pathways have a role in the regulation of PAS. It has been suggested that perhaps 5-HT₃ inhibition has a specific antishivering effect, but given the variety of neurotransmitter systems known to be also involved in regulating shivering, an inhibitory effect at the 5HT₃ receptor probably results from a generalized thermoregulatory inhibition at the level of hypothalamus where the bulk of thermoregulatory control occurs.⁶

Therefore, we decided to compare the effect of Ondansetron, in 2 different doses (4mg and 8mg) given just before the induction of general anesthesia, on the incidence of PAS in a randomized, placebo controlled, double blinded study.

SUBJECTS AND METHODS: With approval from ethics committee and after written and informed consent, a double blind, placebo- controlled study was adopted to study 90 ASA I and II patients of either sex divided into 3 equal groups undergoing elective general surgeries of up to 2 hours duration. Group – A (n=30) received Ondansetron 4 mg I/V. Group – B (n=30) received Ondansetron 8 mg. I/V & Group – C (n=30) received Normal Saline 4 ml I/V immediately before anesthetic induction.

Group allocation was done by an anesthesiologist who was not aware of the study protocol. He/she allocated the patients to each group in a random manner so as to include 30 patients in each of the three groups. He/she was not responsible for the anesthesia administration to these patients. Core (rectal) and fingertip temperature (dorsum of middle finger) was recorded every 10 minutes from baseline to recovery. After recovery from anaesthesia the occurrence of shivering was documented clinically by an observer who was unaware of the group assignment.

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Exclusion criteria were pyrexial illness, allergy to ondansetron, surgery anticipated to be longer than 120 minutes (2 hours), age <18 years or >60 years or if use of vasoconstrictors or vasodilators is planned.

The trial preparation was prepared freshly by anaesthesia department technologists/nursing staff who were not involved in the study. The anesthesiologist recording the data & caring for the patient was unaware of what the preparation contained.

All patients received a 4ml injection, the volume of Ondansetron being made up with normal saline to 4ml when necessary. This injection of trial medication was given immediately after the placement of i/v cannula & 3-5 minutes before the induction of anesthesia.

Routine pre-operative preparation consisted of fasting 6-8 hrs prior to surgery. All patients were pre-medicated with Tab. Alprazolam 0.5mg night prior to surgery. On arrival in the operating room, a peripheral i.v access with venous cannula of 18/20 G was achieved. Monitors recording ECG, Blood pressure, SpO₂ & Respiratory rate were attached. I.V fluid in the form of Normal Saline/Ringer Lactate warmed to 37°C was infused as the maintenance fluid according to the body weight. Base line core & fingertip temperature was recorded on the contra-lateral hand to the i/v infusion. & repeated at 10 minutes intervals during surgery & in recovery.

General Anesthesia was induced with i.v midazolam 0.01 mg/kg, i.v fentanyl 2µg/kg, followed by i.v propofol 2.0 – 2.5 mg/kg. After securing the airway anesthesia was maintained with Isoflurane in the ratio of 50:50 Nitrous oxide and Oxygen.

The patients were having standard cotton surgical drapes & were not actively heated. Ambient temperature was maintained at 20^o-22^oC with constant humidity.

PAS was documented visually by 3 specified members of the recovery room staff who were unaware of the study group allocation. They were also be briefed about the definition of shivering used the study. Shivering was defined as readily detectable fasciculations or tremors of face, trunk or limbs of a minimum of 15-seconds duration.

Data was entered in excel and later on analysed using SPSS 14.0. Chi-square tests were applied. Differences from baseline within groups and between groups were evaluated using ANOVA (Analysis Of Variance). P < 0.05 was considered as significant.

RESULTS: Mean age, height, weight, sex ratio and ASA Class of three groups were statistically comparable (Table I). Mean blood pressure and heart rate were recorded intra-operatively at various time intervals and were comparable in all the groups (Table III and IV). Ondansetron did not alter the hemodynamic profile of either group intraoperatively.

There was no statistically significant difference in the Mean Core Temperature at various time intervals in between the groups, although there was decrease from baseline to the end of surgery in all the three groups (Figure 1).

There was no statistically significant difference in the Mean Peripheral Temperature at various time intervals in between the groups, although there was increase from baseline to the end of surgery in all the three groups (Figure 2).

In our study, the incidence of PAS was 60% in the Saline group compared with 16.7% in the group receiving the larger dose of Ondansetron (8 mg), with an intermediate incidence of shivering (36.7%) observed in patients receiving the smaller dose (4 mg)(Table IV and Figure 3). PAS was significantly low in the group receiving 8 mg ondansetron.

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	Ondansetron 4mg	Ondansetron 8mg	Control
Age(Years)	39.6±12.28	40.26±13.76	42.3±12.52
Weight(kgs)	59.56±9.78	61.4±9.49	59.23±10.05
Sex(Male/female)	10/20 10/20	11/19	9/21
Height(cms)	170.96±4.87	171.83±5.47	172.43±5.47
ASA Class(I/II)	22/8 22/8	21/9	20/10

Table I: Demographic Data

Data are mean ± SD.

Time Interval (minutes)	Ondansetron 4mg	Ondansetron 8mg	Control
Baseline (Before GA)	96.65± 7.90	95.94±7.25	95.29±7.69
10	94.28 ±8.51	92.94±10.79	93.0±9.01
20	98.02± 8.72	95.4±9.92	96.18±10.53
30	95.9 ± 7.15	95.67±9.22	96.15±7.81
40	94.90 ±5.52	95.92±7.64	94.88±7.31
50	94.76 ±5.55	96.51±7.45	93.56±7.14
60	94.50±6.09	95.74±7.74	96.0±9.03
70	95.01±4.19	94.56±7.17	96.89±7.61
80	96.20±5.28	95.4±5.18	96.45±5.94
90	95.96±4.79	97.26±4.72	95.61±6.45
120	98.30±1.49	95.65±2.33	95.53±3.21
RECOVERY	96.50±5.30	93.27±7.70	93.10±5.59

Table II: Comparison of mean blood pressure (mmHg) at different time intervals (mean±SD)

Time Interval (minutes)	Group A	Group B	Group C
Baseline (Before GA)	77.56 ± 6.70	77.93 ± 4.92	75.73 ± 5.00
10	76.20 ± 4.56	75.7 ± 4.54	74.03 ± 3.77
20	76.93 ± 7.02	77.26 ± 4.20	76.23 ± 4.92
30	74.7 ± 5.90	76.43 ± 3.32	74.83 ± 4.38
40	74.10 ± 5.40	75.48 ± 2.60	74.66 ± 3.70
50	72.82 ± 4.24	74.30 ± 2.86	74.11 ± 3.12
60	73.42 ± 5.00	72.57 ± 2.50	74.11 ± 2.81
70	73.4 ± 4.44	72.37 ± 2.72	73.33 ± 2.53
80	74.82 ± 3.57	72.46 ± 1.76	73.41 ± 2.76
90	75.0 ± 4.02	74.45 ± 2.01	73.72 ± 3.19
120	77.33 ±2.42	75.0 ± 2.58	74.66 ± 4.16
RECOVERY	73.36±4.04	73.33 ± 3.82	72.26 ± 3.97

Table III: Comparison of heart rate (per min) at different time intervals (mean±SD)

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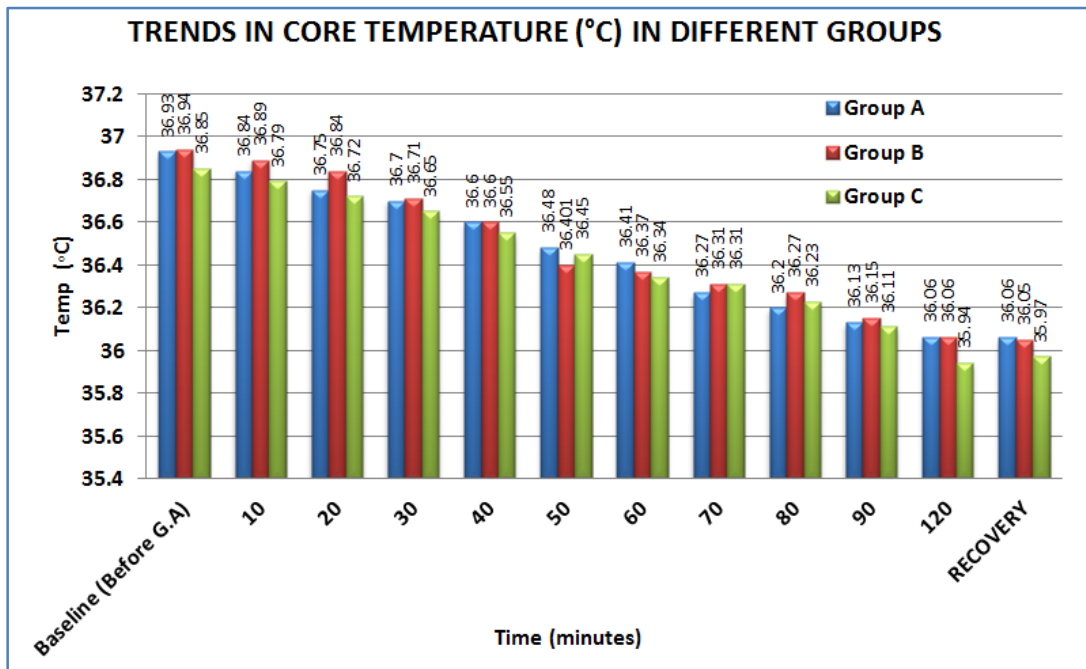


Figure 1

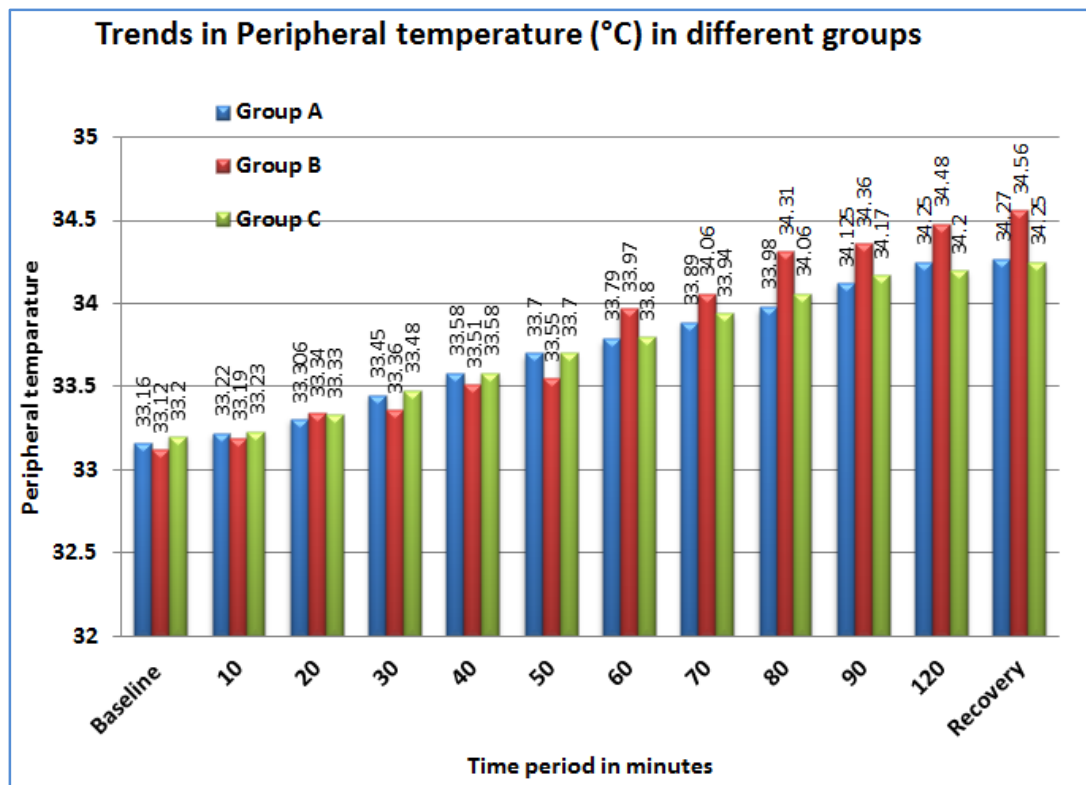


Figure 2

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SHIVERING	Ondansetron 4mg	Ondansetron 8mg	Control
YES	11(36.7%)	5*(16.7%)	18(60%)
NO	19(63.3%)	25(83.3%)	12(40%)

Table IV: Incidence of shivering:

*P=0.001, Control vs Ondansetron 8mg.

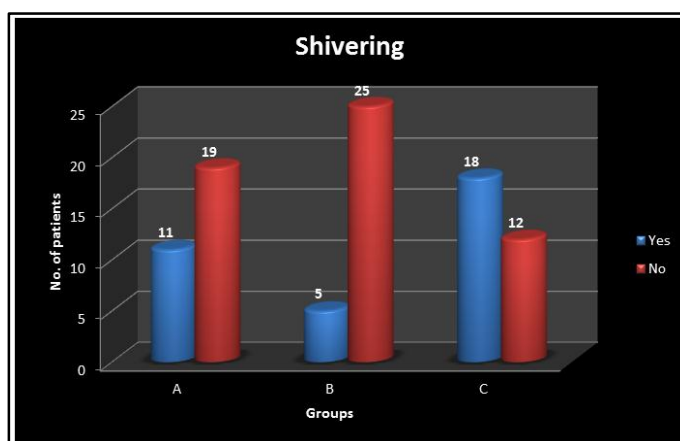


Figure 3

DISCUSSION: Surgery and general anesthesia impair the normal balance between heat production and loss.^{7,8,9} Prevention and treatment of Post Anesthetic Shivering (P.A.S) is an important aspect of patient care, as it may be associated with a number of deleterious sequelae, including sympatho-adrenal stimulation, increased oxygen consumption, and carbon dioxide production which may lead to increased incidence of surgical wound infection, prolonged hospitalization, morbid cardiac events, increased blood loss and prolonged postoperative recovery.^{10,7,11}

Various observations suggest that the serotonergic system has a role in the control of post anesthesia shivering. It has been shown that a 5-Hydroxytryptamine-3 (5-HT₃) antagonist, Ondansetron has anti-shivering effects.^{6,12,13} An inhibitory effect at the 5-HT₃ receptor probably results from a generalized thermoregulatory inhibition at the level of the hypothalamus, where the bulk of thermoregulatory control occurs. Ondansetron is notable for its lack of hemodynamic side effects.¹⁴

Clonidine may be associated with significant hypotension and sedation,¹⁵ but this has not been consistently shown, with other studies indicating no significant hypotensive or sedative effect.^{16,17} Tramadol, a nonopioid analgesic which inhibits 5-HT re-uptake and enhances synaptosomal concentration of 5-HT and noradrenaline, also inhibits shivering after the administration of general anesthesia.¹⁸ It also reduces the sweating, vasoconstriction, and shivering thresholds.¹⁹ Doxapram, a cerebral stimulant, is also effective in suppressing PAS, but is associated with significant hemodynamic effects.²⁰ Physostigmine increases heart rate and blood pressure,^{17,21} which may be detrimental to myocardial oxygen demand in some patients with coronary artery insufficiency. It is also commonly associated with postoperative nausea and vomiting.¹⁷ In contrast,

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ondansetron effectively relieves postoperative nausea and vomiting. Although meperidine in the doses effective in treating post-anesthetic shivering (0.33–0.4 mg/kg) rarely produces untoward cardiovascular effect,^{22,23,24,25,17} it may potentially cause respiratory depression, especially if it or other opioids have been given intraoperatively.

The results of our study are comparable to the results of various studies done from time to time like those done by R. Komatsu et al²⁶ and Powell et al.⁶

We came to the conclusion that Ondansetron 4mg as well as 8 mg given before the induction of anesthesia, reduces the incidence of PAS in adults, but the decreased incidence of shivering is however statistically significant only with ondansetron 8 mg as compared to the 4mg dose. However, the core-to-peripheral redistribution of temperature normally observed during the administration of general anesthesia is not affected. This implies that Ondansetron probably acts by a central inhibitory mechanism, and that 5-Hydroxytryptaminergic pathways have a role in regulating postanesthetic shivering, but this needs further validation.

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