

The Effect of Granisetron, Ondansetron, and Meperidine in Preventing Postoperative Shivering: Controlled Clinical Trial

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ABSTRACT

Background: Recently, use of HT35 receptor antagonists to prevent postoperative shivering has attracted a great deal of attention. This study was conducted with the aim of investigating the effectiveness of granisetron as an HT35 antagonist when compared with ondansetron and meperidine in preventing postoperative shivering.

Material and Methods: In this triple blind random clinical trial study, 90 patients 18-50 years of age with ASA Class I and II undergoing general anesthesia were randomly assigned into one of the three drug groups: O (4-mg ondansetron), G (40 µg/kg of granisetron), and P (25 mg meperidine), immediately before induction of anesthesia. After anesthesia induction, at the end of the surgery, after the entrance and after leaving the recovery state, central temperature, peripheral temperature, heart rate, systolic blood pressure, diastolic blood pressure, and shivering were measured and documented. Two-tailed $P < 0.05$ was considered significant.

Results: In the meperidine, ondansetron, and granisetron groups, 4 (13.3%), 3 (10%), and 10 (33.3%) of patients experienced shivering during recovery, where the difference between the ondansetron and granisetron groups was significant (p -value=0.02). The variations in the mean arterial pressure during the investigation stages only in the ondansetron group were not significant ($p > 0.05$). At the beginning of recovery, the reduction of peripheral temperature significantly was lower in the ondansetron group ($p < 0.05$), while reduction of the central temperature was significantly ($p < 0.05$) higher in the granisetron group. By the end of the recovery, the variations in the peripheral temperature across the three groups were consistent with the changes at the beginning of recovery, but variations of the central temperature across the three groups was not significantly diverse.

Conclusion: Granisetron was not found to be much effective in preventing postoperative shivering. Ondansetron and meperidine were equally effective in preventing postoperative shivering. Ondansetron also causes less hemodynamic changes compared to other drugs, while granisetron is more effective in terms of preventing nausea and vomiting.

Keywords: Shivering, Anesthesia, Granisetron, Meperidine, Ondansetron.

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INTRODUCTION

The body temperature as a vital sign, is regulated for preserving the physiology of the human body. Any inadvertent changes in this parameter including intraoperative hypothermia results in problems such as postoperative shivering, coagulation disorders, impaired nitrogen balance of the body, and changes of pharmacological effects on the human body¹.

Mild hypothermia through sympathoneural and adrenomedullary responses or through the direct unfavorable effect on immune defenses has resulted in the incidence of adverse outcomes such as a three-fold increase in the risk of developing shivering following cardiac operation, in patients².

Postoperative shivering, asynchronous and random involuntary contractions of one or more skeletal muscles to increase basal metabolism, is observed in 8.15 up to 80% of patients³.

The postoperative shivering event is very common and causes various complications such as increased oxygen uptake, hypercarbia and lactic acidosis, increased carbon dioxide production, tachycardia, hypertension and thus aggravation of coronary heart disease⁴. Moreover, increasing intracranial and intraocular pressure, increased pain at the site of surgery, and patient's discomfort and malaise, are some another complications⁵. Under general anesthesia, patient relies on autonomic defenses and external thermal management for thermoregulation. Autonomic responses also are markedly impaired under anesthesia (increasing warm response and reducing cold response thresholds). During general anesthesia sweating act as a best preserved thermoregulatory defense. In contrast, vasoconstriction and shivering thresholds are markedly reduced⁶.

Shivering can be a result of hypothermia during surgical operation and re-regulation of the body heat center or because of fever and chills in response to activation of inflammatory response and release of cytokines⁷.

To reduce shivering, there are pharmacological and nonpharmacological methods. The nonpharmacological method involves use of moisturizers, using warming blankets, and inhaling warm and humid oxygen. The medical method, on the other hand, most exerts its effect through reducing the shivering temperature threshold³.

However, which pharmacological method is more suitable for patients following surgery is still controversial.

To prevent postoperative shivering, various pharmacological methods have been used, where meperidine has been shown to be one of the most effective agents⁸. In other studies, the drugs did not differ significantly regarding suppression of shivering and recurrence of shivering⁹. Most probably, meperidine exerts its effect on temperature regulation center or through opioid central receptors.

Granisetron and ondansetron have also been used in some studies to prevent postoperative shivering and have had positive effects¹⁰⁻¹³. These medications exert their anti-vomiting effects through blocking 5-HT₃ receptors both peripherally, on gastrointestinal vagal nerve terminals, and centrally in the chemoreceptor trigger zone. In this way, by inhibiting vomiting reflex, they prevent nausea and vomiting and can be used to prevention of PONV (Post-Operative Nausea and Vomiting). Serotonin (5-hydroxy tryptamine) is a monoamine which is found in the central nervous system and nerve fiber, and has a neuro-transmitting role. Some studies believe that the serotonergic system is involved in controlling postoperative shivering¹³.

Eventually, since no study was found on comparing the effect of ondansetron, granisetron, and meperidine in preventing postoperative surgery, the present study was conducted with the aim of comparing ondansetron and granisetron when compared with meperidine as a well-known drug in preventing and treating postoperative surgery.

MATERIALS AND METHODS

Study design and setting

The present study is a triple blind randomized clinical trial study that was conducted in Ardabil University of Medical Sciences (ARUMS) as one of northwestern medical university of Iran

Sample

Since the probability of reduction of incidence of shivering using ondansetron in previous studies was around 40% compared to the control group with $\alpha=0.05$ and $\beta=0.2$, the sample size for each group was calculated 29 to determine the difference between the groups with a power of 80%.

Finally, 30 patients (18-50-year-old), who had referred to Imam Khomeini Hospital affiliated with ARUMS for general surgery, after obtaining a written informed consent regarding the medications to be used preoperatively from each patient, were considered for each group.

Exclusion Criteria

Very obese patients (a weight above 100 kg), patients with a fever above 38°C, those with a history of endocrine diseases and Parkinson's disease, the patients who needed blood transfusion or peripheral vasodilators or vasoconstrictors, and the subjects whose surgical operation lasted for more than 90 minutes were excluded from the research Figure 1.

Study process and variables

The patients were blocked randomly and placed in one of the three groups of ondansetron, granisetron, and meperidine. For the first, second, and third groups, 4 mg of ondansetron, 40 µg/kg of granisetron, and 25 mg of meperidine were intravenously injected respectively two

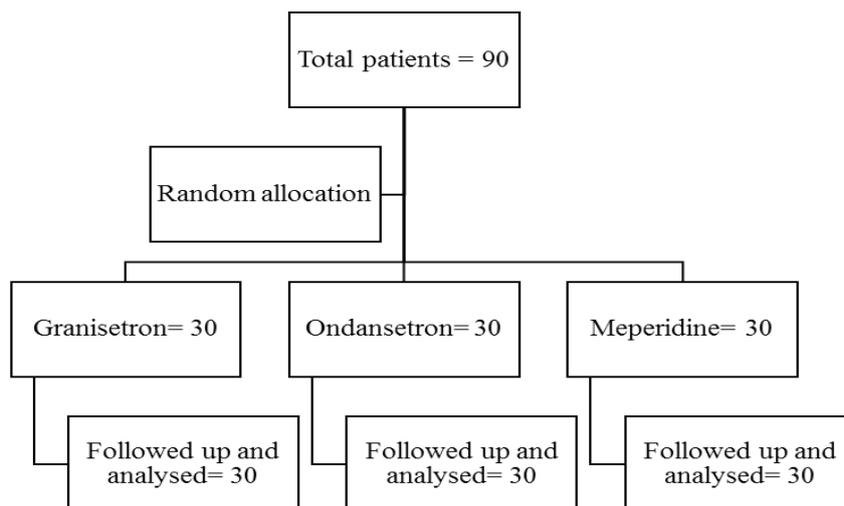


Figure 1: Randomly allocation and followed up flowchart.

minutes before the initiation of anesthesia. All of the three utilized injections were prepared in identical 2-cc syringes where the investigator responsible for controlling and recording the clinical signs was not informed about the type of drug injected to the patients.

Induction of anesthesia was initiated by injecting fentanyl 1 $\mu\text{g}/\text{kg}$, propofol 2 mg/kg , and atracurium 0.5 mg/kg in the same way for all of the three groups. After tracheal intubation, the anesthesia was sustained through infusion of propofol 100 $\mu\text{g}/\text{kg}/\text{m}$ along with an inhalation gas mixture containing 50% oxygen and 50% N_2O . To preserve muscular relaxation during the operation and facilitate intubation, atracurium was given and the patients were ventilated mechanically throughout the operation.

For all of the patients when entering the operation room, tympanic thermometer was used for measurement of the central temperature, and the skin temperature was measured using the forehead skin. Further, hemodynamic indexes, including systolic and diastolic blood pressure, and heart rate were also recorded in all patients, and the mentioned points were measured again immediately after induction of anesthesia, during the operation, and after entrance of the patients to the recovery room, and by the time patient left the recovery state.

The operation room temperature was also recorded by thermometer which was kept at 20-22°C during the entire time of surgery.

After entrance of patients to the recovery room and during the duration of residence in recovery, observation of postoperative shivering in the form of shivers of the face, trunk, or limbs which continued for at least 15 seconds were recorded by an anesthesiology resident who was not aware of the type of injected drug. The shiver score was 0-4, and it will be graded according to the following table.

Data Analysis

Statistical analysis was conducted by SPSS 20. One-way ANOVA and Post hoc tests was used to comparing

means of parametric data between three groups. Kruskal Wallis and chi-square tests to comparing means of nonparametric data between three groups were used. A *P*-value of <0.05 was considered significant.

Ethical Statement

Ethical permission was acquired from Ethics Committee of Ardabil University of Medical Sciences and its registration in IRCT with the number of IRCT201204284093N4.

RESULTS

The demographic characteristics including the age, gender, height, weight, and basic data of patients including duration of the operation and duration of anesthesia did not differ significantly across the three groups Table 1.

In meperidine, ondansetron, and granisetron groups, 4 (13.3%), 3 (10%), and 10 (33.3%) of patients respectively experienced shivering in the recovery room, where this difference was statistically significant (p -value=0.04). Inpaired comparisons of groups, there was no significant difference between meperidine and ondansetron (p -value=0.05) as well as between meperidine and granisetron (p -value=0.063) in terms of shivering. On the other hand, ondansetron and granisetron indicated a significant difference in this regard (p -value=0.02, $RR=4.5$, $CI=1.09-18.5$).

The number of patients with shivering grades of 4, 3, and 2 was higher in the ondansetron, granisetron, and meperidine groups, respectively Table 2. However, no difference in the incidence of shivering was observed between the groups ($p = 0.063$).

In terms of hemodynamic variations when comparing the three groups, the changes in the mean arterial pressure during the investigation stages were not significant only in the ondansetron group. In this regard, it has been more effective than the two other drugs in developing hemodynamic stability Table 3.

In terms of changes in the heart rate, significant variations were observed in the three groups in different stages

Table 1: Demographic profile of groups.

Variable	Meperidine	Ondansetron	Granisetron	p-value
Age ($\mu \pm \delta$)	43.9 \pm 13	42.6 \pm 17.6	39.3 \pm 17.7	0.71
Sex (M/F)	6/24	9/21	10/20	0.48
Weight ($\mu \pm \delta$)	72.6 \pm 12.7	72.6 \pm 14.7	66.1 \pm 12.8	0.10
Height ($\mu \pm \delta$)	161.5 \pm 9.2	162.6 \pm 10.1	164.5 \pm 10.1	0.51
Duration of Surgery (min)	71.8 \pm 25.5	70.5 \pm 32.5	74.1 \pm 27.7	0.88
Duration of Anesthesia (min)	94.9 \pm 26.9	98.5 \pm 35.3	98.8 \pm 32.5	0.87

Table 2: Incidence and score of shivering in groups.

Variable	Meperidine	Ondansetron	Granisetron	P-value
Shivering in recovery (%)	4 (13.3)	3 (10)	10 (33.3)	0.04
Shivering score (1/2/3/4)	0/3/0/1	0/0/1/2	0/5/4/1	0.063

Table 3: Comparison of hemodynamic and temperature variations in groups at time sections ($\mu \pm \delta$).

Variables	Basal	After Anesthesia	End Operation	Beginning of Recovery	End of Recovery	P-value
Granisetron						
Mean Arterial pressure	97.9 \pm 12.1	88.9 \pm 18.9	†84.7 \pm 15.4	92.2 \pm 12.7	91.9 \pm 10.8	<0.0001
Diastolic Blood Pressure	81.7 \pm 11.7	74.2 \pm 18.6	†69.5 \pm 14.5	76.6 \pm 10.7	76.5 \pm 10.2	0.002
Systolic Blood Pressure	130.5 \pm 15.8	118.5 \pm 21.4	115.2 \pm 20.1	123.3 \pm 19.7	122.8 \pm 14.9	0.54
Heart Rate Central	88.9 \pm 15	82.9 \pm 12.2	77.8 \pm 13.6	83.3 \pm 15.1	77.2 \pm 18.1	0.002
temperature Peripheral	37 \pm 0.58	36.6 \pm 0.48	††35.7 \pm 0.66	††35.8 \pm 0.57	36.4 \pm 0.59	<0.0001
temperature	36.2 \pm 0.87	*†35.9 \pm 0.59	*†34.8 \pm 1.14	*†35.1 \pm 0.73	*†35.4 \pm 0.83	<0.0001
Ondansetron						
Mean Arterial pressure	91.5 \pm 10.2	98.5 \pm 18.9	95.2 \pm 11.9	91.5 \pm 11.8	92.6 \pm 11.9	0.075
Diastolic Blood Pressure	75.7 \pm 8.2	84 \pm 16.8	80.5 \pm 11.3	77 \pm 9.7	78.4 \pm 10.4	0.017
Systolic Blood Pressure	123.2 \pm 17.3	127.6 \pm 24.5	124.6 \pm 16.3	120.3 \pm 18	120.8 \pm 16.3	0.3
Heart Rate Central	81.4 \pm 13.6	85.8 \pm 18.2	78.5 \pm 10.3	78.5 \pm 14.5	74.1 \pm 13.1	0.009
temperature Peripheral	37.1 \pm 0.59	36.9 \pm 0.67	36.3 \pm 0.67	36.5 \pm 0.51	36.5 \pm 0.57	<0.0001
temperature	36.9 \pm 0.46	36.6 \pm 0.41	35.7 \pm 0.82	35.7 \pm 0.67	36.1 \pm 0.58	<0.0001
Meperidine						
Mean Arterial pressure	100.6 \pm 14.9	94.5 \pm 16.6	98.5 \pm 13.9	90.3 \pm 12.4	90.7 \pm 7.3	<0.0001
Diastolic Blood Pressure	84.3 \pm 14.6	79.8 \pm 15.6	74.6 \pm 12.6	75.7 \pm 11.1	76 \pm 6.8	0.003
Systolic Blood Pressure	133.1 \pm 17.4	123.8 \pm 20.1	116.3 \pm 17.6	119.5 \pm 16.5	120.1 \pm 10.2	<0.0001

Heart Rate	87.3±14.2	85.2±12.7	79.9±12.6	81±12	71.3±8.3	<0.0001
Central temperature	37.3±0.58	36.8±0.53	36.2±0.63	36.3±0.6	36.6±0.59	<0.0001

†Significant compared with the meperidine group. using repeated measure ANOVA and the Bonferroni test;

‡Significant compared with the ondansetron group

*Significant comparison between ondansetron and meperidine groups

of investigation, where the three drug groups were not significantly different in this regard Table 3.

The verbal response time was statistically significant between the three groups (p -value=0.045), where the longest time was related to granisetron with the mean of 12.01 ± 1.26 , while the shortest time was found for ondansetron with the mean of 11.11 ± 1.02 min.

In investigating the complications across the three groups, 1 (3.3%) of patients from both meperidine and ondansetron groups experienced nausea, while no such case was reported in the granisetron group ($p=0.6$). Note that vomiting was not observed in any of the groups.

At the beginning of recovery, reduction of peripheral temperature was significantly lower in the patients who had received ondansetron than two other groups ($p<0.05$). Further, reduction of the central temperature in the granisetron group was significantly greater than those in two other groups ($p<0.05$).

At the end of recovery, changes in the peripheral temperature across the three groups were in line with those at the beginning of recovery, but no significant difference was observed changes of the central temperature between groups Table 3.

DISCUSSION

Preventing and treating postoperative shivering is an important part of patient care following surgical operations¹⁰. The reason is that more serious complications may develop in the patient in response to sympathetic excitation, increased oxygen uptake, or increased carbon dioxide production⁵.

In this study which, meperidine, ondansetron, and granisetron drugs were studied, and their preventing and controlling effects on shivering were investigated in patients who have been surgically treated under general anesthesia. The extent of incidence of shivering in granisetron group was higher than meperidine and ondansetron. Thus, it can be inferred that ondansetron and meperidine have the same effectiveness when used before termination of surgery to decrease incidence of postoperative shivering. However, use of granisetron in reducing the extent of incidence of postoperative shivering has not been as effective as these two drugs. There was also a significantly difference between ondansetron and granisetron ($p = 0.02$).

Considering the effect of ondansetron on preventing incidence of postoperative shivering and comparing it

with meperidine, various studies have been conducted, in most of which effectiveness of ondansetron has been emphasized. For example, in a study conducted by Entezari et al¹⁰, for patients in the first, second, and third groups, meperidine 0.4 mg/kg, ondansetron 4 mg, and normal saline 2 cc were injected to patients respectively. Postoperative shivering was observed in 13.3% and 20% of the ondansetron and meperidine groups respectively, which showed reduction compared to the control group in which 50% of patients experienced shivering. However, the result of the Mahoori et. al study showed that 8 mg of intravenous ondansetron and meperidine have similar effects on shivering¹⁴.

Further, based on the meta-analysis by Tie et al on the papers related to the effect of ondansetron postoperative shivering in 2014 when compared with placebo, ondansetron decreased the extent of postoperative shivering from 49.3% to 23.4%, but it has had no special superiority over meperidine in mitigating shivering¹⁵.

The effect of granisetron on reducing postoperative shivering has been examined in several studies. For example, in a study by Mohammadi et al on 100 patients undergoing C-section surgery with spinal anesthesia, the extent of shivering in the granisetron group was 8% versus 54% in the placebo group⁵.

The study by Asif Iqbal in India suggested that the extent of postoperative shivering 15 min after the operation was lower in the granisetron and meperidine groups, compared to placebo (17 and 7% versus 60%)¹³.

In the study by Sajedi et al, the extent of incidence of shivering in the granisetron group with a dose of 40 μ g/kg was 9 out of 33 and in meperidine group was 6 out of 33¹⁶.

Considering comparison of ondansetron and granisetron in preventing postoperative shivering, no similar study was found. Nevertheless, Reshad et al compared these two drugs on hemodynamic changes following spinal anesthesia. They concluded that ondansetron is more effective than granisetron in reducing hypotension¹⁷, which is to a large extent in line with the results of the present study, in which hemodynamic changes have been lower in receiving ondansetron than granisetron.

The observed difference can be due to difference at the site of effect of ondansetron on mix receptors and more specific effect of granisetron on 5-hydroxy tryptamine receptors and its less affinity on other 5-hydroxy tryptamine, adrenergic, histaminergic, dopaminergic receptors and those of opiates¹⁸.

Considering comparison of these drugs in preventing postoperative nausea and vomiting, Gupta et al¹⁹ studied patients undergoing laparoscopy surgery. They concluded that the extent of nausea after operation was 30% in the ondansetron group, which was 10% in the granisetron group ($p < 0.05$). Kabade et al also concluded that prophylactic granisetron reduces the need of antiemetic's²⁰. This finding also largely corroborate with the results of our study.

The limitation of the present study was not assessing the effect of different doses of ondansetron and granisetron on reducing the extent of postoperative shivering. Also, use of placebo group can also be another limitation of the present study, which underrepresents the results of the present research.

CONCLUSION

Based on the findings, use of intravenous ondansetron 4 mg when compared with granisetron 40 mcg/kg has had a significant effect on preventing postoperative shivering, and has been as effective as meperidine. Further, hemodynamic changes by this drug have been lower than those of granisetron and meperidine, while granisetron has been more effective than these two drugs in terms of preventing nausea and vomiting.

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CONFLICT OF INTERESTS

One of the authors is Anesthesiology, but there are no conflicts of interest for declaration.

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