



A STUDY OF EFFICACY OF ONDANSETRON AND GRANISETRON IN PREVENTING POST-OPERATIVE SHIVERING IN PATIENTS RECEIVING GENERAL ANAESTHESIA

Dnyaneshwar R. Fating

Associate Professor, Department of Anesthesiology, Indira Gandhi Government Medical College, Nagpur-440018

Vaishnavi Kulkarni

Assistant Professor, Department of Anesthesiology, Trauma Care Centre, Government Medical College, Nagpur-440003

Teilang Khar Syiemlieh

Department of Anesthesiology, Indira Gandhi Government Medical College, Nagpur-440018

ABSTRACT

Introduction: Post-operative shivering is a very unpleasant finding after general anesthesia. It is distressing to patients especially with ischemic heart diseases as shivering increases oxygen consumption. 5-HT₃ receptor blockers are routinely given as a premedication to patients receiving general anesthesia as an anti-emetic. The 5-HT₃ receptors blockers have antishivering property as well and their efficacy as an antishivering agent is studied here. **Methods:** 80 patients were included in the study with 40 patients in each group. Group G received intravenous granisetron and Group O received intravenous ondansetron along with other drugs as premedication. The study was conducted in patients undergoing laparoscopic appendicectomy and laparoscopic cholecystectomy. **Results:** Keeping all the parameters like demography and duration of surgery comparable in both the groups, The total patients who had shivering post-operatively in Group G were 3 (7.5%) and in Group O were 10(25%) with a significant p value. **Conclusion:** Granisetron is better than Ondansetron in preventing post-operative shivering in the anti-emetic doses administered preoperatively, without affecting the hemodynamic state of the patients.

KEYWORDS : Ondansetron, Granisetron, Post-operative shivering.

INTRODUCTION

Postoperative shivering is a prevalent and unpleasant finding after general anaesthesia. Incidence of this varies from 5% to 65% after general anaesthesia.¹ It is associated with multiple complications.

The body core temperature is one of the most important and stable parameters in preserving the human body's physiology. Any disorder in this parameter including hypothermia during surgical operation results in problems such as post-operative shivering, coagulation disorders, impaired nitrogen balance of the body, and changes of pharmacological effects on the human body.

There are various mechanisms for shivering. It may be due to core hypothermia or may result from the release of cytokines by the surgical procedure, or could be due to intraoperative heat loss. Moreover, it is a well-known fact that all general anaesthetic agents can impair thermoregulatory mechanism.^{1,2}

Postoperative shivering is distressing to the patients. Shivering increases oxygen consumption, which may be harmful in patients with ischemic heart disease. Shivering is also associated with an increase in cardiac output, carbon dioxide production and catecholamine release.⁴ It also increases intracranial pressure and intraocular pressure. Shivering interferes with SPO₂, ECG, NIBP monitoring and artificial pacemaker function.⁵ Recent studies have found that 5HT₃ receptor antagonists effectively prevent postoperative shivering.⁶

Although its mechanism of action is not entirely understood, it is found to act at the hypothalamic level by inhibiting serotonin reuptake.⁷

Hence the present study was conducted to compare the efficacy of 5-HT₃ receptor blockers in the prevention of postoperative shivering after general anaesthesia.

MATERIAL AND METHODS

This is a prospective observational study. Patients admitted to our tertiary Institute, who underwent elective Laparoscopic Appendicectomy/Cholecystectomy procedures under general anaesthesia were included. During the study period 80 patients were included in the study with 40 patients in each group. Study was conducted over a period of 2 years from 2019 January to 2020 September. Patients satisfying the following criteria were included ASA grade I and grade II, Age 18 to 60 years, Cases under Surgery - laparoscopic appendicectomy and laparoscopic cholecystectomy under general anaesthesia. Exclusion criteria consists of patients not willing to participate in the study, Patients with a duration of surgery of more than 2 hours, History of hypersensitivity to 5-HT₃ Antagonists, Patients

with Cardiovascular diseases, Obstetric patients, Obese Patients, Blood/blood products transfused during the procedure.

Methodology

At the preanesthetic visit, pre-anesthesia check-up was done. Patients were explained about the study and informed written consent was obtained. They were screened for inclusion and exclusion criteria. In the patients consenting the study, detailed history regarding comorbidities or any allergic history to the drugs, other coexistent diseases like cardiac diseases, and other medications, if any, was obtained. Even patients of the study received ondansetron and odd patients received granisetron.

Patients were premedicated with -Inj. Pantoprazole 0.8mg/kg in drip, Inj. glycopyrrolate 0.004mg/kg IV, Inj. Midazolam 0.02mg/kg IV, Inj. Fentanyl 2 microgram/kg IV, Patients either received inj. Ondansetron 0.08mg/kg (GROUP O) or inj. Granisetron 0.04mg/kg (GROUP G). The patients were pre-oxygenated with 100% O₂ for 3 minutes and were induced with inj. propofol 2mg/kg and inj. suxamethonium 2mg/kg intravenously. Patients were maintained on oxygen, nitrous oxide, inhalational agent sevoflurane and muscle relaxant vecuronium.

Intra-operatively temperature variation, heart rate, systolic blood pressure, diastolic blood pressure spo₂ and were monitored. Temperature of operation theatre was maintained between 20-22 degree. After surgery patients were reversed with inj. Neostigmine and inj. Glycopyrrolate. Patients were extubated after thorough oropharyngeal suction return of reflexes.

First reading was taken as baseline and after that readings were noted at interval of 10 minutes up to one hour after extubation in recovery room. Patients with grade 3 and 4 shivering were given Inj Tramadol 25mg IV as rescue drug.

GRADES OF SHIVERING (Crossley and Mahajan)¹⁸

GRADE 0: No Shivering, GRADE 1: Piloerection or peripheral vasoconstriction, but no visible shivering, GRADE 2: Muscular activity in only 1 muscle group, GRADE 3: Muscular activity in more than 1 muscle group, but not generalised shivering, GRADE 4: Shivering involving the whole body.

OBSERVATION AND RESULTS

Table 1 : Demographic Variables.

Demographic variables	Group G	Group O	p value
Mean Age	38.05	41.75	0.09

Mean Weight	62.75	60.65	0.3324
Mean Height	159	158	0.85
BMI	24.65	24.09	0.38

We included 40 patients in both the groups, making a total of 80 patients. The groups were comparable in terms of demographic data as the p value was insignificant.

Table 2: Distribution Of The Patients Based On Gender(n=80)

Gender	Group G		Group O		P value
	No	%	No	%	
Female	26	65.00	24	60.00	0.6441
Male	14	35.00	16	40.00	
Total	40	100.00	40	100.00	

Male and female patients were comparable in both the groups as the p value was not significant.

Table 3 : Timing Of Surgeries

	Group G		Group O		p value
	Mean	SD	Mean	SD	
Timing of surgery in minutes	114.13	47.65	110.34	36.95	0.4432

The timing of surgery as shown in the table were similar. P value was 0.4 which was insignificant.

Table 4 : Table Showing Temperature Variation In Two Groups At Various Intervals

Temperature	Group G		Group O		p value
	Mean	SD	Mean	SD	
Pre operative	97.78	0.32	97.65	0.30	0.0812
Post operative					
0 min	95.57	0.48	95.69	0.52	0.2868
10 mins	96.34	0.86	96.70	0.92	0.0745
20 mins	97.38	0.63	97.55	0.49	0.1818
30 mins	97.97	0.69	98.12	0.43	0.2468
40 mins	98.22	0.75	98.46	0.38	0.0749
50 mins	98.30	0.63	98.48	0.33	0.1135
60 mins	98.38	0.58	98.46	0.36	0.4608

The p value of the two groups pre-operative temperature was 0.0812 which means the two groups were comparable. Post-operatively, the p value of the temperature of the two groups at 0 minute (immediately after extubation), 10 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes, 60 minutes was not significant.

Table 5: Distribution Of The Patients Based On The Shivering Postoperatively

Post Operative Shivering	Group G		Group O		p value
	No	%	No	%	
Present	3	7.5	10	25	0.0332
Absent	37	92.5	30	75	
Total	40	100	40	100	
If present, grades were as follows					
Grade 1	1		1		
Grade 2	1		5		
Grade 3	1		3		
Grade 4	0		1		

The total patients who had shivering post-operatively in Group G were 3 (7.5%) and in Group O were 10(25%). The p value was 0.03 which was significant. The 3 patients in Group G had Grade 1, Grade 2, Grade 3 shivering. In Group O, 1 patient had Grade 1 shivering, 5 patients had Grade 2 shivering, 3 patients had Grade 3 shivering, 1 patient had Grade 4 shivering.

DISCUSSION

Managing Postoperative shivering is an important aspect of patient care since it may cause serious complications such as sympatho-adrenal stimulation, increased oxygen consumption, and carbon dioxide production.

Serotonin inhibition may have a direct effect on shivering; however, neurotransmitter systems are also effective in control of shivering. An inhibitory effect on the 5-HT₃ receptor might result from a generalized thermoregulatory inhibition at the level of the hypothalamus, where the main thermoregulatory control occurs. Due to redistribution of heat from center to the peripheral parts and body surface, the core

temperature reduces by after induction of anesthesia. In this study, surface temperature was measured in recovery and no significant difference was found between the groups.

This was a prospective observational study. The study was carried out in tertiary care institution to compare incidences of post-operative shivering in patients receiving ondansetron and granisetron in premedication.

Surface temperature (axillary) of patients was measured in recovery room. Temperature of OT and temperature of post-operative room was kept same. Patients were given warm fluids during the surgery.

As shivering is a response to hypothermia, body temperature should be normally maintained within limits of 36.5–37.5°C.⁶ For these reasons, in our study, all patients were covered with cotton surgical drapes, the temperature of the operating room was actively maintained between 20-22 degree celcius and infusions of warm crystalloid solutions were done intra-operatively.

As per observations and statistical analysis the differences between two groups concerning the age, sex, weight, BMI are non-significant as indicated by the p value.

The mean duration of surgery in the two groups were comparable. The two groups received comparable amount of fluids during the surgery as indicated by the p value. The systolic blood pressure, diastolic blood pressure and pulse rate were comparable in both the groups pre-operatively and post-operatively. It was seen in both the groups that immediately after extubation the pulse rate, systolic and diastolic blood pressure increased. The increase was comparable in both the groups, this finding could be due to extubation response.

This study included only laparoscopic surgeries particularly Laparoscopic Appendicectomy and Laparoscopic Cholecystectomy. Various other general surgeries were not included in the study because of the variation in the incision size and heat loss from the exposed viscera. By selecting these two surgeries the intraoperative fluid loss due to evaporation from the incision site, one of the factor for intra-operative heat transfer was avoided.

In this study 25% of the patients had shivering in Ondansetron Group and only 7.5% of the patients had shivering in granisetron Group. The analysis of this data is significant as indicated by the p value.

When we look at the effect of ondansetron in preventing shivering post-operatively, only 25% of the patients had post-operative shivering, at the dose of 0.08mg/kg (~4 mg iv). This was similar to the meta-analysis done by Hong-Tie et al.¹¹ However, at same doses, the incidence was higher in the studies conducted by Powell et al and Alireza et al, 33% and 41% respectively.^{8,17} This variation can be probably because of variation in population group. But, in the same studies, when the dose was increased to 8 mg, post-operative shivering incidence was reduced to 15% and 19%, respectively.^{8,17} This suggests that the effect of ondansetron is dose dependent and the anti-emetic doses used in a premedication may not be effective in preventing post-surgery shivering.

There are certain studies where Ondansetron has been compared with placebo like a study conducted by ShrinivasaRao et al where Ondansetron 8mg was given and compared with Normal saline and shivering was seen in 10% in Ondansetron group and 42.5% in Normal Saline group again a significant finding with higher doses of Ondansetron.

In one study where Ondansetron 8mg was compared with Normal Saline conducted by Roger browning et al, the incidence of shivering did not differ significantly between the two groups. It was seen that 41% of the patients in Ondansetron group had shivering and 47% in Normal Saline group had shivering with p value 0.54 suggesting ondansetron had no better results.

When we look at the efficacy of granisetron in preventing post-anesthesia shivering, our study had only 7.5% patients who developed shivering after receiving granisetron. This was similar to that of studies conducted by Kabade et al (10%) and Mohammedi et al (8%) but was less than that of studies compared to that of Iqbal et al (17%) and Sajedi et al (27%). The reason it was less in these two studies could be due to comparison of granisetron with more potent antishivering drugs.

In our study 7.5% of the patients had shivering in granisetron group which was much less than that seen by Asif Iqbal et al⁷ where shivering in granisetron group (17%) was comparable to pethidine group (7%) which is a known antishivering drug. They concluded that antishivering effect of granisetron and pethidine were comparable.

Another study where granisetron was compared with tramadol, meperidine and pethidine conducted by Sajedi et al.⁶ They observed shivering in 27% of the patients who received granisetron which is much higher compared to our study. But the results found with granisetron (27%) in their study was comparable to known antishivering agents like tramadol (21%) and meperidine (18%). Also in this study the results have shown that granisetron is a better antishivering agent than known antishivering agent pethidine.

Savitri Kabade et al¹² compared granisetron with pethidine in patients receiving spinal anesthesia and 10% of the patients in both the groups had shivering. Our study has shown only 7.5% patients having shivering which is lesser than their study.

In a study by Mohammadi et al¹⁰ on 100 patients undergoing C-section surgery with spinal anesthesia, the extent of incidence of postoperative shivering in the granisetron group was 8% versus 54% in the placebo group. This was comparable to the finding in our study where 7.5% patients in Granisetron group had shivering.

All these studies indicate that granisetron being compared with known antishivering opioids has shown comparable results. There has been just one study conducted by M Entezari et al which compares the efficacy of ondansetron and granisetron in preventing post-operative shivering.¹⁹ In their study, ondansetron was found to be more efficacious than that of granisetron. The granisetron group had shivering in 33%, whereas in the ondansetron group, the incidence of shivering was only 10%. In contrast, in our study group that is 7.5%, the ondansetron group had shivering in 10% than that in our study showing 25%. The reasons for the same could be the difference in patient population, difference in the anaesthetic agents used or type of surgery. We have used sevoflurane and injvecuronium in the maintenance of intra-operative anesthesia where as M Entezari et al has used injpropofol infusion and injatracurium for intra-operative anesthesia. Also, the sample size in both the groups were less, hence to confirm the efficacy, a more robust study would be necessary.

The two groups in our study did not show any significant difference in the postoperative temperature and hemodynamic changes. There was a fall in temperature in both the groups immediately after extubation may be because of lower OT temperature than the room temperature and generalized thermoregulatory inhibition at the level of the hypothalamus under general anesthesia. But the fall in both the groups were comparable.

The observed difference in anti-shivering effect between these two drugs can be due to the action of ondansetron on various receptors like 5-HT₃, 5-HT₄ and more specific effect of granisetron on 5-HT₃ receptors and its less affinity on other 5-HT receptors, adrenergic, histaminergic, dopaminergic receptors and those of opiates.

The usefulness of opioids in the treatment and prevention of shivering is limited because of the risk of respiratory depression, sedation, nausea and vomiting, especially when repeated doses are necessary. This was also demonstrated in some studies where Meperidine and tramadol caused some side-effects such as respiratory depression, hypotension, nausea and vomiting.^{7,9,12,16,19} These side effects were not seen in our study.

The two drugs did not affect the hemodynamics of the patients as indicated by the analysis. Also, the values are within the normal limits. This is comparable to various other studies like Powell et al, Asif et al where the 5-HT₃ receptor blockers have shown no effect on the patient's hemodynamics.

Limitations of Study

- Did not have a control group (placebo or other anti-emetic) to standardise the efficacy
- Small sample size
- Status of shivering after one hour was not recorded

CONCLUSION

From the above study we conclude that granisetron is better than

ondansetron in preventing post-operative shivering in the anti-emetic doses administered preoperatively, without affecting the hemodynamic state of the patients.

REFERENCES

- (1) Sessler, D. I.; Warner, D. S.; Warner, M. A. Temperature Monitoring and Perioperative Thermoregulation. *Anesthesiology* 2008, 109, 318–338. <https://doi.org/10.1097/ALN.0b013e31817f6d76>.
- (2) Horosz, B.; Malec-Milewska, M. Inadvertent Intraoperative Hypothermia. *Anaesthesiol Intensive Ther* 2013, 45 (1), 38–43. <https://doi.org/10.5603/AIT.2013.0009>.
- (3) Bindu, B.; Bindra, A.; Rath, G. Temperature Management under General Anesthesia: Compulsion or Option. *J Anaesthesiol Clin Pharmacol* 2017, 33 (3), 306. https://doi.org/10.4103/joacp.JOACP_334_16.
- (4) Diaz, M.; Becker, D. E. Thermoregulation: Physiological and Clinical Considerations during Sedation and General Anesthesia. *Anesthesia Progress* 2010, 57 (1), 25–33. <https://doi.org/10.2344/0003-3006-57.1.25>.
- (5) Nallam, S. R.; Cherukuru, K.; Sateesh, G. Efficacy of Intravenous Ondansetron for Prevention of Postspinal Shivering during Lower Segment Cesarean Section: A Double-Blinded Randomized Trial. *Anesth Essays Res* 2017, 11 (2), 508–513. https://doi.org/10.4103/aer.AER_26_17.
- (6) Sajedi, P.; Yaraghi, A.; Moseli, H. A. Efficacy of Granisetron in Preventing Postanesthetic Shivering. *Acta Anaesthesiologica Taiwanica* 2008, 46 (4), 166–170. [https://doi.org/10.1016/S1875-4597\(09\)60004-7](https://doi.org/10.1016/S1875-4597(09)60004-7).
- (7) Iqbal, A.; Ahmed, A.; Rudra, A.; Wankhede, R. G.; Sengupta, S. T.; Das, T.; Roy, D. Prophylactic Granisetron Vs Pethidine for the Prevention of Postoperative Shivering: A Randomized Control Trial. *Indian Journal of Anaesthesia* 2009, 53 (3), 330.
- (8) Mahoori, A.; Noroozina, H.; Hasani, E.; Soltanahmadi, M. Comparison of Ondansetron and Meperidine for Treatment of Postoperative Shivering: A Randomized Controlled Clinical Trial. *Iran Red Crescent Med J* 2014, 16 (8). <https://doi.org/10.5812/ircmj.13079>.
- (9) Asl, M. E.; Isazadefar, K.; Mohammadian, A.; Khoshbaten, M. Ondansetron and Meperidine Prevent Postoperative Shivering after General Anesthesia. *Middle East J Anaesthesiol* 2011, 21 (1), 67–70.
- (10) Movassaghi Gargari, R.; Mohammadi Poor Anvari, H. Effect of Different Doses of Granisetron on Preventing Postoperative Shivering in Patients Undergoing Septorhinoplasty under General Anesthesia. *ABC Med* 2017, 5 (2), 21. <https://doi.org/10.7575/aiac.abcmed.17.05.02.04>.
- (11) Tie, H.-T.; Su, G.-Z.; He, K.; Liang, S.-R.; Yuan, H.-W.; Mou, J.-H. Efficacy and Safety of Ondansetron in Preventing Postanesthesia Shivering: A Meta-Analysis of Randomized Controlled Trials. *BMC Anesthesiology* 2014, 14 (1), 12. <https://doi.org/10.1186/1471-2253-14-12>.
- (12) Kabade, S.; Venkatesh, Y.; Karthik, S.; Kumar, V. Comparative Study of Granisetron versus Pethidine for the Prevention of Perioperative Shivering under Spinal Anesthesia. *Karnataka Anaesth J* 2016, 2 (1), 14. <https://doi.org/10.4103/2394-6954.190769>.
- (13) Ma, J.; Si, B.; Liang, X.; Cui, D.; Pan, D.; Wang, Z. Prophylactic Granisetron for Prevention of Postoperative Shivering: A Meta-Analysis of Randomized Controlled Trials. 10.
- (14) He, K.; Zhao, H.; Zhou, H. Efficiency and Safety of Ondansetron in Preventing Postanaesthesia Shivering. *annals* 2016, 98 (6), 358–366. <https://doi.org/10.1308/rcsann.2016.0152>.
- (15) Teymourian, H.; Mohajerani, S. A.; Bagheri, P.; Seddighi, A.; Seddighi, A. S.; Razavian, I. Effect of Ondansetron on Postoperative Shivering After Craniotomy. *World Neurosurg* 2015, 84 (6), 1923–1928. <https://doi.org/10.1016/j.wneu.2015.08.034>.
- (16) Gupta, R.; Kulshreshtha, S.; Mehta, R. K. Comparison of Ondansetron and Pethidine for Prevention of Shivering after Spinal Anesthesia. 11 (2), 5.
- (17) Powell, R. M.; Buggy, D. J. Ondansetron Given Before Induction of Anesthesia Reduces Shivering After General Anesthesia. *Anesthesia & Analgesia* 2000, 90 (6), 1423–1427. <https://doi.org/10.1097/0000539-200006000-00032>.
- (18) Crossley, A. W. A.; Mahajan, R. P. The Intensity of Postoperative Shivering Is Unrelated to Axillary Temperature. *Anaesthesia* 1994, 49 (3), 205–207. <https://doi.org/10.1111/j.1365-2044.1994.tb03422.x>.
- (19) Entezari et al., M.; Zandian, H.; Isazadefar, K. The Effect of Granisetron, Ondansetron, and Pethidine in Preventing Postoperative Shivering: Controlled Clinical Trial; preprint; In Review, 2019. <https://doi.org/10.21203/rs.2.19384/v1>.