

Effects of Granisetron on Postoperative Nausea and Vomiting in Non-smoking Women Undergoing Thyroidectomy: A Prospective Randomized Double Blind Placebo Controlled Study

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Background: Postoperative nausea and vomiting is a relatively common complication after thyroidectomy. The aim of this study was to determine the effectiveness of granisetron for prevention of postoperative nausea and vomiting in non-smoking women undergoing elective thyroidectomy.

Material and Methods: In this prospective, randomized, double-blind, placebo-controlled study, 260 non-smoking female patients ASA physical status I-II, who had undergone elective thyroidectomy under general anesthesia, received granisetron (Kytril®, Roche, Basel, Switzerland) 40 µg kg⁻¹ in 3ml saline or placebo as 3ml saline IV 30 min before operation end. Patients were observed at 0, 2, 4, 6, 12 and 24. hours after anesthesia. Age, weight, operation and anesthesia duration, total amount of fentanyl (Fentanyl®, Janssen Cilag, Hong Kong, China) dose, nausea and vomiting episodes and adverse effects were recorded.

Results: 234 patients were analyzed statistically. Demographic characteristics, including age, height and body weight were comparable in both groups. In addition, there were no differences in the peroperative total amounts of fentanyl and fluid, operation and anesthesia duration. The overall incidence of PONV differed significantly among the two groups ($p < 0.001$). PONV occurred in 117 patients (98%) receiving placebo, 45 patients (39%) receiving granisetron.

Conclusion: The study suggested that granisetron might be a good choice among alternative drugs for its few adverse effects and good tolerability.

Keywords: Granisetron, thyroidectomy, postoperative nausea, non-smoking women

Introduction

During the recovery period, postoperative vomiting and nausea (PONV) affect patient's quality of wake up in a bad way. This causes a prolonged hospital stay, patient dissatisfaction, unexpected hospital admission, delayed to work and therefore increase costs for the operation.

The most important factors determining the risk of PONV are being female gender, non-smoking status, history of PONV, opioid dependence (1). There are also some additional risk factors like history of motion sickness, weight, use of inhaled anesthetic agents, use of nitrous oxide and the site of surgery (2). With each major risk factor, the estimated PONV

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Received: Aug 16, 2018 **Accepted:** Nov 15, 2018

Published: Dec 29, 2018

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incidence increases by about 20%. For patients with moderate or high PONV risk; application of an antiemetic agent for prophylaxis may be beneficial (2,3). If a prophylactic antiemetic agent is not given, especially after thyroidectomy operations, PONV is seen as 65% (4,5).

Granisetron is a selective antagonist of the 5-HT₃ receptor and is effective for the treatment of patients receiving cytotoxic drugs (6). It affects the vomiting center of the Medulla Oblongata via reducing the activity of the vagus nerve. It blocks the 5-HT₃ receptors at both the central and the peripheral sites (7). Granisetron stays in the body for a long time (half-life 8-9 hours). It is excreted through the liver and kidneys. Although there are a few side effects, granisetron is generally well tolerated (8). A previously studied randomized controlled trial in a homogenous group with female patients undergoing thyroidectomy proved granisetron to be excellently effective on PONV (9).

We wanted to determine the efficacy of granisetron for the prevention of PONV in non-smoking women after elective thyroidectomy with a prospective, randomized, double-blind, placebo-controlled study.

Materials and Methods

After we gained the approval of the hospital's ethic committee and the patient's informed consent, 240 non-smoker female patients between 18-70 years of age underwent elective thyroidectomy with general anesthesia. All patients with previously known motion sickness, menstruation, previous PONV, cardiovascular, neurologic, renal or gastrointestinal disease were not included in the study. Especially those who have a history of allergy to granisetron or other 5HT₃RA drugs and those who have received chemo or radiotherapy now or in

the last month; excluded from the study. In addition, nausea and vomiting within 24 hours prior to anesthesia, breastfeeding, history of any ophthalmic surgery, and those who did not sign informed consent were considered inappropriate for our study.

This study was designed as a prospective, randomized and double-blind. Patients were randomly divided into two groups. Group G (n:114), receiving granisetron (Kytril®, Roche, Basel, Switzerland) 40 µg kg⁻¹ in 3 ml solution intravenously (IV) and Group P (n:120) receiving 3 ml saline solution as placebo IV approximately 30 minutes before operation end. The nurses prepared the medications and gave them with packaged syringes, unaware of the receiving group. Normal saline was added to all syringes in a total of 3 ml. The investigator administering the injections was unaware of randomization and the presence of a control group.

The patients did not use any medication before anesthesia. Non-pressive blood pressure, pulse oximetry and electrocardiography were used for the follow-up of the patients during surgery. Anesthesia induction was initiated with thiopental 7 mg kg⁻¹ IV, and fentanyl (Fentanyl®, Janssen Cilag, HongKong, China) 1 µg kg⁻¹ IV; atracurium (Tracrium®, Glaxo-Smith Kline, San Polo di Torille, Italy) 0.5 mg kg⁻¹ IV was used to facilitate tracheal intubation. Anesthesia was continued with sevoflurane after intubation (Sevorane®, Abbott, Chicago, USA) 1.0% to 3.0% (inspired concentration) and N₂O 50% in oxygen. The Pressure Controlled Volume (PCV) Mode was used for mechanical ventilation (Draeger, Primus, Luebeck, Germany) and adjusted to maintain an end-tidal pressure of CO₂ between 35 and 40 mm Hg throughout surgery, as measured by an anesthetic respiratory gas analyzer. Atracurium was used for muscle

relaxation. Fentanyl was used when analgesia was required. Mean arterial blood pressure (MABP) was not allowed to decrease less than 60 mmHg, ephedrine (Efedrin Hidroklorür®, Osel, Istanbul, Turkey) 0.05 mg kg⁻¹ IV was administered. Bradycardia was treated with atropine (Atropin Sülfat®, Osel, Istanbul, Turkey) 0.01 mg kg⁻¹ IV. Oxygen saturation was not permitted to fall under 96%. N₂O and sevoflurane delivery was stopped with the end of operation. The residual neuromuscular blockade was antagonized with atropine 0.01 mg kg⁻¹ IV and neostigmine (Neostigmine Metil Sülfat®, ADEKA, Samsun, Turkey) 0.03 mg kg⁻¹ IV; the trachea was extubated when the patient awakened. The amount of fentanyl used in the operation, the duration of surgery and anesthesia was recorded. All patients were taken to the post-anesthesia care unit (PACU) after waking up and were followed up for 2 hours. Patients were observed for a further 24 hours in bed.

Episodes of PONV, nausea and vomiting were recorded at 0, 2, 4, 6, 12 and 24 hours after anesthesia in the PACU and in the surgery service by specifically trained nurses without knowledge of which drugs the patients had received. Nausea was defined as a bad feeling causing vomiting, and vomiting was defined as the forced excretion of stomach contents from mouth. Another rescue antiemetic, droperidol (Inapsira®, Hospira, Lake Forest, USA) was given 1-2.5 mg IV when needed within 24 hours after anesthesia. Postoperative analgesia was provided by diclofenac (Diclomec®, Abdi Ibrahim, Istanbul, Turkey) 75 mg intramuscular (IM). All side effects (a headache, increased hepatic enzymes, anxiety, dry mouth, and constipation) were recorded during the study. A headache was treated with paracetamol

(Parol®, Atabay, Istanbul, Turkey) 1g IV and ketoprofen (Profenid®, Sanofi Aventis Co., Lüleburgaz, Turkey) 50 mg when necessary.

The number (n) for the study group were established using power analysis. According to a previous study of similar patients who underwent similar anesthesia, this study including only patients with at least two risk factors will result in an average control event rate (CER) of approximately 50%, assuming relative reduction rate is 40%, the absolute risk reduction would, therefore, be 20 % and n: 103 patients would be required in each group with an expected treatment event rate of 30%. The α -error was set at 0.05 and the β -error at 0.2. We have limited patient control after discharge because our hospital is a training hospital. That's why communication with patients is difficult. This is a prospective randomized trial, and every single subject is significant, so we estimated a loss of patient's account and enlarged the study groups to 130. Statistical analyzes were performed using variance analysis (Student-t Test) for normal-range quantitative parameters and chi-square tests for qualitative variables. Demographic data were expressed as number or mean $\pm$ standard deviation (SD). The incidence of episodes of nausea, moderate or severe vomiting at any grade among the four patient groups at different time intervals was expressed as a percentage (%). Data were evaluated using the SPSS for Windows version 14.0 (Program, Chicago, IL, USA).

Results

A total of 260 patients were eligible for the study. However, 16 patients in the granisetron group, ten patients in the placebo group were excluded from the final data analysis due to

the lack of postoperative data and protocol violations. Data of 234 patients were analyzed statistically. All demographic characteristics, including age, height, and body weight were comparable in both groups (Table-1).

There was also no difference in the total amount of fentanyl and fluid delivered during preoperative period, operation and anesthesia. The overall incidence of PONV was significantly different between the two groups ($p < 0.001$).

During the postoperative 24 h, nausea was noted 414 times in the placebo group, while it was noted 60 times in the granisetron group. Vomiting occurred 135 times in the placebo group, 21 times in the the granisetron group. Rescue treatment was necessary 120 times in the placebo group, 12 times in the granisetron group. PONV occurred in 117 patients (98%)

receiving placebo, 45 patients (39%) receiving granisetron. Rescue treatment was the most needed in the 0-2 hours interval (Table-2).

Table-1. Demographic and operative characteristics

Variables	Granisetron (n=114)	Placebo (n=120)	p
Age (years)	41.9±11.9	44.1±12.4	NS
Height (cm)	160.7±4.9	160.6±5.8	NS
Body weight (kg)	68.3±13.1	66.8±11.9	NS
Peroperative total amount of fentanyl (µg)	231±76.1	252.3±64.2	NS
Peroperative total amount of fluid (ml)	1548.0±434.9	1558.6±380.8	NS
Duration of operation (min)	156.1±55	170.5±50	NS
Duration of anaesthesia (min)	172.2±56	188.1±51.8	NS

Values are mean±SD. Student t test; $p < 0.05$ is significant; NS: no significant differences: $p > 0.05$.

Table-2. PONV early and delayed symptoms

Intervals	Incidence of	Granisetron (n)	Placebo (n)	P value
0-24 h	Nausea	60	414	$p < 0.001$
	Vomiting	21	135	$p < 0.001$
	Nausea and Vomiting	18	6	NS
	Rescue treatment	12	120	$p < 0.001$
	PONV, overall incidence n (%)	45 (39)	117 (98)	
0-2 h	Nausea	12	117	$p < 0.001$
	Vomiting	9	51	NS
	Nausea and Vomiting	6	3	NS
	Rescue treatment	9	33	NS
	PONV, overall incidence (n/%)	12 (11)	69 (58)	
2-6 h	Nausea	30	153	$p < 0.001$
	Vomiting	12	63	NS
	Nausea and Vomiting	12	3	NS
	Rescue treatment	3	72	NS
	PONV, overall incidence (n/%)	30 (26)	108 (90)	
6-12 h	Nausea	15	108	NS
	Vomiting	0	21	NS
	Nausea and Vomiting	0	0	NS
	Rescue treatment	0	15	NS
	PONV, overall incidence (n/%)	12 (11)	78 (65)	
12-24 h	Nausea	3	36	NS
	Vomiting	0	0	NS
	Nausea and Vomiting	0	0	NS
	Rescue treatment	0	0	NS
	PONV, overall incidence (n/%)	3 (3)	30 (25)	

** $p < 0.05$ is significant; significant differences between the two groups, $p < 0.001$; no significant (NS) differences between the two groups, $p > 0.05$. Results are expressed as incidence of value and number n (%) of patients

The critical period for PONV was the 2-6 h interval, where the highest overall incidence of both groups (90% in placebo, 26% in granisetron) was noticed (Figure-1).

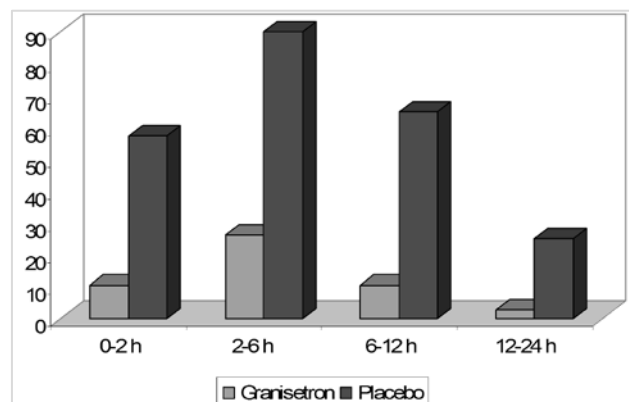


Figure-1. Evaluation of PONV incidence between the groups by time intervals

Granisetron was effective with 11%, 26%, 11% and 3% compared to placebo with 58%, 90%, 65% and 25% in time interval 0-2 h, 2-6 h, 6-12 h and 12-24 h. All time intervals resulted with $p < 0.001$ (Table-3).

Table-3. Comparison of the PONV incidences

Intervals	Granisetron n (%)	Placebo n (%)	P value
0-2 hours	12 (10.5%)	69 (57.5%)	0.001
2-6 hours	30 (26.3%)	108 (90%)	0.001
6-12 hours	12 (10.5%)	78 (65%)	0.001
12-24 hours	3 (2.6%)	30 (25%)	0.001
0-24 hours	45 (39.5%)	117 (97.5%)	0.001

** Chi square test was applied to the groups.

Researchers have concluded that most of the side effects to be mild or moderate intensity were not associated with the study medication. No clinically meaningful changes in vital signs were noted. A headache (12%), constipation (11%), anxiety (6%), dry mouth (5%) and hepatic enzymes increased (4%) were noted with granisetron (Table-4).

Table-4. Comparison of adverse events

Adverse Effect	Granisetron (%)	Placebo (%)	P value
Headache	12	8	NS
Increased Hepatic Enzymes	4	4	NS
Anxiety	6	4	NS
Dry Mouth	5	3	NS
Constipation	11	11	NS

** Chi-square test; $p < 0.05$ is significant; no significant (NS) differences between the two groups, $p > 0.05$.

Discussion

Several studies using different drugs have been carried out for the prevention of PONV (10). This prospective, randomized, and double-blinded study demonstrates that granisetron is effective for the prevention of PONV in the non-smoking women undergoing elective thyroidectomy in the overall postoperative period 0 to 24 hours.

Intravenous anesthetic propofol versus volatile anesthetics, air versus nitrous oxide and remifentanyl versus fentanyl have antiemetic effects during general anesthesia (11, 12). That's why we preferred IV penthotal and volatile anesthesia with sevoflurane, nitrous oxide, and fentanyl in this study. Studies have shown that a risk score dependent antiemetic approach effectively reduces postoperative nausea and vomiting (13). According to Apfel et al., Major risk factors for PONV are following; female, non-smoker, history of PONV and motion sickness and postoperative opioids (14, 15). Based on this knowledge we provided a group of the patients with female gender, non-smoking status, undergoing elective thyroidectomy; which resulted with two major risk factors for PONV and an additional minor risk factor, the surgical type. So, efficiency and adverse effects of granisetron could be studied specifically

compared to placebo. This and naturally ethnic factors might explain the high PONV incidence (98%) in the placebo group.

Based on the management of postoperative nausea and vomiting guidelines of the Society for Ambulatory Anesthesia, the recommended antiemetic prophylaxis in the adults includes granisetron for patients at moderate to severe risk for PONV (2). Prophylaxis with granisetron reduced overall PONV incidence in the post operative period 0-24 h from 98% to 39%. As expected PONV occurred frequently in the 0-2 h (57.5%), 2-6 h (90%) and 6-12 h (65%) time intervals. Granisetron was statistically effective in protection from PONV $p < 0.001$. So prophylaxis with granisetron reduced PONV overall incidence of 61% in the patients of the study group, while only 2% in the placebo group did not suffer from PONV.

The most important reason for preferring 5-HT₃ receptor antagonists in PONV treatment is the lower incidence of side effects such as sedation, dry mouth and extrapyramidal symptoms that are associated with traditional antiemetic agents (6,16). Granisetron stays in the body for a long time and breaks down very slowly. It is eliminated by the liver and kidneys. Although it is well tolerated, headaches, dizziness, constipation are the most common side effects. No significant drug interactions have been reported with this drug. It is broken down by the liver's cytochrome P 450 system, and it has little effect on the metabolism of other medicines impaired by this system (17).

Administration dose of granisetron is an important factor for ideal prophylaxis, though lower doses like 0.1 mg are less effective than 3mg granisetron (18, 19). Recommended dose 3 mg granisetron correlates to a variable dose

of 40 $\mu\text{g kg}^{-1}$ assuming a body weight of 75 kg (20). So we administered 40 $\mu\text{g kg}^{-1}$ granisetron in the study group. Metaxari et al. studied antiemetic prophylaxis with three 5-HT₃ agents and determined granisetron 3 mg to provide the best prophylaxis (9). Timing of administration of antiemetic drugs is also important, though peak plasma concentration reaching time of granisetron is about 30 min after administration (21). So prophylaxis 30 min before operation end was ideal. Granisetron was tolerated well in this study and the most frequent adverse effect noticed was headache with 14%, which was similar in previous studies (17,18).

Several studies show that the combination of granisetron with other antiemetic agents increases success in the prevention of PONV in high-risk patients and patients receiving granisetron for prophylaxis combined with another antiemetic group for rescue treatment. In one of the studies, droperidol was combined with granisetron; in another one, dexamethasone was combined with granisetron. These combinations were effective than granisetron alone (22,23). We didn't compare combinations of granisetron with other drugs for more effectiveness, because the purpose of this study is to demonstrate the effectiveness of granisetron in a selective moderate to a high-risk group for PONV.

However, unlike patients with chemotherapy-induced nausea and vomiting, perioperative patient with failed ondansetron prophylaxis did not receive a significant response to cross-dose with granisetron (24). That's why we didn't prefer another 5-HT₃ receptor blocker for a rescue antiemetic treatment. We chose droperidol for rescue antiemetic therapy, when necessary, because of its equivalent efficacy in PONV prophylaxis to that of ondansetron (25)

Conclusion

PONV are major side effects of surgical operations and a great burden to patients' quality of life. Prevention of PONV is important for patient satisfaction, postoperative recovery, hospital staying time and decrease of costs. Therefore further studies are still necessary to find an ideal solution. This prospective randomized trial has shown that the use of granisetron in PONV prophylaxis is more effective than placebo and it can be used in nonsmoking women undergoing the thyroid surgery.

Conflict of Interests

The authors declare that they have no conflict of interest in the current study.

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How to cite?

Cinar AS, Celayir MF. Effects of Granisetron on Postoperative Nausea and Vomiting in Non-smoking Women Undergoing Thyroidectomy: A Prospective Randomized Double Blind Placebo Controlled Study *Ulutas Med J*. 2018;4(4):213-220

DOI: [10.5455/umj.20180816070933](https://doi.org/10.5455/umj.20180816070933)