

Optimal Dose of Granisetron for Prophylaxis Against Postoperative Emesis After Gynecological Surgery

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We previously reported that 20 and 40 $\mu\text{g}/\text{kg}$ of granisetron given during anesthesia prevented postoperative emesis with no severe complications. The aim of the current study was to determine the optimal dose of granisetron for the prevention of postoperative nausea and vomiting (PONV) after gynecological surgery. Two hundred female patients (ASA physical status I) were randomly allocated to one of five groups ($n = 40$ for each): saline (as a control), granisetron 2 $\mu\text{g}/\text{kg}$, granisetron 5 $\mu\text{g}/\text{kg}$, granisetron 10 $\mu\text{g}/\text{kg}$, and granisetron 20 $\mu\text{g}/\text{kg}$. Saline or granisetron was given intravenously immediately after induction of anesthesia. PONV was assessed 24 h after surgery. The percentage of emesis-free patients was significantly greater in the 5- to 20- $\mu\text{g}/\text{kg}$ granisetron groups than in the control and 2- $\mu\text{g}/\text{kg}$ granisetron groups (18%, 23%, 68%, 78%, and 75% of patients receiving saline or granisetron 2 $\mu\text{g}/\text{kg}$, 5 $\mu\text{g}/\text{kg}$, 10 $\mu\text{g}/\text{kg}$, and 20 $\mu\text{g}/\text{kg}$, respectively). Granisetron doses of 5 $\mu\text{g}/\text{kg}$ or larger were also superior to the saline and 2- $\mu\text{g}/\text{kg}$ granisetron treatment for the prevention of nausea over the 24-h study

period (nausea visual analog scales 24 h after surgery: 49, 41, 18, 16, and 14 mm in the control and granisetron 2 $\mu\text{g}/\text{kg}$, 5 $\mu\text{g}/\text{kg}$, 10 $\mu\text{g}/\text{kg}$, and 20 $\mu\text{g}/\text{kg}$ groups, respectively). A smaller proportion of patients received "rescue" antiemetic in the 5- $\mu\text{g}/\text{kg}$ or larger granisetron groups than in the control and 2- $\mu\text{g}/\text{kg}$ granisetron groups (48%, 40%, 18%, 13%, and 10% of patients in the control and granisetron 2 $\mu\text{g}/\text{kg}$, 5 $\mu\text{g}/\text{kg}$, 10 $\mu\text{g}/\text{kg}$, and 20 $\mu\text{g}/\text{kg}$ groups, respectively). The antiemetic effect of granisetron was similar among the groups who received 5- $\mu\text{g}/\text{kg}$ or larger doses. In conclusion, we suggest that the optimal dose of granisetron is 5 $\mu\text{g}/\text{kg}$ for the prevention of PONV after gynecological surgery. **Implications:** Nausea and vomiting postoperatively after gynecologic surgery is a significant problem. The authors found that granisetron, a selective antagonist of serotonin, markedly decreases the incidence of postoperative nausea and vomiting at doses of 5 $\mu\text{g}/\text{kg}$ or larger.

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Postoperative nausea and vomiting (PONV) is one of the most unpleasant experiences associated with surgery (1). A variety of pharmacological modalities have been advocated to prevent PONV, including antihistamines, anticholinergics, and dopamine receptor antagonists (2). We previously reported that 20 or 40 $\mu\text{g}/\text{kg}$ of granisetron, a selective antagonist of 5-hydroxytryptamine type 3 (5-HT₃) receptors, is effective in the prevention of these postoperative complications without severe adverse effects, and that the efficacy was similar between the two doses (3). However, smaller doses of granisetron may be effective and less expensive for prophylaxis against PONV because 10 $\mu\text{g}/\text{kg}$ of the drug decreases the incidence of cisplatin-induced nausea and vomiting (4). To test this hypothesis, we assessed in a prospective, randomized,

and double-blind study, the prophylactic effects of smaller doses (2, 5, and 10 $\mu\text{g}/\text{kg}$) of granisetron on PONV in patients who were scheduled to undergo gynecological surgery. This population has a great likelihood of experiencing these complications (5,6). Granisetron produces several adverse effects, including headache, rash, diarrhea, and liver dysfunction. We also examined whether smaller doses of granisetron may reduce the incidence of untoward side effects in this setting.

Methods

We studied 200 otherwise healthy inpatients (ASA physical status 1) aged 20-67 yr undergoing elective gynecological surgery after obtaining institutional approval and the informed consent of all patients. Exclusion criteria included antiemetic medication within 24 h before surgery, gastrointestinal disease, pregnancy, obesity (more than 25% heavier than ideal

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body weight), liver and/or renal dysfunction, vomiting in the 24 h preceding surgery, and need for postoperative nasogastric tube. None of the patients underwent laparoscopic techniques.

The patients were randomly assigned to one of five groups ($n = 40$ for each group) to receive saline (control) or granisetron (Kytril®; SmithKline Beecham Seiyaku, Tokyo, Japan) at four different doses (2 $\mu\text{g}/\text{kg}$, 5 $\mu\text{g}/\text{kg}$, 10 $\mu\text{g}/\text{kg}$, or 20 $\mu\text{g}/\text{kg}$). Saline or granisetron was administered intravenously over 5 min immediately after the induction of anesthesia (immediately before surgery) by anesthetists who were blinded to the nature of treatment. These medications had been prepared beforehand in equivalent volume by an assistant. Vital signs (arterial blood pressure and heart rate) were recorded at 1-min intervals for the first 10 min and subsequently at 2.5-min intervals for 30 min after administration of the study drugs.

Premedication included diazepam 4–6 mg per os and atropine 0.5 mg intramuscularly. All patients underwent endotracheal intubation and received the same anesthetic technique, consisting of thiopental 5 mg/kg for induction and 60% nitrous oxide and 1%–2% isoflurane in oxygen for the maintenance of anesthesia. Isoflurane concentrations were adjusted to maintain arterial blood pressure and heart rate within 20% of preinduction values. This anesthetic management is our routine technique. Muscle relaxation was achieved with vecuronium and reversed by a combination of neostigmine and atropine. Body temperature was measured at the tympanic membrane and maintained between 36.0 and 37.5°C. An epidural catheter was inserted into all patients before surgery, but no drug was given through the catheter during surgery. Placement of the epidural catheter was confirmed using 4–5 mL of 1% lidocaine with epinephrine. Postoperative analgesia was provided by an epidural bolus injection of 0.2 mg buprenorphine (diluted with 10 mL of saline) at the end of surgery, followed by continuous epidural administration of buprenorphine (10 $\mu\text{g}/\text{mL}$) and bupivacaine (2.5 mg/mL) mixture (1.25 mL/h). We used this timing of the postoperative analgesics to minimize the influence of buprenorphine on nausea or vomiting at emergence from anesthesia. No patients received blood transfusion or narcotics (IV or IM), or had hypotension (defined as systolic blood pressure <80 mm Hg) throughout the study. Patients who had undergone hysterectomy received carbazochrome 100 mg and tranexamic acid 500 mg to prevent hemostasis, as routine postoperative management in our hospital. As a postoperative analgesic supplement, 5–11 patients in each group received a diclofenac suppository.

Blind observers monitored patients for emetic episodes, severity of nausea, and vital signs for a 24-h

command after surgery. Adverse events (rash, headache, and diarrhea) within 24 h after surgery were assessed by questionnaire. At the completion of the study period, patients provided blood samples to be assessed for hematologic, blood chemistry, and renal and hepatic variables.

No distinction was made between vomiting and retching for data collection. Vomiting was defined as the expulsion of stomach contents through the mouth. Retching was defined as an involuntary attempt to vomit that did not produce stomach contents. An emetic episode was defined as a vomiting or retching event or any combination of these events that occurred in rapid succession (less than a 1-min interval between events). A patient who had no emetic episodes during the specified time period was described as emesis-free.

Nausea was rated on linear vertical visual analog scale (nausea VAS) (0 = no nausea, 100 = severe nausea). Nausea assessment was made preoperatively, postoperatively (immediately after tracheal extubation), and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h thereafter. Those patients who scored their nausea as 0 (no nausea) over the specified time period were termed nausea-free.

The efficacy of the study medication was assessed in terms of the number of emetic episodes, the percentage of emesis-free patients, and the percentage of nausea-free patients during the 24 hr postoperative period, and in terms of the mean nausea VAS score. Metoclopramide 10 mg/kg IV was given as a “rescue” antiemetic for vomiting or persistent nausea at the discretion of a physician blinded to group classification or at the patient’s request.

Comparisons of data between the groups were made using the one-way analysis of variance with Bonferroni’s correction for multiple comparisons of parametric data (age, weight, height, last menstrual cycle, duration of anesthesia, duration of surgery, blood loss, infusion volume, and awakening time [time from the end of surgery to eye opening spontaneously or in response to verbal stimuli]). Nonparametric data (no history of general anesthesia or postoperative nausea or vomiting, incidence of the adverse effects, and types of surgery) were analyzed using the χ^2 test and Fisher’s exact test. The Wilcoxon ranked sum test was used to compare treatments with respect to the number of emetic episodes. The χ^2 test and Fisher’s exact test were used to compare the study groups with regard to the proportion of emesis-free and nausea-free patients over the 24-h study period, and the number of patients withdrawn for rescue medication. The mean nausea VAS scores were compared using analysis of variance. In the analysis of nausea VAS data, the data of the patients who were withdrawn from the study due to administration of the rescue antiemetic were excluded. $P < 0.05$ was

Table 1. Demographic Data

	Saline (control)	Granisetron ($\mu\text{g}/\text{kg}$)			
		2	5	10	20
Patients (<i>n</i>)	40	40	40	40	40
Age (yr)	48 \pm 13	46 \pm 12	44 \pm 12	48 \pm 12	43 \pm 11
Weight (kg)	57 \pm 9	55 \pm 8	59 \pm 9	57 \pm 9	58 \pm 9
Height (cm)	157 \pm 6	155 \pm 5	159 \pm 7	156 \pm 7	156 \pm 5
Last menstrual cycle (days) [<i>n</i>] ^a	15 \pm 3 [24]	16 \pm 3 [26]	15 \pm 4 [28]	16 \pm 4 [23]	16 \pm 3 [29]
No previous general anesthesia	34	33	32	33	32
History of PONV	3	2	4	3	2
Type of surgery					
AH	34	33	33	36	35
AH with salpingo-oophorectomy	4	5	4	2	5
Oophorectomy	1	2	3	2	0
Duration of anesthesia (min)	159 \pm 46	151 \pm 43	147 \pm 39	161 \pm 42	156 \pm 42
Duration of surgery (min)	119 \pm 35	112 \pm 32	109 \pm 34	122 \pm 41	114 \pm 37
Blood loss (mL)	340 \pm 170	330 \pm 160	310 \pm 150	360 \pm 180	310 \pm 150
Fluid infused (mL)	1210 \pm 330	1210 \pm 320	1170 \pm 300	1250 \pm 350	1190 \pm 300
Awakening time (min)	8 \pm 4	7 \pm 3	8 \pm 4	7 \pm 3	8 \pm 3

Data are expressed as mean \pm SD.

There were no significant differences among the groups.

PONV = postoperative nausea and vomiting, AH = abdominal hysterectomy.

^a Patients who had experienced the menopause were excluded.

^b Time from the end of surgery to eye opening.

Power analysis revealed that sample size ($n = 40$ for each group) in the current study was sufficient to detect antiemetic effects of small doses of granisetron (moderate differences in efficacy [$d = (\mu_1 - \mu_2)/s = 0.6 - 0.7$]) provided that the power is 70%–80% (7).

Results

The study groups were comparable with respect to characteristics of patients and surgery (Table 1).

Patients receiving 5–20 $\mu\text{g}/\text{kg}$ of granisetron experienced significantly fewer emetic episodes than those receiving saline or 2 $\mu\text{g}/\text{kg}$ of granisetron over the entire 24-h study period (Table 2). More patients treated with 5- $\mu\text{g}/\text{kg}$ or larger doses of granisetron were emesis-free during the 24 h after surgery compared with the saline- or granisetron 2 $\mu\text{g}/\text{kg}$ -treated patients. The frequency distribution of emetic episodes and the number of emesis-free patients were similar between the 5-, 10-, and 20- $\mu\text{g}/\text{kg}$ granisetron groups. There was a decreased need for rescue antiemetic medication in the patients who received 5–20 $\mu\text{g}/\text{kg}$ granisetron compared with those who received saline (Table 2). The number of patients who required postoperative metoclopramide was similar between the granisetron 2 $\mu\text{g}/\text{kg}$ and control groups.

More patients receiving 5- $\mu\text{g}/\text{kg}$ or larger doses of granisetron reported no nausea over the entire 24-h study period than those receiving saline or 2 $\mu\text{g}/\text{kg}$ granisetron (3, 4, 19, 21, and 22 patients in the control, 2- $\mu\text{g}/\text{kg}$, 5- $\mu\text{g}/\text{kg}$, 10- $\mu\text{g}/\text{kg}$, and 20- $\mu\text{g}/\text{kg}$ granis-

≥ 5 $\mu\text{g}/\text{kg}$ of granisetron reported less nausea throughout the study period than did those who received saline or 2 $\mu\text{g}/\text{kg}$ granisetron (Figure 1). The nausea VAS scores in the 5- to 20- $\mu\text{g}/\text{kg}$ granisetron groups were similar.

The adverse events in the granisetron groups were similar to those in the control group. One to three patients in each group experienced a headache of mild severity. No rash or diarrhea was observed in any patient. None of the patients had tachycardia or hypotension during or after any dose of granisetron. Changes in vital signs were similar and remained within the clinically acceptable ranges in all groups. We found no significant changes in postoperative laboratory values among the five study groups.

Discussion

The incidence of PONV in female patients undergoing gynecological surgery varies from 24% to 75% (8–11). Although various antiemetics (e.g., anticholinergics, antihistamines, dopamine receptor antagonists) are available to treat PONV, their use is limited by untoward side effects (12). Granisetron is a potent antiemetic with high selectivity for 5-HT₃ receptor, resulting in fewer adverse side effects than other antiemetics (13). Several studies have shown that granisetron at doses of 20–40 $\mu\text{g}/\text{kg}$ successfully prevent PONV (3,14). However, the high cost of these doses may result in an undesirable cost/effectiveness ratio in gynecological surgery. Granisetron, 1 mg (approximate-

Table 2. Distribution of the Number of Emetic Episodes over 24 Hours for Each Treatment Group

	Saline (control)	Granisetron ($\mu\text{g}/\text{kg}$)			
		2	5	10	20
Patients (<i>n</i>)	40	40	40	40	40
Patients per no. of emetic episodes [<i>n</i> (%)]					
0	7 (18)	9 (23)	27 (68)*	31 (78)*	30 (75)*
1	5 (13)	6 (15)	4 (10)	3 (8)	5 (13)
2	6 (15)	5 (13)	2 (5)	1 (3)	1 (3)
3	3 (8)	3 (8)	0 (0)	0 (0)	0 (0)
4	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Patients withdrawn for rescue medication [<i>n</i> (%)]	19 (48)	16 (40)	7 (18)†	5 (13)†	4 (10)*

* $P < 0.05$ versus control and granisetron 2 $\mu\text{g}/\text{kg}$ groups, † $P < 0.05$ versus control group alone.

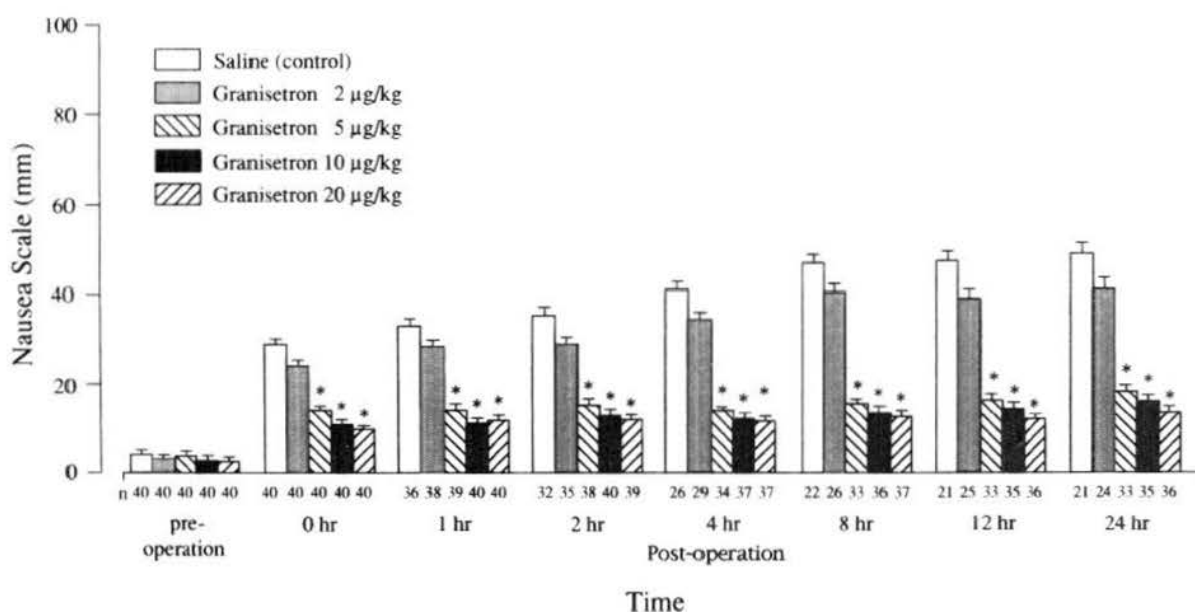


Figure 1. Nausea visual analog scale scores (mean \pm SEM) during the 24-h study period. 0 = none to 100 = severe. * $P < 0.05$ versus control and granisetron 2 $\mu\text{g}/\text{kg}$. Data at 0.5, 1.5, 3, and 6 h after surgery were omitted. The numbers below the x-axis denote the number of patients used for the analysis.

effective than 0.1 mg (approximately 1.6 $\mu\text{g}/\text{kg}$) in preventing PONV (15). In this previous research, the efficacy of doses between 1.6 $\mu\text{g}/\text{kg}$ and 16 $\mu\text{g}/\text{kg}$ was not evaluated. In the current study, 5 $\mu\text{g}/\text{kg}$ of granisetron was as effective as 20 $\mu\text{g}/\text{kg}$ in the prevention of PONV without any severe untoward side effects; 2 $\mu\text{g}/\text{kg}$ failed to provide effective prophylaxis against these complications. These findings suggest that the optimal dose of granisetron as a prophylaxis against PONV is 5 $\mu\text{g}/\text{kg}$. However, in pediatric outpatients undergoing tonsillo-adenoidectomy, strabismus surgery, or dental rehabilitation, 10 $\mu\text{g}/\text{kg}$ of granisetron has been shown to be ineffective in preventing PONV (16). This inconsistency may be due to differences in patients' age and types of surgery.

Cost-effectiveness analysis of antiemetic therapy for ambulatory surgery by Watcha and Smith (17) indi-

favorable than ondansetron, another 5-HT₃ receptor antagonist, although there was less incidence of PONV in the patients receiving ondansetron (17). Antiemetic prophylaxis with ondansetron (4 mg) has been reported to be comparable with that of granisetron (3 mg) in laparoscopic surgery (18). Granisetron, 40 $\mu\text{g}/\text{kg}$, has been shown to be superior to droperidol (1.5 or 2.5 mg) in the prevention of PONV in gynecological surgery without cost-effectiveness analysis (14). The multifactorial etiology of PONV includes the type and duration of surgery (6). Because moderate doses of granisetron are rather costly, the prophylactic use of granisetron may be less cost-effective than droperidol in surgeries that are expected to have low incidence of PONV, despite the high efficacy of granisetron. In contrast, in gynecological surgery, in which a high incidence of PONV is expected, an antiemetic

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