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Efficacy of prophylactic intravenous granisetron in postoperative emesis in adults

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Abstract

Purpose. This randomized, double-blind, placebo-controlled trial evaluated the efficacy, safety, and optimal dose of granisetron in the prophylactic control of postoperative nausea and vomiting in patients undergoing gynecologic surgery or cholecystectomy.

Methods. Three-hundred and fifteen patients (age, 20–65 years) received intravenous granisetron (1 mg or 3 mg) or placebo immediately before the end of anesthesia. After treatment, patients were observed for 24 h, and the occurrence of nausea and vomiting was recorded and safety was assessed. The no-vomiting rate, time-to-first vomiting episode, and severity of nausea were recorded.

Results. The no-vomiting rates in patients receiving granisetron 1 mg and 3 mg were significantly higher than that in the placebo group (83.7%, 78.8%, and 57.9%, respectively; $P = 0.0004$ for 1 mg vs placebo, $P = 0.001$ for 3 mg). Time-to-first vomiting episode was longer in the granisetron 1-mg and 3-mg groups than in the placebo group (time-to-event analysis, Kaplan-Meier, log-rank test; 83.2%, 80.1%, and 59.1%, respectively; $P = 0.0002$ and $P = 0.0010$). The severity of nausea was also less in granisetron-treated patients (25.2%, 11.5%, and 15.4% severe nausea incidence for placebo, granisetron 1 mg, and granisetron 3 mg, respectively; $P = 0.00003$ and $P = 0.002$). Fewer rescue medications were required in the two granisetron-treated groups compared with those receiving placebo. Adverse events were similar in all groups. No differences in efficacy or safety were observed between granisetron doses.

Conclusion. Granisetron is well-tolerated and more effective than placebo in the prophylactic control of nausea and vomiting after surgery. This study suggests that the optimum dose of granisetron is 1 mg.

Key words Granisetron · Prophylaxis · Postoperative nausea and vomiting

Introduction

Postoperative nausea and vomiting (PONV) is extremely distressing and uncomfortable, and is noted frequently in patients who have undergone surgery under general anesthesia [1]. The incidence of PONV is estimated to be 20%–40% following any type of surgery, but greater than 50% after some high-risk gynecologic procedures [2,3]. Further risk factors for experiencing PONV include female sex, a history of motion sickness, middle ear surgery, duration of anesthesia, and use of nitrous oxide. In addition, in female patients, certain menstrual cycle phases and an irregular menstrual cycle are known to increase the likelihood of PONV [4]. However, the precise mechanisms that trigger PONV have not been clarified [5].

PONV not only causes distress to the patient but can also result in problems in managing their condition (e.g., dehydration, electrolyte imbalance, tension on suture strings) and can increase the risk of pulmonary aspiration of vomit [6]. Furthermore, PONV experienced following an outpatient procedure can result in hospitalization or later re-admission, thus increasing both healthcare costs and the psychological burden to the patient. Currently used antiemetics may induce undesirable side-effects, such as extrapyramidal symptoms and excessive sedation [6] and, consequently, recent research has centered on the search for effective and well-tolerated antiemetic agents which lack the adverse effects of older agents.

Granisetron is a highly selective and potent 5-HT_3-receptor antagonist which is thought to specifically inhibit 5-HT_3 receptors on vagal afferent nerve terminals in the alimentary tract [7]. Studies have shown that granisetron, alone or in combination with a corticosteroid, is a potent and well-tolerated antiemetic agent in adults and children when used for the prevention of nausea and vomiting induced by cytotoxic chemotherapy agents, radiation therapy, and surgical procedures [8–13].

* See Appendix.

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In Japan, intravenous granisetron is approved for the control of nausea and vomiting induced by chemotherapy and total body irradiation [14,15]. This study was undertaken to assess the efficacy and safety of two different doses of intravenous granisetron (1 mg and 3 mg) vs placebo for the prevention of PONV in patients undergoing gynecologic surgery or cholecystectomy under general anesthesia.

Subjects and methods

Eligibility criteria for the trial included the following characteristics: age between 20 and 65 years; scheduled to undergo gynecologic surgery (hysteromyoma, ovarian cyst, or other benign gynecologic diseases; enucleation of benign tumor; and laparoscopic surgery); gynecologic diagnostic laparoscopy; or cholecystectomy under inhalation anesthesia, alone or in combination with epidural anesthesia; ASA (American Society of Anesthesiologists) grade 1–3 preoperative physical status.

Patients were excluded from the trial if they: had severe hepatic, renal, cardiac, or pulmonary dysfunction or hemopoietic organ disorder; had a history of drug allergy or anaphylactic symptoms; had a gastrointestinal transit disorder or an active peptic ulcer; had a brain tumor or epilepsy or were receiving a psychotropic agent with an antiemetic effect; had experienced nausea and/or vomiting during the 24-h period before the administration of the study medication; had received another study drug within 3 months of starting the study or were due to use another investigational drug concurrently; had undergone radiotherapy or chemotherapy within the 24-h period before dosing with the study medication or were due to undergo radiotherapy or chemotherapy during the observation period; were pregnant, nursing, or might be, or wished to be, pregnant within 30 days of receiving the study medication.

The institutional review board of each participating medical institution approved the protocol and statement of informed consent. Written informed consent was obtained from each patient.

Granisetron was provided as a colorless clear injection, each tube containing 1 mg of granisetron (1.12 mg as granisetron hydrochloride). Placebo injection containing 1 ml of physiological saline appeared identical, to maintain the integrity of the study blinding. Patients received a single dose of either three ampoules of granisetron 1-mg injection (the 3-mg group), one ampoule of granisetron 1-mg injection and two ampoules of placebo injection (the 1-mg group), or three ampoules of placebo injection (the placebo group), given intravenously over at least 30 s immediately before stopping inhalation anesthesia.

Drugs or therapies that were considered to affect efficacy evaluation were prohibited within the 24-h period before and after administration of the study drug: anticancer drugs, antiemetic agents, adrenocorticosteroid preparations with an antiemetic effect, central nervous system (CNS) drugs with an antiemetic effect or an indication for postoperative nausea and vomiting, propofol, other investigational products, and radiotherapy.

Antiemetic rescue with another antiemetic therapy (except for 5-HT_3-receptor antagonists) was allowed if the patient experienced two or more vomiting episodes or severe persistent nausea within 24 h after stopping inhalation anesthesia.

This multicenter, randomized, placebo-controlled, double-blind trial was conducted in Japan at 26 university hospitals and one general hospital. After assessment for eligibility, a medical and surgical history was obtained. Demographic information and significant presenting signs and symptoms were recorded as part of the baseline evaluation. Patients were allocated to intravenous granisetron 3 mg, granisetron 1 mg, or placebo, by central randomization and minimization, using medical institution, sex, presence/absence of concurrent use of extradural anesthesia, and surgical procedure (laparoscopic surgery, laparotomy) as adjusting factors.

Clinical laboratory tests, which were performed within 1 week before administration of the study medication and on the day after administration, included: hematology (red blood cell count, hemoglobin, hematocrit, white blood cell count, platelet count); blood biochemical examinations (glutamine-oxaloacetic transaminase, glutamic-pyruvic transaminase, γ-glutamic-pyruvic transaminase, alkaline phosphatase, total bilirubin, total protein, blood urea nitrogen, creatinine); and physical examinations (blood pressure, body temperature, and pulse rate), measured immediately before the induction of general anesthesia, immediately before the study treatment, and on completing the observation period.

The anesthetic drugs used, and their dose, route, and duration of administration were recorded. Surgery and postoperative procedures, such as recovery time and postoperative feeding, were also documented. In addition, all drugs administered within 2 days of the induction of anesthesia were noted.

The condition of patients (occurrence of nausea, vomiting, and any other relevant information) was recorded for 24 h before the induction of anesthesia. The presence or absence of nausea and vomiting was then documented for 24 h after the end of inhalation anesthesia, and the following parameters were recorded on the basis of medical records: the presence/absence of vomiting (including retching) and the number of vomiting episodes (vomiting episodes occurring at intervals of

≥1 min counted as separate episodes); time-to-first vomiting episode; and presence/absence and severity of nausea (no nausea, mild nausea, severe nausea). If rescue medication was required, the number of vomiting episodes before rescue and the presence/absence and severity of nausea before and after rescue were recorded.

According to studies reported in the literature, the calculated no-vomiting rates for placebo and granisetron in the prevention of PONV were 35% and 55%–65%, respectively. Based on these data, together with three statistical assumptions, it was estimated that a minimum of 100 individuals per treatment group was required to have adequate power to detect significant differences between placebo and treatment groups.

The primary efficacy variable was the no-vomiting rate (defined as the proportion of patients who did not experience vomiting during the 24-h period after the end of inhalation anesthesia). Efficacy in controlling vomiting was rated on a two-point scale: effective (no vomiting); not effective (one or more vomiting episodes). The secondary efficacy variables were the time-to-first vomiting episode and the number of vomiting episodes, evaluated for 24 h after the end of anesthesia; the efficacy in controlling nausea for 24 h after the end of anesthesia (effective, no nausea; slightly effective, mild nausea [e.g., occurring transiently at a postural change]; not effective, severe nausea [e.g., persisting even at rest or with retching-like episodes]).

Any medical event considered problematic to the subject, including an abnormal change, infection, accident, or symptom aggravation, that occurred during the study period (from the obtaining of consent to the day of performing clinical laboratory tests after administration of the investigational product), was observed until it disappeared or the patient recovered to the state before administration of the investigational product.

Adverse experiences were elicited from patients by the investigator asking non-leading questions such as, "Have you felt different in any way since the last examination?" Adverse events occurring within 30 days of the administration of the study medication were recorded, and the following items were examined: date and time of onset and disappearance; course; severity (mild, moderate, or severe); relationship with the investigational product (unrelated, probably not related, probably related, or related); need for corrective treatment; and outcome. Serious adverse events were defined as any that were fatal, life-threatening, permanently or temporarily disabling or incapacitating, resulted in hospitalization or a prolonged hospital stay, or were associated with a congenital abnormality, cancer, or an overdose.

Efficacy was evaluated by comparing the rate of patients with no-vomiting episodes in the placebo group with the rates in the granisetron 1-mg group and the granisetron 3-mg group, using Fisher's exact test; the time-to-first vomiting episode, determined by time-to-event analysis (Kaplan-Meier, log-rank test); and the severity of nausea, determined by the Wilcoxon two-sample test. Each granisetron dose group was compared to the placebo group, and $P < 0.025$ (two-tailed) was interpreted as statistically significant, using the Bonferroni adjustment.

Statistical analyses were performed on two populations who entered the trial. Population 1 included all eligible patients who received the study medication and were observed for 24 h after the end of anesthesia (per-protocol set). Population 2 included all patients who received the study medication (full-analysis set). Primary efficacy analyses were carried out on population 1 and safety was evaluated in population 2.

Results

Of the 365 patients who entered the trial, 341 patients received the study medication and were included in population 2: 117 patients in the placebo group, 110 in the granisetron 1-mg group, and 114 in the granisetron 3-mg group. Twenty-six patients were excluded from population 1 due to withdrawal for protocol violations ($n = 25$) or adverse events ($n = 1$; ventricular fibrillation), resulting in a total of 315 patients: 107 patients in the placebo group, 104 in the granisetron 1-mg group, and 104 in the granisetron 3-mg group. The majority of patients were female (301/315; 95.5%) and the mean ages in the placebo, 1-mg group and 3-mg group were 40.1, 39.8, and 40.4 years, respectively. All patient characteristics were comparable among treatment groups (Table 1). Patient demographics were also comparable in population 2.

The no-vomiting rates over the entire 24-h monitoring period in the granisetron 1-mg (83.7%) and 3-mg (78.8%) groups were significantly higher than that in the placebo group (57.9%); Fisher's exact test, $P = 0.0004$ for granisetron 1 mg vs placebo; $P = 0.001$ for granisetron 3 mg vs placebo. No difference was observed in the no-vomiting rates between the two granisetron doses (Table 2). Fewer patients receiving granisetron, 1 mg and 3 mg, experienced vomiting in the early postoperative phase (0–6 h) and between 6–12 h compared to the placebo group (Table 2). Furthermore, rescue medications were required less frequently in the two granisetron groups compared to those receiving placebo (Table 2). Similarly, the time-to-first vomiting episode, analyzed by time-to-event analysis, was significantly longer in the granisetron-treated patients compared with placebo-treated patients. After 24 h, 83.2% of patients treated with granisetron 1 mg, and

Table 1. Patient demographic data (population 1)

	Placebo (n = 107)	Granisetron 1 mg (n = 104)	Granisetron 3 mg (n = 104)
Sex			
Female	102	99	100
Male	5	5	4
Age (years; mean ± SD)	40.1 ± 10.2	39.8 ± 9.1	40.4 ± 10.2
Height (cm; mean ± SD)	157.8 ± 6.1	157.6 ± 5.4	157.6 ± 6.6
Weight (kg; mean ± SD)	55.6 ± 8.7	55.7 ± 8.8	54.1 ± 9.3
Presence/absence of motion sickness			
None	60	61	61
Experienced in childhood (<15 years)	25	14	15
Experienced occasionally	20	26	21
Experienced frequently	2	3	7
Duration of surgery (min; mean ± SD)	125.7 ± 60.8	115.4 ± 38.2	129.3 ± 58.4
Duration of anesthesia (min; mean ± SD)	158.3 ± 65.5	148.4 ± 40.9	163.8 ± 60.7
Surgical procedure			
Abdominal surgery	58	55	56
Vaginal surgery	6	12	11
Laparoscopy	43	37	37
Days from last menses			
(postmenopausal)	10	8	9
0–7	15	10	11
8–15	20	23	21
16–23	27	24	19
24–31	5	10	7
32+	22	19	24
Unknown, or male	8	10	13

Table 2. No-vomiting rate, time-to-first vomit, and the number of patients requiring rescue medications in the placebo, granisetron 1-mg, and granisetron 3-mg groups over the 24-h postoperative monitoring period

	Number of patients (%)		
	Placebo (n = 107)	Granisetron 1 mg (n = 104)	Granisetron 3 mg (n = 104)
No vomiting in 24 h	62 (57.9)	87 (83.7)*	82 (78.8)*
0–6 h	29 (27.1)	12 (11.5)	13 (12.5)
6–12 h	13 (12.1)	2 (1.9)	2 (1.9)
12–18 h	2 (1.9)	2 (1.9)	3 (2.9)
18–24 h	1 (0.9)	1 (1)	4 (3.8)
Rescue medication	30 (28)	15 (14.4)	17 (16.3)

* $P < 0.025$ vs placebo; Fisher's exact test

80.1% treated with granisetron 3 mg, were free of vomiting vs 59.1% in the placebo-treated group; log-rank test; $P = 0.0002$ and $P = 0.0010$, respectively (Fig. 1). Fewer patients treated with granisetron experienced more than three episodes of vomiting compared to those given the placebo (Table 3). The severity of nausea was also less in the patients who had received granisetron 1 mg and 3 mg than in those who had received placebo. For example, 25.2% of placebo-treated patients suffered severe nausea compared with 11.5% of patients who received granisetron 1 mg, and 15.4% of those receiving granisetron 3 mg (Wilcoxon two-sample test, $P = 0.00003$ and $P = 0.002$, respectively; Table 4).

The most frequently reported adverse events that occurred in at least four patients are listed in Table 5. The incidence of adverse reactions that were considered at least possibly related to the study medication was 22.2% (26/117) in the placebo group, 20.9% (23/110) in the 1-mg group, and 18.4% (21/114) in the 3-mg group. No adverse reactions were specific to the granisetron groups, with adverse events comparable to those in the placebo group. No dose-dependent incidence was noted. A serious adverse reaction, ventricular fibrillation, was noted in one patient who received granisetron 1 mg. A causal relationship with the investigational product was deemed unlikely, due to the mechanism of

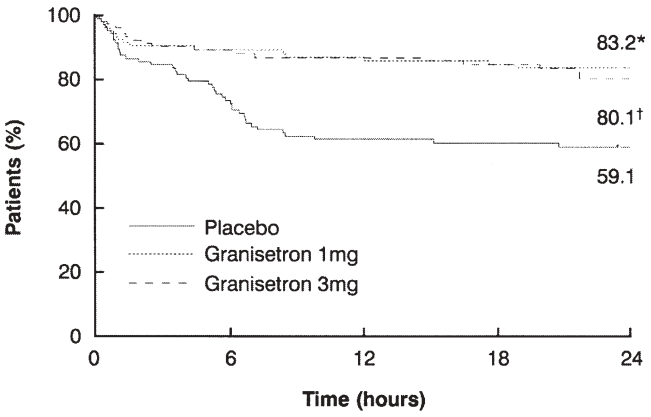

Fig. 1. Onset time of the first vomiting episode during the 24 h immediately after the end of operation, shown as Kaplan-Meier curves. *$P = 0.0002$, Granisetron 1 mg vs placebo; †$P = 0.0010$, granisetron 3 mg vs placebo; log-rank test

action of granisetron and previous adverse effects observed with this agent.

Discussion

In the current study, the no-vomiting rates during the 24-h period after surgery were significantly higher in the granisetron-treated patients: 83.7% in the granisetron 1-mg group and 78.8% in the 3-mg group, compared with 57.9% in the placebo group. Because the efficacy of the granisetron 1-mg dose was almost equivalent to that of the 3-mg dose, the recommended dose of granisetron injection for the prophylactic control of PONV is considered to be 1 mg.

PONV is one of the most common complications occurring after anesthesia and surgery, and causes great distress to patients, with the possibility of further medical problems occurring, such as dehydration and

Table 3. The number (percentage) of patients experiencing episodes of vomiting during the 24-h treatment period with granisetron or placebo

	Number of patients (%)		
Number of vomiting episodes	Placebo ($n = 107$)	Granisetron 1 mg ($n = 104$)	Granisetron 3 mg ($n = 104$)
0	62 (57.9)	87 (83.7)	82 (78.8)
1	18 (16.8)	7 (6.73)	11 (10.6)
2	10 (9.35)	4 (3.85)	5 (4.81)
3	10 (9.35)	1 (0.96)	3 (2.88)
4	1 (0.93)	0 (0)	1 (0.96)
5	2 (1.87)	2 (1.92)	1 (0.96)
6	0 (0)	3 (2.88)	0 (0)
≥7	4 (3.74)	0 (0)	1 (0.96)

Table 4. Severity of nausea experienced in the placebo, granisetron 1-mg, and granisetron 3-mg groups

	Severity of nausea			
Treatment group	None (%)	Mild (%)	Severe (%)	*P* Value
Placebo ($n = 107$)	35 (32.7)	45 (42.1)	27 (25.2)	
Granisetron 1 mg ($n = 104$)	64 (61.5)	28 (26.9)	12 (11.5)	0.00003*
Granisetron 3 mg ($n = 104$)	57 (54.8)	31 (29.8)	16 (15.4)	0.002*

* $P < 0.025$ vs placebo, Wilcoxon two-sample test

Table 5. Number of patients with the most frequently reported (occurring in ≥4 patients) adverse events (population 2)

Adverse event	Total ($n = 341$)	Placebo ($n = 117$)	Granisetron 1 mg ($n = 110$)	Granisetron 3 mg ($n = 114$)
Fever	23	7	9	7
Headache	15	7	6	2
Pruritis	6	2	2	2
Dizziness	4	1	1	2

electrolyte imbalance [6]. In recent years, outpatient surgical procedures have become commonplace in efforts to reduce the psychological burden on patients and their families and also to reduce medical expenditure [16,17]. Control of PONV in the outpatient setting is particularly important, as patients who experience nausea and vomiting are likely to be prevented from leaving on the same day. Furthermore, patients may experience symptoms after discharge, which may lead to increased contact with the physician, an emergency room visit, or even re-admission to hospital. Consequently, a safe and effective antiemetic agent that could reduce the occurrence of PONV would be beneficial both to patients and healthcare professionals.

Although the mechanism behind the initiation of PONV is complex, it is thought to be due in part to the release of serotonin in the gastrointestinal tract following stimulation by the anesthetic agent. Such serotonin release results in the stimulation of 5-HT_3 receptors located on vagal afferent neurons that, in turn, stimulate the vomiting center in the brain. This hypothesis is supported by the fact that 5-HT_3-receptor antagonists are highly effective antiemetic agents [18,19]. Involvement of the gastrointestinal tract is further supported by the fact that patients' risk of experiencing PONV is higher following lower abdominal surgery [1].

The results of this investigation support previous studies which have examined the prophylactic use of granisetron for postoperative emesis in patients undergoing surgical procedures [8,9,13,20]. Wilson et al. [13] have investigated the prophylactic efficacy of granisetron for the prevention of PONV in patients undergoing gynecologic laparotomy, vaginal hysterectomy, or cholecystectomy. These authors reported that the rate of patients experiencing no vomiting within the 24-h period after surgery was 33.8% in the placebo group, compared with 44.7% in the granisetron 0.1-mg group, 63.4% in the 1-mg group, and 61.7% in the 3-mg group ($P < 0.001$ for the 1-mg and 3-mg doses compared with placebo). Granisetron was well tolerated, with no significant difference noted in the occurrence of adverse events between treatment groups. A further study has investigated the efficacy of granisetron in established PONV in patients who had experienced severe nausea or vomiting within 4 h after surgery [20]. In that study, intravenous granisetron, at all doses investigated, was significantly more effective than placebo in controlling vomiting; 38%, 46%, and 49% of patients receiving granisetron (0.1 mg, 1 mg, and 3 mg, respectively) experienced no vomiting in the first 24 h after drug administration compared with 20% of those receiving placebo.

Some studies have also investigated the clinical efficacy of a 5-HT_3-receptor antagonist plus concomitant corticosteroid administration in the postoperative setting, with results suggesting that the combination therapy may enhance antiemetic prophylaxis [8,9,21]. While significantly more patients often benefit from combination therapy (for example, in 120 patients undergoing laparascopic cholecystectomy, 83% of patients treated with granisetron 40 μg/kg were free of PONV during 24 h compared with 98% treated with granisetron supplemented with dexamethasone 8 mg [9]), patient preference suggests that there is no difference between multimodal PONV management *vs* routine monotherapy antiemetic prophylaxis [21]. In addition, multiple therapies increase the risk of drug-drug interactions, especially in patients already taking multiple medications for co-morbid conditions [22]. Furthermore, there are cost considerations with multiple therapies.

Although the no-vomiting rates were higher in the present study than previously reported [13,20], this difference is likely to be due to variations in data recording. In previous studies, patients who had received another antiemetic agent before the onset of vomiting were recorded as having experienced a vomiting episode, whereas in the present study, such patients were recorded as patients with no vomiting episodes.

Results from a recent study, which performed a meta-analysis of granisetron in the prevention of PONV, suggested that the total and dose-response effects may be significantly affected by the dominant study center. The authors suggested that, if the data from the dominant center should differ significantly from other data, that these data should not be included in the final analysis [23]. However, in the present study, patients were allocated to intravenous granisetron 3 mg, granisetron 1 mg, or placebo by central randomization and minimization by computer.

No differences in the incidence of adverse reactions were noted among the three treatment groups, and none of the adverse events were specific to granisetron. Furthermore, adverse events in the granisetron groups did not appear to be dose-dependent. One serious adverse event, ventricular fibrillation (cardiac arrest), was noted in one patient in the granisetron 1-mg group. During the 24-h period prior to commencement of the study, this patient had received no antiemetic agent known to exhibit serious cardiotoxic effects and influence the patient's outcome [24,25]. The event was judged as unlikely to be related to the administration of granisetron, because cases of ventricular fibrillation have been reported in 944 patients who have received the agent in previous clinical studies of PONV, nor have any such cases been reported in the postmarketing surveillance of more than 20000 granisetron-treated patients. Furthermore, the cardiac safety of granisetron has been demonstrated in studies involving both healthy volunteers and cancer patients [24,26–31].

Granisetron and other 5-HT_3-receptor antagonists are expensive compared with other antiemetic agents such as droperidol and metoclopramide. Consequently, PONV medication guidelines have recommended that 5-HT_3-receptor antagonists be used prophylactically only in patients with a high risk of PONV (≥60%) [32]. However, the use of droperidol and metoclopramide can be associated with undesirable adverse effects, such as excessive sedation and extrapyramidal symptoms [1]. Furthermore, a number of studies have demonstrated that granisetron has superior efficacy to both droperidol and metoclopramide in the control of PONV [33–36]. Consequently, the choice of antiemetic in the postoperative setting should not be limited by cost alone but should also consider both the drug efficacy and tolerability.

In conclusion, intravenous granisetron is more effective than placebo for preventing PONV in patients undergoing gynecologic surgery or cholecystectomy. This study recommends granisetron, 1 mg, as effective prophylaxis.

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Appendix

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