A Randomized, Double-Blind Comparison of Granisetron Alone and Combined with Dexamethasone for Post-Laparoscopic Cholecystectomy Emetic Symptoms

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ABSTRACT

Background: Granisetron hydrochloride, a selective serotonin receptor antagonist, has been used to treat established postoperative nausea and vomiting (PONV). Dexamethasone has been shown to reduce the incidence of chemotherapy-induced emesis when added to an antiemetic regimen.

Objective: The aim of this study was to examine the differences in efficacy and tolerability between the combination of granisetron plus dexamethasone and granisetron alone for the treatment of PONV.

Methods: This study was a randomized, double-blind trial conducted at Toride Kyodo General Hospital (Toride, Ibaraki, Japan). Men and women aged 25 to 65 years and experiencing emetic symptoms after laparoscopic cholecystectomy were eligible for the study. Patients received IV therapy with either granisetron 40 µg/kg alone or with dexamethasone 8 mg. Patients were observed for 24 hours. Emetic episodes and the need for a rescue antiemetic were recorded by nursing staff, who were blinded to treatment assignment.

Results: One hundred patients (63 women, 37 men; mean [SD] age, 47 [10] years; range, 25–65 years) were enrolled; 50 patients were randomized to each treatment group. No significant differences in baseline demographic or clinical characteristics were observed between the groups. Complete control of established PONV, defined as no emetic symptoms and no need for another rescue antiemetic medication, occurred in significantly more patients who received the combination (49/50 [98%]) than in those who received granisetron alone (41/50 [82%]) ($P = 0.008$). No clinically important adverse effects due to the study drugs were observed in either group.

Conclusion: In this study population of patients experiencing post-cholecystectomy emesis, the combination of granisetron plus dexamethasone was more efficacious than granisetron alone for the treatment of PONV. Tolerability

between the 2 treatments was similar. (*Curr Ther Res Clin Exp.* 2003;64:514–521)
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Key words: nausea, vomiting, emesis, antiemetics, granisetron, dexamethasone, laparoscopic cholecystectomy.

INTRODUCTION

Granisetron hydrochloride, a selective serotonin (5-HT₃) receptor antagonist (SSRA), has been shown to be effective for the treatment of emesis in patients receiving cytotoxic drugs.¹ Granisetron also has been shown to be effective for the prevention of postoperative nausea and vomiting (PONV) in patients undergoing laparoscopic cholecystectomy,² who have a relatively high incidence of PONV.^{3,4} We recently demonstrated that granisetron reduces the incidence of established PONV after laparoscopic cholecystectomy and is a better antiemetic than the traditional ones, droperidol and metoclopramide, for this type of treatment.⁵ However, granisetron alone cannot entirely control established PONV following laparoscopic cholecystectomy.

Beginning with the report by Aapro and Alberts,⁶ dexamethasone, a synthetic glucocorticoid, was shown to be effective in reducing the incidence of emesis in patients undergoing chemotherapy.⁷ The long-term administration of dexamethasone 8 to 10 mg may cause undesirable adverse effects (AEs), such as an increased risk for infection, impaired glucose tolerance, delayed wound healing, superficial ulceration of gastric mucosa, and adrenal suppression.⁸ However, these AEs were not found after a single dose of dexamethasone 8 to 10 mg.⁹ Dexamethasone 8 mg has been reported to decrease chemotherapy-induced emesis when added to an antiemetic regimen.¹⁰

This study was designed to investigate the differences in efficacy and tolerability between the combination of granisetron plus dexamethasone and granisetron alone for the treatment of PONV in patients undergoing laparoscopic cholecystectomy.

PATIENTS AND METHODS

Before randomization, a MEDLINE search was conducted for articles published from January 1990 to December 2001 using the search terms *complications, nausea, vomiting, treatment, antiemetics, granisetron, dexamethasone, surgery, laparoscopy, and cholecystectomy*. This search was performed to identify the literature assessing the efficacy of the combination of granisetron plus dexamethasone for the treatment of established post-cholecystectomy PONV. No such studies were found.

This study was approved by the ethics committee at Toride Kyodo General Hospital (Toride, Ibaraki, Japan), and verbal informed consent was obtained from each patient.

Men and women aged 25 to 65 years who met the criteria for American Society of Anesthesiologists¹¹ physical status I (no organic, physiologic, biochemical, or psychiatric disturbance) and who were experiencing nausea lasting >10 minutes and/or emesis (vomiting, retching) within 3 hours after recovery from general anesthesia for laparoscopic cholecystectomy were eligible for the study. Patients who had gastrointestinal disease, those with a history of motion sickness and/or PONV, and those who had received any antiemetic medication within 24 hours before surgery were excluded from the study. Women who were pregnant, possibly pregnant, or breastfeeding also were excluded.

To maintain the integrity of our results, none of the patients received preanesthetic medication (eg, hydroxyzine). Anesthesia was induced with thiopentone 5 mg/kg IV and fentanyl 2 µg/kg IV. Vecuronium 0.2 mg/kg IV was used to facilitate tracheal intubation, after which anesthesia was maintained with isoflurane 1.0% to 3.0% and nitrous oxide 66% in oxygen, with controlled ventilation adjusted to maintain end-tidal carbon dioxide concentration at 35 to 40 mm Hg using an anesthetic/respiratory gas analyzer (Capnomac Ultima™, Datex-Ohmeda, Helsinki, Finland). A nasogastric tube was inserted, and suction was applied to empty the stomach of air and other contents. At the start of the procedure, all patients were given cefmetazole sodium 1 g IV. Before tracheal extubation, the nasogastric tube was again suctioned and then removed. Neuromuscular block was achieved with vecuronium and antagonized by atropine 0.02 mg/kg IV and neostigmine 0.04 mg/kg IV at the end of surgery. The trachea was extubated while the patient was awake. Rectal temperature was monitored and maintained at 36.5°C to 37.0°C using a warming pad. Postoperatively, all patients were hospitalized for 2 days. Patients were not allowed to have solid food within the first 24 hours after surgery. Clear liquids were not permitted until 6 hours after surgery. For postoperative analgesia, indomethacin 50 mg PR (for moderate pain) or pentazocine 15 mg IM (for severe pain) was given.

Patients who experienced nausea lasting >10 minutes and/or emesis during the first 3 hours in the postanesthetic care unit were assigned, using a computer-generated list of random numbers, to receive IV granisetron 40 µg/kg alone or combined with dexamethasone 8 mg. Immediately after randomization, the study drug was administered to patients by a surgeon. Identical syringes containing each drug (granisetron 40 µg/kg + dexamethasone 8 mg or granisetron 40 µg/kg) were prepared by personnel not involved in this study, according to the list of random numbers. If the volume to be administered was <5 mL, preservative-free saline solution was added to achieve a total volume of 5 mL. The doses of granisetron and dexamethasone chosen in the current study were used in previous studies by us⁵ and Aapro et al.¹⁰

Patients were observed for 24 hours. At various intervals according to typical postoperative routine, the nursing staff (blinded to treatment assignment) asked the patients whether retching or vomiting had occurred and whether they felt nauseated, with only 2 possible answers (*yes* and *no*). All episodes of emetic symptoms (nausea, retching, vomiting) were recorded by the nurses. *Nausea*

was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit; *retching* was defined as the labored, spasmodic, rhythmic contraction of the respiratory muscles, including the diaphragm, chest wall, and abdominal wall muscles, without the expulsion of gastric contents; *vomiting* was defined as the forceful expulsion of gastric contents from the mouth.¹² *Complete control of established PONV* was defined as no emetic symptoms and no need for another rescue antiemetic medication. If ≥ 2 episodes of emesis occurred within a 24-hour period after study drug administration, another rescue antiemetic (eg, domperidone rectally) was given. The details of any other AEs were recorded by nurses throughout the study.

Statistical Analysis

Patient demographic characteristics were compared between the treatment groups and assessed using the 2-sample *t* test and chi-square test. The comparisons of efficacy and tolerability were performed using the Fisher exact test. $P < 0.05$ was considered significant. Statistical analysis was performed using StatView® version 5.0 (SAS Institute, Inc., Cary, North Carolina). Sample size calculation focused on testing whether a difference in complete control of established PONV (the primary end point) of 15% was exceeded at $\alpha = 0.05$ with a power ($1-\beta$) of 80% (ie, power analysis). A total number of 100 patients (50 per group) would be sufficient.

RESULTS

One hundred ten patients (70 women, 40 men) were screened for the study. Of these, 7 women and 3 men were excluded from the study based on the exclusion criteria (ie, gastrointestinal disease [3 women], a history of motion sickness and/or PONV [2 women, 2 men], antiemetic medication within 24 hours before surgery [2 women, 1 man]). One hundred patients (63 women, 37 men; mean [SD] age, 47 [10] years; range, 25–65 years) were enrolled in this clinical trial. The treatment groups were comparable in terms of baseline demographic and clinical characteristics (Table I).

Efficacy

Complete control of established PONV for 24 hours after study drug administration was achieved in significantly more patients who received granisetron plus dexamethasone (49/50 [98%]) than in those who received granisetron alone (41/50 [82.0]) ($P = 0.008$). None of the patients from either group required rescue medication (Table II).

Tolerability

Overall, 6 patients (12%) in the granisetron plus dexamethasone group and 6 patients (12%) in the granisetron monotherapy group experienced AEs. The most common AE was headache (4 patients [8%] in the granisetron plus

Table I. Baseline demographic and clinical characteristics of study patients (N = 100).*

Characteristic	Granisetron + Dexamethasone (n = 50)	Granisetron (n = 50)
Age, y		
Mean (SD)	45 (8)	47 (9)
Range	25–65	26–63
Sex, no. (%)		
Women	31 (62)	32 (64)
Men	19 (38)	18 (36)
Height, cm		
Mean (SD)	156 (11)	156 (12)
Range	144–178	142–179
Body weight, kg		
Mean (SD)	53 (12)	55 (11)
Range	42–73	46–72
Surgery duration, mean (SD), min	86 (30)	85 (33)
Anesthesia duration, mean (SD), min	111 (32)	108 (34)
No. (%) of patients using analgesics postoperatively		
Indomethacin	31 (62)	32 (64)
Pentazocine	5 (10)	5 (10)

*No significant between-group differences were found.

Table II. Treatment efficacy. (Values are expressed as no. [%] of patients.)

Parameter	Granisetron + Dexamethasone (n = 50)	Granisetron (n = 50)
Complete control of established PONV	49 (98)*	41 (82)
Nausea	1 (2)	4 (8)
Vomiting	1 (2)	3 (6)
Retching	0 (0)	2 (4)
Rescue antiemetic	0 (0)	0 (0)

PONV = postoperative nausea and vomiting.

*P = 0.008 versus granisetron group.

dexamethasone group and 3 [6%] in the granisetron monotherapy group), which was considered treatment related but not clinically severe and was not treated in any patient. No difference in the incidence of AEs was observed between the groups (Table III). Other dexamethasone-related AEs, such as infection, were not observed in any of the groups.

DISCUSSION

Patients undergoing laparoscopic cholecystectomy have a relatively high incidence of PONV.^{3,4} This problem is multifactorial in origin, including patient demographic characteristics, the nature of the underlying disease, types of surgery, anesthetic regimen, and postoperative care.¹² The main patient-related factors are age, sex, obesity, and a history of motion sickness and/or PONV. In this study, however, the treatment groups were comparable in terms of patient demographic characteristics, type of surgery, anesthetic drugs administered, and analgesics used postoperatively. Patients with a history of motion sickness and/or PONV were excluded from the study because they had a relatively high risk for PONV. Therefore, the difference between the treatment groups in the rate at which complete control of PONV was achieved can be attributed to the study drugs.

Granisetron is effective for the treatment of emesis in patients receiving cytotoxic drugs.¹ We recently demonstrated that granisetron 40 µg/kg was effective for reducing the incidence of established PONV in patients undergoing laparoscopic cholecystectomy.⁵ Dexamethasone 8 mg has been shown to decrease chemotherapy-induced emesis when added to an antiemetic regimen.¹⁰ In the current study, therefore, the same dose (therapeutic) of dexamethasone was added to granisetron 40 µg/kg.

In the current study, complete control of established PONV within a 24-hour period after study drug administration was achieved significantly ($P = 0.008$) more often in patients who had received granisetron plus dexamethasone than

Table III. Number (%) of patients experiencing ≥ 1 adverse effect.*†

Adverse Effect	Granisetron + Dexamethasone (n = 50)	Granisetron (n = 50)
Headache‡	4 (8)	3 (6)
Dizziness	1 (2)	1 (2)
Constipation	1 (2)	1 (2)
Muscle pain	0 (0)	1 (2)

*No significant between-group differences were found.

†None of the AEs were serious.

‡This AE was treatment related.

in those who received granisetron alone. This suggests that the combination of granisetron plus dexamethasone is more effective than granisetron alone for the control of established PONV in patients undergoing laparoscopic cholecystectomy. Although the exact mechanism by which granisetron plus dexamethasone increases the incidence of complete control of established PONV is not known, our results suggest that dexamethasone may enhance the antiemetic efficacy of granisetron. This is based on the suggestion that granisetron may act on sites containing serotonin receptors with demonstrated antiemetic effect¹³ and that dexamethasone may inhibit stimulation of serotonin receptors.¹⁰

Granisetron does not induce sedation, dysphoria, or extrapyramidal symptoms associated with non-SSRAs such as droperidol and metoclopramide.⁷ In an earlier study,⁵ we found that granisetron was relatively free of AEs for the control of established PONV after laparoscopic cholecystectomy. The most common AE, headache, which was found to be treatment related in this study, was not serious in any of the patients, and no significant difference in the incidence of AEs was found between the 2 groups. Thus, dexamethasone was not associated with an increase in the occurrence of AEs when added to granisetron.

In Japan, granisetron (cost, US \$102.00 for 3 mg) is much more expensive (57%–170%) than other commonly used and well-established antiemetics (eg, droperidol [US \$1.80 for 1.25 mg] and metoclopramide [US \$0.60 for 10 mg]). However, the use of these non-SSRAs has been limited because they cause excessive sedation and/or extrapyramidal symptoms.¹² The US Food and Drug Administration issued a warning about the risk of dysrhythmogenic effects such as prolonged QT interval with droperidol.¹⁴ The combination of granisetron (US \$102.00 for 3 mg) and dexamethasone (US \$5.30 for 8 mg) would increase the cost of antiemetic therapy. In the current study, however, the combination was more effective than granisetron alone in increasing the frequency of achieving complete control of established PONV within a 24-hour period after study drug administration. Therefore, the decision about antiemetics should not be limited to drug costs but also should include consideration of the outcome for the patients. The incremental cost of granisetron plus dexamethasone may be justified by its antiemetic efficacy.

CONCLUSION

In this study population of patients experiencing post-cholecystectomy emesis, the combination of granisetron plus dexamethasone was more efficacious than granisetron alone for the treatment of established PONV. Tolerability was similar in the 2 groups.

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