

A Randomized, Double-Blind Study of Granisetron Plus Dexamethasone Versus Ondansetron Plus Dexamethasone to Prevent Postoperative Nausea and Vomiting in Patients Undergoing Abdominal Hysterectomy

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In this randomized, double-blind study, we evaluated whether small-dose granisetron (0.1 mg) plus dexamethasone 8 mg (G+D) was as effective as ondansetron 4 mg plus dexamethasone 8 mg (O+D) for preventing vomiting during the 0 to 2 h after tracheal extubation in patients undergoing abdominal hysterectomy requiring general anesthesia. Dexamethasone (D) was administered at induction of anesthesia, and granisetron (G) or ondansetron (O) was given approximately 15 min before tracheal extubation. Data on postoperative nausea and vomiting were collected at 0, 2, 6, and 24 h. For the primary efficacy endpoint, most patients in each group had no vomiting in the 0- to 2-h interval (82/87

[94%] for G+D versus 86/89 [97%] for O+D). Effectiveness of G+D was demonstrated versus O+D. Treatment groups were similar with regard to moderate or severe nausea, complete response, rescue medication use, and total control over 24 h. A descriptive assessment of adverse events showed that both combinations were well tolerated with infrequent and similar incidences of adverse events. The combination of small-dose G administered just before tracheal extubation plus D given at induction of anesthesia is an effective alternative to O+D in preventing vomiting during the 0- to 2-h interval after tracheal extubation.

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When therapeutic intervention to prevent postoperative nausea and vomiting (PONV) is warranted, selective serotonin type 3 (5-HT₃) receptor antagonists are considered a first-line therapy because of their efficacy and safety compared with other drugs (1). The 5-HT₃ receptor antagonists currently licensed in the United States for use in PONV prophylaxis include dolasetron, granisetron (G), and ondansetron (O). For patients at high risk of PONV, use of a 5-HT₃ receptor antagonist in combination with another antiemetic drug may be justified to further reduce the likelihood of PONV (1-3).

Although a variety of drugs may have value in combination therapy with 5-HT₃ receptor antagonists (2), droperidol and dexamethasone (D) have been the most extensively investigated. However, the United

States Food and Drug Administration (FDA)'s "black box" warning for droperidol concerning rare, potentially fatal cardiac adverse events has raised concerns about its use as a first-line drug (2). In contrast, a single bolus dose of D for PONV prophylaxis has not been associated with serious side effects, although this conclusion is based on limited data (4,5). With regard to the effectiveness of D, a systematic review of trials of D monotherapy found that the 8-mg dose showed both early and late antiemetic efficacy (4). Combined data from 3 trials conducted in adults, for example, demonstrated that late vomiting occurred in 25% of 77 patients treated with D 8 mg compared with 48% of the 77 patients who received placebo (relative benefit, 1.27; $P < 0.01$). Given the safety and effectiveness of both 5-HT₃ receptor antagonists and D, the combination of these 2 classes of drugs may be an attractive choice for prophylaxis in patients at high risk for PONV (2,4).

Studies evaluating combination therapy in PONV prophylaxis generally have used conventional doses of the 5-HT₃ receptor antagonists and D, but one study

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suggests that smaller doses of the 5-HT₃ receptor antagonists may be effective. The FDA-labeled dose of G recommended for PONV prophylaxis is 1 mg administered before induction of anesthesia or at the end of anesthesia (6), but Mikawa et al. (7) have demonstrated that doses of G in excess of approximately 0.3 mg did not offer additional benefit. The results of a pilot dose-ranging study suggested a trend of improved efficacy compared with placebo with G doses as small as 0.1 mg when administered at the end of surgery in preventing PONV during the 0- to 6-h interval after abdominal hysterectomy (8). Thus, the combination of small doses of G and conventional doses of D may effectively prevent PONV.

Based largely on a study that found repeat doses of O after failure of initial therapy to be ineffective (9), it has been suggested that patients failing initial therapy with a 5-HT₃ receptor antagonist within the first 6 postoperative hours should not receive additional 5-HT₃ receptor antagonist therapy (2). However, studies in patients with chemotherapy-induced nausea and vomiting found that some of those who failed initial therapy with O benefited from subsequent G therapy (10,11). These results have yet to be investigated in patients with PONV.

In the present study, we evaluated the efficacy of small-dose G in combination with 8 mg of D in preventing vomiting during the 0 to 2 h after tracheal extubation in patients undergoing abdominal hysterectomy requiring general anesthesia. The primary efficacy analysis was a comparison of effectiveness between G 0.1 mg plus D 8 mg and O 4 mg plus D 8 mg, using the FDA-labeled prophylaxis dose of O (12).

Methods

For this multicenter, prospective, randomized, double-blind, parallel-group, effectiveness study, we obtained approval from the IRB at each participating center. Patients provided written, informed consent before participation.

Female patients ≥ 18 yr of age, with an ASA physical status of I-III, were eligible if they were scheduled to undergo abdominal hysterectomy requiring general anesthesia. Patients were excluded if they 1) had known hypersensitivity or contraindication to study medications, 2) had chronic nausea and vomiting or experienced retching, vomiting, or moderate or severe nausea in the 24 h before anesthesia, 3) had received an antiemetic drug or a drug with antiemetic properties during the 24 h before anesthesia, 4) had a body mass index ≥ 36 , 5) were pregnant or breast feeding, or 6) had a condition requiring chronic opioid use.

Patients were stratified at randomization by history of motion sickness and PONV and by current smoking status (within the prior 30 days), and were randomly

assigned to receive either G 0.1 mg plus D 8 mg (G+D) or O 4 mg plus D 8 mg (O+D). The randomization lists were computer-generated, centrally determined, and the randomization numbers were allocated sequentially in the order in which patients were enrolled. Study medications were prepared by the site pharmacist, who was not involved in any other part of the study, and presented to blinded investigators as identical 2-mL filled syringes.

For eligible patients, demographic information was collected and a physical examination was performed. A standardized anesthesia regimen was followed. Pre-medication, if desired, was with IV midazolam 1-2 mg. General anesthesia was induced with IV propofol (up to 2.5 mg/kg), with or without lidocaine (up to 50 mg IV), and was maintained with isoflurane titrated between 0.6% and 2.5% and nitrous oxide $\geq 50\%$. Neuromuscular blockers were administered to facilitate endotracheal intubation and intraoperative muscle relaxation. Fentanyl at doses of up to $6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ IV was administered. D was given immediately after induction of anesthesia in both treatment groups. Neuromuscular blockade was reversed with IV neostigmine (up to 0.07 mg/kg) and glycopyrrolate (up to 0.02 mg/kg). G or O was administered approximately 15 min before tracheal extubation (defined as end of surgery). Morphine (1-10 mg IV or IM) or fentanyl (up to 50 μg IV) was permitted as needed for the management of postoperative pain.

The time of each vomiting episode and the time and intensity of each nausea episode were recorded immediately before anesthesia and 2, 6, and 24 h after tracheal extubation. An episode of vomiting was defined as either vomiting (expulsion of stomach contents) or retching (an involuntary attempt to vomit but not productive of stomach contents). Vomiting and/or retching episodes separated by < 5 min were recorded as a single episode. The intensity of each nausea episode was graded as mild (discomfort noticed but no disruption of anticipated normal activity), moderate (discomfort sufficient to reduce or affect anticipated normal activity), or severe (inability to perform anticipated normal daily activity). Rescue medication could be administered to any patient who experienced an episode of moderate or severe nausea, an episode of vomiting, or who requested rescue medication. The initial rescue medication was G 0.1 mg administered as a single IV push. Nausea and vomiting assessments were made 30 min after rescue medication administration, and response was defined as improvement or resolution of PONV symptoms. Subsequent PONV symptoms could be treated with an alternative rescue medication at the discretion of the investigator. If rescue medication was used, both the time of administration and type of medication were recorded. Adverse events were evaluated and recorded by the investigator during the entire observation period.

Table 1. Patient Demographic and Baseline Characteristics (Efficacy Population)

Characteristic	Granisetron 0.1 mg + dexamethasone 8 mg (<i>n</i> = 87)	Ondansetron 4 mg + dexamethasone 8 mg (<i>n</i> = 89)
Age (yr), mean ± SD	48 ± 12	48 ± 10
Race, <i>n</i> (%)		
Caucasian	56 (64)	54 (61)
Black	13 (15)	22 (25)
Hispanic	15 (17)	11 (12)
Other	3 (3)	2 (2)
Weight (kg), mean ± SD	70 ± 14	74 ± 14
Smokers, <i>n</i> (%)	14 (16)	19 (21)
Alcohol consumers, <i>n</i> (%)	32 (37)	37 (42)
History of motion sickness, <i>n</i> (%)	24 (28)	22 (25)
History of PONV, <i>n</i> (%)	24 (28)	23 (26)

PONV = postoperative nausea and vomiting, SD = standard deviation.

The primary efficacy end-point was the proportion of patients with no vomiting during the 0 to 2 h after tracheal extubation. This time period was chosen because it reflects the typical time spent by a patient in a postanesthesia care unit and because comparative data concerning the antiemetic efficacy of O+D were available for this interval (13). Effectiveness was defined when the lower bound of the two-sided 95% confidence interval, using the normal distribution approximation, for the proportion difference in the primary efficacy end-point (G+D - O+D) crossed -15%. This threshold has been used in previous research (14,15) and was chosen to be clinically relevant because of the wide variability in the rates of emesis which is based on multiple patient and procedural factors.

Secondary efficacy end-points included proportions of patients in the 0-6 and 0-24 h intervals with no vomiting, as well as proportions of patients in the 0-2, 0-6, and 0-24 h intervals after tracheal extubation: 1) with no moderate or severe nausea, 2) with complete response (no moderate or severe nausea and no vomiting), 3) using rescue medication, and 4) having total control (no moderate or severe nausea, no vomiting, and no rescue medication use). Additional secondary efficacy variables were times to first vomiting episode, first moderate or severe nausea episode, use of first rescue medication within 24 h, and proportions of patients responding to the initial dose of G as rescue medication.

The proportion difference (G+D - O+D) and a 2-sided 95% confidence interval (CI), using the normal distribution approximation, were calculated and results described for all secondary efficacy end-points, with no emphasis on comparing the lower bound of the 2-sided 95% CI with the margin of -15%.

Time-to-event secondary efficacy variables were analyzed using survival analysis. A Cox proportional hazard regression analysis was conducted with the study center and stratification variables as covariates;

patients not experiencing the event were included as censored observations, and the estimated hazard ratio and 95% CIs were calculated to measure treatment differences.

Adverse events were summarized by body system, treatment group, severity (serious or nonserious), intensity (mild, moderate, severe, or life-threatening), and relationship to study drug. The efficacy evaluable population included all randomized patients receiving at least 1 dose of either G or O and having 2-h nausea and vomiting assessments. The safety population included all randomized patients receiving at least one dose of study medication (either G, O, or D) and having at least one postbaseline safety measurement.

Based on a previous study (13), >90% of patients in both treatment groups were expected to have no vomiting in the 0- to 2-h interval. Recruitment of 85 evaluable patients per treatment group was planned to provide a 90% power to exclude the possibility of a treatment difference of 15% or more in proportions of patients with no vomiting during the 0- to 2-h interval for a 1-sided test at a 0.025 level of significance.

Results

In all, 210 patients were enrolled (G+D, 101; O+D, 109) from October 30, 2003 through April 27, 2004 at 19 centers in the United States. Of the 210 enrolled patients, 176 patients (87 G+D, 89 O+D) were considered evaluable for efficacy. The 34 patients excluded from efficacy analyses either did not receive at least 1 dose of study medication (G+D, *n* = 6; O+D, *n* = 10), received D but not either G or O (G+D, *n* = 6; O+D, *n* = 10), or had no 2-h nausea/vomiting assessment (G+D, *n* = 2); no patient was excluded for reasons related to nausea or vomiting.

Treatment groups were generally similar with regard to baseline characteristics (Table 1). Diagnoses for surgery and types of surgery were comparable

Table 2. Surgery Characteristics

Elapsed time	Granisetron 0.1 mg + dexamethasone 8 mg (<i>n</i> = 87)	Ondansetron 4 mg + dexamethasone 8 mg (<i>n</i> = 89)
Induction to administration of dexamethasone (min)	6 ± 6	5 ± 6
Administration of dexamethasone to administration of granisetron or ondansetron (min)	110 ± 65	112 ± 51
Administration of granisetron or ondansetron to time of tracheal extubation (min)	21 ± 9	23 ± 11
Tracheal extubation to first oral intake postsurgery (h)	16 ± 11	16 ± 10
Tracheal extubation to discharge from PACU (h)	3 ± 3	4 ± 6
Maintenance of anesthesia (min)	123 ± 65	127 ± 50

Data are mean ± SD.

PACU = postanesthesia care unit; SD = standard deviation.

across groups. Eight patients treated with G+D and 2 treated with O+D experienced mild nausea within 24 h before anesthesia. Times from administration of D to administration of G or O and times from administration of G or O to tracheal extubation were similar between treatment groups (Table 2).

For the primary efficacy end-point, 82 of 87 patients (94%) in the G+D group and 86 of 89 (97%) of those receiving O+D had no vomiting in the 0- to 2-h interval. The treatment difference (G+D - O+D) was -2.4% with a 2-sided 95% CI of -8.5% to 3.8%. Because the lower bound of the 2-sided 95% CI (-8.5%) was more than the preset threshold of -15%, it was concluded that G 0.1 mg plus D 8 mg was not inferior to O 4 mg plus D 8 mg in preventing vomiting during the 0- to 2-h interval after surgery.

Fewer patients had no vomiting in the 0-6 and 0-24 h intervals, but patients with no vomiting were similar between treatments at both 0-6 and 0-24 h (Table 3). The mean time to the first vomiting episode was longer for patients receiving O+D than G+D (19.6 versus 10.5 h, respectively; hazard ratio 1.34 [95% CI: 0.6, 2.9]) primarily because the first vomiting episode for 2 patients in the O+D group occurred >20 h after tracheal extubation. However, the hazard ratio and 95% CI indicated that times to first vomiting episodes were similar between treatments.

Patients with no moderate or severe nausea episodes and having complete responses were similar between treatments at all time intervals (Table 3). Patients meeting these secondary efficacy outcomes decreased over time, and maximum between treatment differences was ≤7% at all time intervals. Mean times to first moderate or severe nausea episodes were similar between treatments (hazard ratio 1.09 [95% CI: 0.7, 1.6]).

A comparable number of patients in both groups used rescue medication (Table 3). Additionally, mean times to first rescue medication use were also similar (hazard ratio 1.31 [95% CI: 0.9, 2.0]). First use of rescue medication decreased at a similar rate in both groups

in the first 10 h after tracheal extubation, and few patients used rescue medication for the first time after 10 h (2 in the G+D group, 4 receiving O+D). Total control was achieved by a similar number of patients in each group at each time interval (Table 3).

Forty-eight patients treated with G+D and 40 treated with O+D received G as rescue medication. One patient receiving O+D received prochlorperazine instead of G as first rescue medication and was excluded from these analyses. (Note that this patient was included in overall analyses of rescue medication use [Table 3].) At 30 min postdose, nausea and vomiting symptoms had either resolved or improved in 38 of 48 patients (79%) who initially received G+D and in 31 of 40 patients (78%) treated with O+D. In all, 34 of 87 patients (39%) initially receiving G+D and 28 of 89 (31%) O+D-treated patients used more than one rescue medication in the 24 h after tracheal extubation.

The 194 patients receiving at least 1 dose of study medication were included in safety analyses (G+D, *n* = 95; O+D, *n* = 99). Both regimens were well tolerated, and the incidence of adverse events was similar between treatments (Table 4). Investigators judged most adverse events to be mild or moderate in intensity and unrelated to study medication. No deaths occurred during the study. Serious adverse events were reported by two patients receiving G+D (one patient each: abdominal pain, postoperative fever) and by four receiving O+D (two patients: pneumonia; one patient each: increased body temperature, pyrexia). All serious adverse events were judged to be unrelated to study medication. One patient in the G+D group withdrew as a result of an adverse event (vaginal hemorrhage) which was judged to be unrelated to study medication. No clinically meaningful mean changes in vital signs were noted. Adverse events occurring in ≥5% of patients in G+D versus O+D were: pruritus (4% and 8%, respectively), headache (2% and 8%, respectively), hypertension (2% and 6%, respectively), and bradycardia (5% and 0%, respectively).

Table 3. Summary of Efficacy Results for 0-2-, 0-6-, and 0-24-h Intervals: Secondary Outcomes (Efficacy Population)

Efficacy outcome	Granisetron 0.1 mg + dexamethasone 8 mg (n = 87)	Ondansetron 4.0 mg + dexamethasone 8 mg (n = 89)	Proportion difference ^a (95% CI)
No vomiting			
0-6 h	76 (87)	83 (93)	-5.9 (-14.6, 2.8)
0-24 h	72 (83)	77 (87)	-3.8 (-14.4, 6.9)
No moderate or severe nausea			
0-2 h	66 (76)	67 (75)	0.6 (-12.1, 13.3)
0-6 h	53 (61)	59 (66)	-5.4 (-19.6, 8.8)
0-24 h	42 (48)	45 (51)	-2.3 (-17.1, 12.5)
Complete response			
0-2 h	65 (75)	67 (75)	-0.6 (-13.4, 12.2)
0-6 h	51 (59)	59 (66)	-7.7 (-21.9, 6.6)
0-24 h	40 (46)	44 (49)	-3.5 (-18.2, 11.3)
Required rescue medication			
0-2 h	21 (24)	19 (21)	2.8 (-9.6, 15.2)
0-6 h	35 (40)	27 (30)	9.9 (-4.2, 23.9)
0-24 h	48 (55)	41 (46)	9.1 (-5.6, 23.8)
Total control			
0-2 h	64 (74)	66 (74)	-0.6 (-13.6, 12.4)
0-6 h	50 (57)	57 (64)	-6.6 (-21.0, 7.8)
0-24 h	38 (44)	42 (47)	-3.5 (-18.2, 11.2)

Data are number (%) unless otherwise noted.
CI = confidence interval, complete response = no moderate or severe nausea and no vomiting, total control = no moderate or severe nausea, no vomiting, and no rescue medication use.

^a Difference between groups in proportions of patients experiencing the outcome and 95% CI (normal distribution approximation).

Table 4. Summary of Adverse Events (Safety Population)

	Granisetron 0.1 mg + dexamethasone 8 mg (n = 95)	Ondansetron 4.0 mg + dexamethasone 8 mg (n = 99)
Total number (%) patients with ≥1 adverse event	35 (37)	41 (41)
Total number adverse events	54	65
Number (%) patients with drug-related adverse event	0	3 (3)
Number (%) patients with severe adverse event	9 (9)	8 (8)
Number patient deaths	0	0
Number patients with serious adverse events	2	4
Number patients withdrawing as a result of adverse events	1	0

Discussion

In this randomized, double-blind effectiveness study, G 0.1 mg plus D 8 mg was shown to be as effective as the current standard prophylactic antiemetic combination, O 4 mg plus D 8 mg, in patients experiencing no vomiting during 0-2 hours after tracheal extubation. As expected (13), >90% of patients in each treatment group had no vomiting during the 0- to 2-hour interval. Treatment groups also were comparable at all measurement times with regard to secondary efficacy outcomes, and both therapeutic regimens were well tolerated.

The potential advantages of combination therapy using drugs that act on different pathways in the emetic response include improved efficacy, extended duration of the antiemetic effect, the ability to combine drugs with greater antinausea versus greater antiemetic effects, and the possibility of using smaller

doses of individual drugs compared with monotherapies. A large trial of 6 PONV interventions found 26% reductions in relative risks of nausea and vomiting for each additional antiemetic administered (3). Optimal use of a multimodal approach depends on the individual and combined efficacy and safety of the drugs selected, the dosages used, and the timing of administration. Both G and O administered in combination with D are more effective than the individual drugs (2,4,16-20). With regard to timing, the 5-HT₃ receptor antagonists are most effective when administered at the end of surgery whereas D seems to be most effective when given before the induction of anesthesia (2). When a range of doses is equally effective, the smallest dose is recommended (2). Taking these published criteria for optimal use together, the results of the present study suggest that the combination of small-dose G administered at the end of surgery plus D given at induction is

an effective alternative to similarly administered O+D for patients requiring prevention of PONV.

A strength of our study was its randomized, double-blind, parallel-group, active-control design which allowed combination regimens to be compared directly. The design was limited, however, by the fact that combination therapies were not compared either with their individual components or with placebo. Previous research (16–20) has provided comparisons, but it would be informative to assess a range of therapeutic options in a single study. The study was designed to evaluate whether small-dose G plus D was noninferior to the standard dose of O in combination with D in preventing vomiting during the 0- to 2-hour period after tracheal extubation. This study was not designed to investigate superiority of either combination. In addition, although the preset equivalence difference of 15% for the primary efficacy outcome has been used previously (14,15), we also believe this range to be reasonable and clinically relevant because of the wide variability in the rates of emesis based on multiple patient and procedural factors such as differences in clinical practice, use of analgesia, patient mobilization, resumption of oral intake, and other factors. We also recognize that the impact on actual clinical practice of any difference chosen depends on the incidence, severity, duration, and cost of the outcome—factors that were unaccounted for in the present research. Although G has a longer half-life (8 hours) than O, it is unclear how serum half-life correlates with clinical efficacy, which may be determined by receptor binding kinetics (6).

This is the first study to report the results of the use of G as rescue medication in high-risk patients receiving either G+D or O+D as PONV prophylaxis. Descriptively, 79% and 78%, respectively, of patients reported improvement or resolution of PONV symptoms within 30 minutes, but the study was not designed as a treatment crossover and therefore did not adequately address the efficacy of readministration of either drug. The absence of a placebo group further limits the ability to assess whether the reduction of symptoms was the result of the passage of time alone.

Although >80% of patients in each treatment group had no vomiting during the 24-hour study period, fewer than half in either group experienced complete control. Continued research is needed to identify optimal combinations and dose levels of antiemetic drugs for use in particular groups of high-risk patients. In conclusion, the efficacy of G+D was found to be noninferior to that of O+D in preventing vomiting during the 0- to 2-hour interval after surgery.

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Appendix 1

The following investigators comprised the Kytril Study Group and had a substantial role in the conduct of this study: Richard Beers, MD, State University of New York Upstate Medical University, Syracuse, NY; Kumar G. Belani, MD, University of Minnesota, Minneapolis, MN; Keith Candiotti, MD, University of Miami School of Medicine, Miami, FL; Jacques Chelly, MD, University of Pittsburgh Medical Center Shadyside, Pittsburgh, PA; Patricia Dalby, MD, Magee Women's Hospital of the University of Pittsburgh Medical Center, Pittsburgh, PA; Robert D'Angelo, MD, Wake Forest University, Winston-Salem, NC; Dennis Doblar, MD, University of Alabama Birmingham, Birmingham, AL; Ashraf Habib, MD, Duke University, Durham, NC; Charles Hantler, MD, Washington University Medical Center—Barnes Jewish Hospital, St. Louis, MO; Hugh C. Hemmings, Jr., MD, Weill Medical College of Cornell University, New York, NY; Daniel Katz, MD, California Anesthesia Associates, Newport Beach, CA; Robert Knapp, DO, Brigham and Women's Hospital, Boston, MA; Anthony Kovac, MD, University of Kansas School of Medicine, Kansas City, KS; Timothy I. Melson, MD, Helen Keller Hospital, Sheffield, AL; Harold Minkowitz, MD, Memorial Hermann-Memorial City Hospital, Houston, TX; Naila Moghul, MD, Brigham and Women's Hospital, Boston, MA; James Philip, MD, Brigham and Women's Hospital, Boston, MA; Kenneth Rosenfeld, MD, State University of New York at Stony Brook, Stony Brook, NY; Lee Silk, MD, Brigham and Women's Hospital, Boston, MA; Neil Singla, MD, Huntington Memorial Hospital, Pasadena, CA; Richard A. Steinbrook, MD, Beth Israel Deaconess Medical Center, Boston, MA; Tracey Stierer, MD, Johns Hopkins University Hospital, Baltimore, MD.

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