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Antiemetic Prophylaxis for Office-based Surgery

Are the 5-HT$_3$ Receptor Antagonists Beneficial?

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Background: **Office-based surgery has become increasingly popular because of its cost-saving potential. However, the occurrence of postoperative nausea and vomiting (PONV) can delay patient discharge. Prophylaxis using a combination of antiemetic drugs has been suggested as an effective strategy for minimizing PONV. The authors designed this randomized, double-blinded, placebo-controlled study to assess the efficacy of ondansetron and dolasetron when administered in combination with droperidol and dexamethasone for routine antiemetic prophylaxis against PONV in the office-based surgery setting.**

Methods: **Following institutional review board approval, 135 consenting outpatients with American Society of Anesthesiologists physical status I–III who were undergoing superficial surgical procedures lasting 20–40 min were randomly assigned to one of three antiemetic treatment groups. Propofol was administered for induction of anesthesia, followed by 2–4% desflurane with 67% nitrous oxide in oxygen. Desflurane was subsequently adjusted to maintain a clinically adequate depth of anesthesia with an electroencephalographic Bispectral Index value between 50 and 60. All patients received 0.625 mg intravenous droperidol and 4 mg intravenous dexamethasone after induction of anesthesia. The study medication, containing normal saline (control), 12.5 mg intravenous dolasetron, or 4 mg intravenous ondansetron, was administered prior to the end of surgery. All patients received local anesthetics at the incisional site and 30 mg intravenous ketolorac to minimize postoperative pain. Recovery profiles, incidence of PONV, requirement for rescue antiemetic drugs, complete response rates, and patient satisfaction were assessed.**

Results: **The recovery times to patient orientation, oral intake, ambulation, and actual discharge did not differ among the three groups. The incidence of PONV, nausea scores, and requirement for rescue antiemetics were also similar in all three groups during the 24-h study period. In addition, the complete response rates to the prophylactic antiemetics (96–98%) and percentages of very satisfied patients (93–98%) were equally high in all three groups. However, the antiemetic drug acquisition costs were US $2.50, $15.50, and $18.50 in the control, dolasetron, and ondansetron groups, respectively.**

Conclusion: **The addition of dolasetron (12.5 mg) or ondansetron (4 mg) failed to improve the antiemetic efficacy of droperidol (0.625 mg intravenous) and dexamethasone (4 mg intravenous) when they were used for routine prophylaxis in the office-based surgery setting.**

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BECAUSE of its cost-saving potential,[1] office-based surgery is expected to continue to grow in the United States.[2] Anesthetic techniques used in the office-based setting should be safe, effective, and associated with a rapid recovery.[3] Nausea and vomiting after ambulatory surgery remains a major problem[4] and has been found to prolong the time to discharge after office-based surgery.[5] Postoperative nausea and vomiting (PONV) has also been demonstrated to reduce patient satisfaction in the office-based setting.[5] As a result, White and Watcha[6] have recommended routine antiemetic prophylaxis of outpatient populations at increased risk of developing PONV.

Since the causes of PONV are multifactorial, with at least four different neurotransmitter systems implicated in the etiology of PONV,[7] no single antiemetic drug possesses the ability to prevent PONV in all patient populations. Therefore, combination antiemetic therapy using drugs that act at different neuroreceptor sites has been recommended for the at-risk patient.[8] Recently, Scuderi *et al.*[9] demonstrated that multimodal management with a combination of three antiemetic drugs was superior to single-drug therapy in preventing PONV. In an earlier study, we found that antiemetic prophylaxis with a combination of droperidol, ondansetron, and metoclopramide was highly effective in minimizing PONV after office-based surgery with a desflurane-based anesthetic technique.[10]

A recent meta-analysis suggested that combining dexamethasone with a 5-HT$_3$ receptor antagonist provided greater antiemetic efficacy, and this combination therapy was recommended as the "optimal" choice for prophylaxis against PONV.[11] Another meta-analysis reported that dexamethasone also enhanced the antiemetic efficacy of other antiemetics (*e.g.*, do-

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pamine antagonists) when administered as part of a combination therapy.[12] Therefore, we designed a study to test the hypothesis that adding a 5-HT_3 receptor antagonist would improve the ability of dexamethasone and droperidol to prevent PONV after office-based surgery.

Materials and Methods

After obtaining institutional review board approval at Cedars-Sinai Medical Center (Los Angeles, CA) and written informed consent, 135 outpatients with American Society of Anesthesiologists physical status I–III who were undergoing superficial surgical procedures lasting 20–40 min were enrolled in this placebo-controlled, double-blinded study. Patients were randomly assigned to one of three study groups according to a computer-generated random numbers table. The groups comprised the following: (1) control (saline), (2) dolasetron (12.5 mg), and (3) ondansetron (4 mg). The study was performed at a private office-based surgical center (Bedford Surgicenter, Beverly Hills, California) with a single operating room and one recovery bed. Exclusion criteria included pregnancy; active menstruation; body weight more than 50% above the ideal body weight; vomiting or retching within 24 h before the operation; administration of antiemetic or psychoactive medication within 24 h before surgery; a previous history of severe (or unstable) cardiovascular, respiratory, metabolic, endocrine, or neurologic disease; alcohol or drug abuse; and impaired renal or hepatic function.

Patients were asked to provide a detailed medical history and demographic information, including age, weight, height, alcohol or drug consumption, and any history of PONV or motion sickness. Before entering the operating room, patients completed baseline visual analog scales for sedation, fatigue, comfort, pain, and nausea using a 100-mm scale (0 = none; 100 = maximum). Upon arrival in the operating room, standard monitoring devices were applied, as well as the electroencephalographic Bispectral Index (BIS®) monitor (Aspect Medical Systems, Natick, MA). The mean arterial pressure, heart rate, and hemoglobin oxygen saturation were recorded during surgery. The inspired and end-tidal concentrations of oxygen, carbon dioxide, desflurane, and nitrous oxide were measured continuously using a calibrated infrared gas analyzer.

These unpremedicated outpatients received 100% oxygen *via* a face mask for 2–3 min before induction of general anesthesia with 2 mg/kg intravenous propofol. Anesthesia was maintained with 2–4% inspired desflurane and 67% nitrous oxide in oxygen. The inspired desflurane concentration was adjusted to maintain a clinically adequate depth of anesthesia with a Bispectral Index value between 50 and 60. All patients were allowed to breathe spontaneously *via* a face mask or laryngeal mask airway, and local anesthetic (consisting of a mixture of 2% lidocaine and 0.5% bupivacaine) was injected at the incision site by the surgeon for intraoperative and postoperative analgesia. Ketorolac, 30 mg intravenous, was also administered during surgery to minimize postoperative pain. Droperidol, 0.625 mg intravenous, and dexamethasone, 4 mg intravenous, were administered to all patients after induction of anesthesia. The study medications were prepared by the local pharmacy in identical-appearing 5-ml syringes containing saline (control), dolasetron (12.5 mg), or ondansetron (4 mg) and were administered intravenously 10–15 min prior to the end of surgery. The maintenance anesthetics were discontinued at the start of skin closure. On awakening from anesthesia, the patients' abilities to meet specific fast-track discharge criteria were assessed at 2-min intervals.[13] After applying the surgical dressing, the patients were asked to sit up on the operating room table. After standing up, they were allowed to walk to the recovery area with assistance.

Anesthesia time (from induction of anesthesia to discontinuation of nitrous oxide) and surgery time (from incision to placement of the dressing) were recorded. The times at which patients were able to open their eyes, were able to follow commands (*e.g.*, squeeze the investigator's hand), and were oriented to their name and their place and date of birth were assessed by a blinded observer at 1-min intervals. The times to sitting up, standing, ambulating without assistance, and tolerating oral fluids were assessed at 5-min intervals. The duration of the recovery room stay and actual discharge times were recorded. Home readiness was also determined using standardized postanesthetic discharge criteria.[14,15] The discharge criteria for the office-based surgery center required that the patients be awake and alert with stable vital signs, be able to ambulate without assistance, and not be experiencing intractable side effects.

The visual analog scale assessments were repeated at 30 min after the end of anesthesia and at the time of discharge home. Side effects occurring during the postoperative period (*e.g.*, dizziness, headaches), as well as episodes of PONV and need for rescue medication, were noted. An emetic episode was defined as a single vomiting or retching event or any combination of these events separated by less than 2 min. Rescue medications for PONV (*e.g.*, 10 mg intravenous metoclopramide) and pain management (*i.e.*, 500 mg acetaminophen with 5 mg hydrocodone) were administered upon patient request. A complete response was defined as a situation in which the patient did not experience a single emetic episode and did not require rescue antiemetic medication during the 24-h study period. A trained interviewer who was blinded to the study medication contacted each patient by telephone at home approximately 24 h after discharge to inquire about postdischarge side ef-

Table 1. Demographic Characteristics, Duration of Anesthesia and Surgery, Dosage of Anesthetics, and Adjunctive Local Anesthetics and Analgesics prior to Discharge in the Three Study Groups

	Control (Saline)	Dolasetron (12.5 mg IV)	Ondansetron (4 mg IV)
Number, n	45	45	45
Age, yr	57 ± 15	54 ± 18	53 ± 17
Weight, kg	67 ± 13	64 ± 16	66 ± 14
Height, cm	165 ± 10	166 ± 9	164 ± 10
Sex (male/female), n	16/29	16/29	18/27
ASA physical status (I/II/III), n	21/19/5	19/19/7	20/18/7
Previous PONV (yes/no), n	8/37	10/35	7/38
Previous motion sickness (yes/no), n	9/36	10/35	8/37
Baseline nausea score, n*	2 ± 3	2 ± 3	2 ± 2
Type of surgery, n			
Inguinal hernia repair	18	18	20
Partial mastectomy	22	23	18
Other	5	4	7
Anesthesia time, min	36 ± 16	37 ± 18	40 ± 20
Surgery time, min	33 ± 15	34 ± 17	36 ± 19
Propofol dose, mg	166 ± 30	163 ± 24	169 ± 33
End-tidal desflurane, %	2.3 ± 0.4	2.4 ± 0.5	2.3 ± 0.6
2% lidocaine, ml	18 ± 10	18 ± 9	21 ± 11
0.5% bupivacaine, ml	24 ± 12	22 ± 10	20 ± 9
Patients receiving oral analgesic, n	6	7	6
Oral opioid-containing analgesic pills, n	0 (0–1)	0 (0–2)	0 (0–1)

Values are mean ± SD, median (range), or number (n).

* Visual analog score: 0 = none to 100 = maximal.

PONV = postoperative nausea and vomiting.

fects and the need for any therapeutic interventions. The patients were also asked to rate their overall satisfaction with the anesthetic experience on a three-point scale (0 = dissatisfied; 1 = satisfied; 2 = very satisfied).

An *a priori* power analysis suggested that group sizes of 45 should be adequate to detect a significant difference in the incidence of PONV based on an expected incidence of PONV with a volatile anesthetic-based technique (15–40%)[5] and assuming that the combination therapies would produce a 50% or greater reduction in the incidence of PONV, with $\alpha = 0.05$ and $\beta = 0.80$. The statistical analysis consisted of one-way analysis of variance to compare the continuous variables among the three antiemetic treatment groups (when significant differences were determined, a Newman–Keuls multiple comparison test was used to determine intergroup differences) and a chi-square test (or Fisher exact test) to analyze the categorical variables. *P* values less than 0.05 were considered statistically significant. Data are presented as mean values ± SDs, median values (ranges), numbers, or percentages.

Results

The three treatment groups were comparable with respect to their demographic characteristics. The duration of anesthesia and surgery, the amount of local anesthetic solution injected during the intraoperative period, and the dosage of analgesic medication administered in the recovery area were similar among the three groups (table 1).

The early recovery times, including eye opening, following commands, and orientation, did not differ among the study groups. There were also no differences among the three groups with respect to the times to sitting, standing, ambulating, or tolerating fluids. Finally, the time intervals required to meet specific fast-track criteria, home readiness, and actual discharge did not differ among the three groups (table 2).

Table 2. Recovery Times After the End of Anesthesia in the Three Study Groups

	Control (Saline)	Dolasetron (12.5 mg IV)	Ondansetron (4 mg)
Eye opening, min	4 ± 2	4 ± 2	4 ± 3
Responds to commands, min	4 ± 2	4 ± 2	4 ± 2
Orientation, min	5 ± 2	5 ± 2	5 ± 2
Sitting up, min	14 ± 4	14 ± 8	12 ± 5
Standing up, min	15 ± 5	16 ± 6	14 ± 5
Ambulates, min	17 ± 6	16 ± 7	16 ± 6
Tolerates oral fluids, min	23 ± 6	21 ± 10	22 ± 7
"Fitness" for discharge, min	24 ± 10	23 ± 12	22 ± 9
Recovery room stay, min	33 ± 12	37 ± 15	32 ± 9
Actual discharge, min	48 ± 12	51 ± 14	46 ± 10

Values are mean ± SD.

Table 3. Incidence of Postoperative Nausea and Vomiting in the Recovery Room and in the First 24-h Period After Surgery in the Three Study Groups

	Control (Saline)	Dolasetron (12.5 mg IV)	Ondansetron (4 mg IV)
Number, n	45	45	45
Postoperative nausea score, n*			
At 30 min	5 ± 12	5 ± 10	3 ± 9
At discharge	2 ± 3	3 ± 4	2 ± 3
PONV prior to discharge, n (%)			
Nausea	5 (11)	4 (9)	2 (4)
Vomiting	0	0	0
Rescue	2 (4)	1 (2)	1 (2)
Complete response	43 (96)	44 (98)	44 (98)
PONV after discharge, n (%)			
Nausea	5 (11)	3 (7)	4 (9)
Vomiting	1 (2)	1 (2)	1 (2)
Rescue	0	0	0
Complete response	44 (98)	44 (98)	44 (98)
Overall incidence of PONV, %	18	11	13
Cost of antiemetic drugs, US$	2.5	15.5	18.5
Satisfaction with anesthesia, n (%)			
Very satisfied	42 (93)	43 (96)	44 (98)
Satisfied	3 (7)	2 (4)	1 (2)
Dissatisfied	0	0	0

Values are mean ± SD, number (n), or percentage (%).

* Visual analog score: 0 = none to 100 = maximal.

PONV = postoperative nausea and vomiting.

The incidences of PONV and the nausea scores did not differ among the three groups during the 24-h study period (table 3). Prior to discharge from the office-based surgery center, there were only five patients (11%) in the control group, four patients (9%) in the dolasetron group, and two patients (4%) in the ondansetron group who reported nausea. The requirement for rescue antiemetics was equally low (2–4%) in all three groups. During the 24-h follow-up period, five patients (11%) in the control group, three patients (7%) in the dolasetron group, and four patients (9%) in the ondansetron group reported experiencing transient nausea. However, none of these patients required rescue antiemetic therapy. Only three patients in the entire study population experienced vomiting or retching. The 95% confidence intervals for the incidence of PONV prior to discharge were 2–20, 1–17, and 0–8% in the control, dolasetron, and ondansetron groups, respectively. Similarly, the 95% confidence intervals for PONV after discharge were 2–20, 0–14, and 1–17% in the control, dolasetron, and ondansetron groups, respectively. Of importance, 96–98% of the patients in all three groups experienced complete responses to the combination antiemetic therapies, and 93–98% were highly satisfied with their anesthetic experience (table 3). Compared to the ondansetron group, the antiemetic drug costs were decreased by 86% and 16% in the control and dolasetron groups, respectively. Finally, the preoperative and postoperative visual analog scores for sedation, fatigue, comfort, pain, and nausea, as well as the overall incidences of adverse side effects (*e.g.*, headache, dizziness), did not differ among the three groups (data not reported).

Discussion

Despite the extensive literature describing strategies for the prevention of PONV,[16] the optimal prophylactic antiemetic regimen has not been established. The deleterious effects of PONV are not limited to the patients but can also have a profound economic impact on a surgical unit. The estimated cost of PONV to a busy ambulatory surgical unit was estimated to range from US $0.25 million to $1.5 million per year in lost surgical revenue.[17] Although 5-HT_3 receptor antagonists, dopamine antagonists, and benzamides have all been shown to be safe and effective for the prevention of PONV, no single antiemetic is completely effective.[7,8] A multimodal strategy[8] has been developed for managing patients at high risk for developing PONV. This approach involves a combination of antiemetics that block different neuroreceptors in the central nervous system, use of less emetogenic anesthesia techniques, adequate intravenous hydration, and effective pain control involving both opioid and nonopioid analgesics.[3]

Although an article by Scuderi *et al.*[18] and an accompanying editorial by Fisher[19] suggested that antiemetic prophylaxis offered no advantage over symptomatic treatment, Tang *et al.*[20] and Sedhasivam *et al.*[21] have presented cost-efficacy and cost-benefit data supporting the use of antiemetic prophylaxis in outpatients at in-

creased risk for developing PONV. A more recent study by Scuderi's group also demonstrated the value of a predefined multimodal clinical care algorithm that included triple antiemetic prophylaxis using a combination of ondansetron, droperidol, and dexamethasone in outpatients undergoing laparoscopic cholecystectomy procedures.[9] This multimodal technique was not only highly effective in minimizing PONV, but also led to improved patient satisfaction. Our research group has also reported that a triple antiemetic prophylaxis regimen consisting of 4 mg intravenous ondansetron, 0.625 mg intravenous droperidol, and 10 mg intravenous metoclopramide significantly decreased the incidence of PONV[10] compared to single-drug therapy with droperidol alone[5] after general (volatile) anesthesia for office-based surgery.

Since the concept of combination antiemetic therapy was first introduced for reducing the incidence of chemotherapy-induced vomiting, various combinations of antiemetics have been evaluated for the prevention of PONV.[9–11,22] For example, MacKenzie *et al.*[22] demonstrated the benefit of combining ondansetron and droperidol in women undergoing minor gynecologic surgery procedures. However, the 5-HT_3 antagonists are very expensive when used for routine antiemetic prophylaxis. Since droperidol is the most cost-effective monoantiemetic therapy,[23,24] we were interested in combining it with a less costly adjuvant (*e.g.*, dexamethasone). A recent meta-analysis demonstrated the antiemetic efficacy of dexamethasone,[11] in particular when it was combined with other commonly used antiemetic drugs.[25]

The antiemetic efficacy of droperidol has also been reported to be enhanced by dexamethasone,[26] and this observation has been confirmed in a systematic review of studies in which dexamethasone was used in combination with other antiemetics.[12] In a recently published study involving patients undergoing minor ambulatory surgery, the combination of droperidol and metoclopramide was reported to be highly effective in preventing PONV and led to improved patient satisfaction.[27] Interestingly, the combination of 0.625 mg intravenous droperidol and 10 mg intravenous metoclopramide has also been reported to be more effective than 4 mg intravenous ondansetron in preventing PONV[28] (with complete responses in 96–98% of the cases), and the droperidol–metoclopramide combination was alleged to be comparable to the combination of 4 mg intravenous ondansetron and 0.625 mg intravenous droperidol in patients undergoing laparoscopic cholecystectomy procedures.[29]

In the present study, variables that are known to influence the incidence of PONV (*i.e.*, gender, type and duration of operation, history of PONV and motion sickness, as well as anesthetic and analgesic drugs) were similar in all three study groups. While there were two to five patients in each group who experienced transient nausea, only one or two patients in each group requested rescue antiemetic medication. None of the patients experienced vomiting or retching before discharge from the office-based surgery center. Of interest, all of the patients in this study met the fast-track recovery criteria and were discharged from the office surgery center within 1 h after their operation. During the 24-h follow-up period, there were only three patients who experienced vomiting or retching after discharge home. In all three cases, the emesis followed the use of an oral opioid-containing analgesic. Although we failed to achieve a 100% complete response rate in any group, these data clearly demonstrated that the use of a combination of droperidol and dexamethasone was highly effective in preventing PONV (with a complete response achieved in 96–98% of the cases) and that the addition of an expensive 5-HT_3 antagonist provided no additional benefit.

It should be emphasized that none of the patients in this study received either opioid analgesics or muscle relaxant (or reversal) drugs during the perioperative period. The avoidance of opioid analgesics and neuromuscular reversal drugs during surgery minimizes the risk of PONV.[30,31] Given the comparable antiemetic efficacy of the three antiemetic combinations, use of droperidol and dexamethasone alone was clearly the most cost-effective choice. The local pharmacy acquisition cost in 2002 for a 4-mg vial of ondansetron was US $16, and a 12.5-mg vial of dolasetron was US $13. In contrast, a 5-mg vial of droperidol was US $1.60, and a 4-mg vial of dexamethasone was only US $0.90.

This study could be criticized because the "control" group received droperidol and dexamethasone. However, in a previous study involving a similar patient population undergoing the same type of operations with a volatile anesthetic–based anesthetic technique,[5] prophylaxis with low-dose droperidol alone was associated with a 15–40% incidence of PONV. Another concern relates to the Food and Drug Administration "black box" warning regarding the use of droperidol for antiemetic prophylaxis.‖

The agency suggested that use of droperidol (even in low doses) may be associated with clinically significant QTc prolongation and/or torsades de pointes dysrhythmias. The current study was completed before the Food and Drug Administration warning, and there were no arrhythmias observed when 0.625 mg intravenous droperidol was administered during general anesthesia with continuous electrocardiographic monitoring. Since there has not been a single case report in the peer-reviewed literature describing cardiac arrhythmias following antiemetic doses of droperidol, this warning has recently been challenged.[32] Most experts in the field

‖ http://www.fda.gov/bbs/topics/ANSWERS/2001/ANSO1123.html. December 5, 2001

would agree that low-dose droperidol has been proven to be a safe and cost-effective antiemetic over the past 30 yr.[33]

In conclusion, the combination of 0.625 mg intravenous droperidol and 4 mg intravenous dexamethasone was highly effective in preventing PONV without the addition of a 5-HT_3 antagonist. As ambulatory anesthesia continues to advance,[3] it is important to examine the cost-effectiveness of "routine" clinical practices. These data suggest that 5-HT_3 antagonists are not beneficial for routine antiemetic prophylaxis in the ambulatory setting when a droperidol–dexamethasone combination is used.

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