A Factorial Trial of Six Interventions for the Prevention of Postoperative Nausea and Vomiting

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ABSTRACT

BACKGROUND

Untreated, one third of patients who undergo surgery will have postoperative nausea and vomiting. Although many trials have been conducted, the relative benefits of prophylactic antiemetic interventions given alone or in combination remain unknown.

METHODS

We enrolled 5199 patients at high risk for postoperative nausea and vomiting in a randomized, controlled trial of factorial design that was powered to evaluate interactions among as many as three antiemetic interventions. Of these patients, 4123 were randomly assigned to 1 of 64 possible combinations of six prophylactic interventions: 4 mg of ondansetron or no ondansetron; 4 mg of dexamethasone or no dexamethasone; 1.25 mg of droperidol or no droperidol; propofol or a volatile anesthetic; nitrogen or nitrous oxide; and remifentanil or fentanyl. The remaining patients were randomly assigned with respect to the first four interventions. The primary outcome was nausea and vomiting within 24 hours after surgery, which was evaluated blindly.

RESULTS

Ondansetron, dexamethasone, and droperidol each reduced the risk of postoperative nausea and vomiting by about 26 percent. Propofol reduced the risk by 19 percent, and nitrogen by 12 percent; the risk reduction with both of these agents (i.e., total intravenous anesthesia) was thus similar to that observed with each of the antiemetics. All the interventions acted independently of one another and independently of the patients' baseline risk. Consequently, the relative risks associated with the combined interventions could be estimated by multiplying the relative risks associated with each intervention. Absolute risk reduction, though, was a critical function of patients' baseline risk.

CONCLUSIONS

Because antiemetic interventions are similarly effective and act independently, the safest or least expensive should be used first. Prophylaxis is rarely warranted in low-risk patients, moderate-risk patients may benefit from a single intervention, and multiple interventions should be reserved for high-risk patients.

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NESTHESIA IS GIVEN TO MORE THAN 75 million surgical patients annually, worldwide. Untreated, one third will have postoperative nausea, vomiting, or both.[1-3] Patients often rate postoperative nausea and vomiting as worse than postoperative pain.[4,5] It is not surprising, therefore, that prevention of postoperative nausea and vomiting improves satisfaction among patients who are likely to experience them.[6] Vomiting increases the risk of aspiration and has been associated with suture dehiscence, esophageal rupture, subcutaneous emphysema, and bilateral pneumothoraxes.[7,8] Postoperative nausea and vomiting frequently delay discharge from postanesthesia care units, and they are the leading cause of unexpected hospital admission after planned ambulatory surgery.[9] The annual cost of postoperative nausea and vomiting in the United States is thought to be several hundred million dollars.[10,11]

More than 1000 randomized, controlled trials have evaluated pharmacologic methods of preventing and treating postoperative nausea and vomiting. Most have compared a single intervention with placebo. Serotonin (5-hydroxytryptamine type 3) antagonists (e.g., ondansetron), dexamethasone (a corticosteroid), and droperidol (a neuroleptic drug) are among the best-studied antiemetic agents. Alternatively, the avoidance of emetogenic factors during anesthesia can reduce the baseline risk of postoperative nausea and vomiting. This strategy includes the use of propofol instead of volatile anesthetics, the substitution of nitrogen for nitrous oxide, and the use of remifentanil, an ultra–short-acting opioid, instead of fentanyl.[12,13]

The limited efficacy of treatment with single antiemetics[14] has prompted evaluations of several antiemetic strategies used in combination.[15] However, no previous study of postoperative nausea and vomiting has had an appropriate design or sufficient power to evaluate all the major pharmacologic interventions simultaneously or to determine the extent to which combining multiple interventions improves outcome. A recent consensus conference was thus unable to support a definitive statement on the benefits of combining antiemetic strategies.[16] We therefore conducted a large clinical trial of factorial design with sufficient power to compare the efficacy of six well-established antiemetic strategies and to determine the extent to which efficacy could be improved by combining two or three interventions.

METHODS

The design of the study, the recruitment of patients at each center, the acquisition and management of data, the statistical analyses, the interpretation of the data, and the writing and editing of the manuscript were performed independently of the sponsors. The contributions of the individual authors are listed in the Appendix.

After obtaining approval from the institutional review boards of the 28 participating centers, we enrolled 5199 adults who were scheduled to undergo elective surgery during general anesthesia that was expected to last at least one hour. All the patients had a risk of postoperative nausea and vomiting that exceeded 40 percent, according to a simplified risk score,[17] based on the presence of at least two of the following risk factors: female sex, nonsmoker status, previous history of postoperative nausea and vomiting or motion sickness, and anticipated use of postoperative opioids.[18,19] We excluded patients in whom any of the study drugs were contraindicated, those who had taken emetogenic or antiemetic drugs within the 24 hours before surgery, those who were expected to require postoperative mechanical ventilation, and those who were pregnant or lactating. All the patients provided their written informed consent.

PROTOCOL

The antiemetic efficacy of six individual treatments and combinations of them was simultaneously evaluated according to a 2^6 factorial design.[20] Three of the prophylactic interventions involved the use of an antiemetic drug: ondansetron, dexamethasone, or droperidol. The other three interventions consisted of the use of propofol instead of a volatile anesthetic, the omission of nitrous oxide, and the substitution of remifentanil for fentanyl. Thus, according to the study design, each patient was to be randomly assigned to one of each of the following six interventions: ondansetron (4 mg intravenously) or no ondansetron; dexamethasone (4 mg intravenously) or no dexamethasone; droperidol (1.25 mg intravenously) or no droperidol; propofol or a volatile anesthetic (i.e., isoflurane, desflurane, or sevoflurane) in a 2:1 ratio; nitrogen or nitrous oxide; and remifentanil or fentanyl.

These 6 treatments lead to a possible 64 (i.e., 2^6) different treatment combinations. However, propofol is associated with a reduced risk of postopera-

tive nausea and vomiting,[21] so to ensure sufficient power to quantify the effect of antiemetics in the propofol subgroup, we assigned twice as many patients to propofol as to volatile anesthetics (for a 2:1 randomization ratio). Therefore, permuted blocks of 96 ($2^3 \times 3 \times 2^2$) patients were generated. Each center received four blocks with a unique computerized randomization, stored in sequentially numbered, sealed, opaque envelopes.

The envelopes were opened after consent was obtained, just before the induction of general anesthesia. The anesthesiologists responsible for intraoperative management were not blinded to the treatment, but they were not involved in the postoperative assessment. Supplemental oxygen may[22,23] or may not[24,25] have an antiemetic effect. Consequently, at three centers patients were randomly assigned to 30 percent oxygen in nitrous oxide, 30 percent oxygen in nitrogen, or 80 percent oxygen in nitrogen, in a randomization ratio of 1:1:1. As a result, a minimum of 144 (3×48) patients were required per block. To provide sufficient power, each center agreed to study 288 patients, twice as many as the minimum.

The patients were given premedication with a benzodiazepine. Three minutes before the induction of anesthesia, they received either a bolus of fentanyl (100 to 200 µg) or an infusion of remifentanil (0.25 µg per kilogram of body weight per minute), according to the treatment to which they had been assigned. Anesthesia was induced with intravenous propofol (Disoprivan or Diprivan, AstraZeneca) at a dose of 2 to 3 mg per kilogram, and tracheal intubation was facilitated with rocuronium.

Normocapnic mechanical ventilation was instituted with the assigned gas combination. Anesthesia was maintained with either propofol (starting at about 80 µg per kilogram per hour) or a standardized concentration of a volatile anesthetic. If the heart rate or blood pressure deviated by more than 20 percent from the preoperative value, an intravenous bolus of fentanyl (50 to 100 µg) was given or the rate of remifentanil infusion was increased slightly. In addition, the concentration of volatile anesthetics or the propofol infusion rate could be adjusted as clinically appropriate. In the designated patients, 4 mg of dexamethasone (if assigned) and 1.25 mg of droperidol (if assigned) were given intravenously within 20 minutes after the start of anesthesia,[10,26] and 4 mg of ondansetron (if assigned) was given intravenously during the last 20 minutes of surgery.[27]

Postoperatively, the patients received supplemental oxygen, and pain was ameliorated with the use of nonsteroidal antiinflammatory medications administered intraoperatively. The patients who had been assigned to receive intraoperative remifentanil were given 50 µg of morphine per kilogram or an equivalent opioid at the end of surgery. The need for a postoperative opioid was left to the discretion of the anesthesiologist, and the dose was adjusted according to clinical needs. Patients who requested antiemetic therapy or who had an emetic episode were given 4 mg of ondansetron; if symptoms persisted, 4 mg of dexamethasone and 1.25 mg of droperidol were added.

MEASUREMENTS

Our primary outcome measure was the incidence of any nausea, emetic episodes (retching or vomiting), or both (i.e., postoperative nausea and vomiting) during the first 24 postoperative hours. After the 2nd and 24th postoperative hours, trained investigators who were fully blinded to the intraoperative management and random treatment assignments recorded the number of emetic episodes and the time each one occurred. At both these time points, patients orally rated their worst nausea episode during the preceding interval on an 11-point scale, where 0 represented no nausea and 10 the most severe nausea possible.

STATISTICAL ANALYSIS

Different sample-size estimations were performed and indicated that about 5000 patients would be needed for the analysis of interactions involving as many as three factors, whereas the number of patients required for the analysis of two-factor interactions or of single factors was considerably smaller.[20] An interaction was defined as present if the effect of two factors in combination was significantly different from the separate effects of each factor multiplied together on an odds-ratio scale.

For each of the six randomized treatments, the numbers of patients who had postoperative nausea and vomiting were compared with the use of chi-square tests for each main effect, and reductions in the relative risk of nausea and vomiting were estimated. Logistic-regression analyses were used to quantify the relative effects of the six interventions as odds ratios and to identify potential two- or three-factor interactions by a stepwise forward-inclusion algorithm. This analysis was repeated to compensate for the specified covariates (female sex, nonsmoking status, age, a history of postoper-

ative nausea and vomiting or motion sickness, use of postoperative opioids, type of surgery, and study center). A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Patients were recruited from February 2, 2000, until July 30, 2002, at 28 centers; 5199 patients underwent factorial randomization to ondansetron or no ondansetron, dexamethasone or no dexamethasone, droperidol or no droperidol, and propofol or a volatile anesthetic. Outcome data were incomplete for 38 patients, leaving 5161 patients (99 percent) for whom complete outcome data were available. One center each did not randomize with respect to carrier gas (424 patients), use of remifentanil or fentanyl (191 patients), or both of these factors (181 patients). Three centers randomly assigned a total of 280 patients to 80 percent oxygen in nitrogen (as a third alternative to 30 percent oxygen in nitrogen or in nitrous oxide). A total of 4123 patients were thus randomly assigned with respect to all six primary factors, and outcome data were incomplete in 37 of them (1 patient with incomplete data was among those not randomly assigned with respect to carrier gas), leaving 4086 patients (99 percent) for whom complete outcome data could be analyzed (Fig. 1).

Of the 5161 patients, 81.5 percent were women, 81.2 percent were nonsmokers, 54.5 percent had a history of postoperative nausea and vomiting or motion sickness, and 78.1 percent received postoperative opioids. Hernia repair was performed in 2.8 percent of the patients, cholecystectomy in 7.7 percent, hysterectomy in 16.9 percent, thyroid surgery in 5.9 percent, breast surgery in 2.8 percent, hip replacement in 3.5 percent, knee arthroscopy in 2.2 percent, arm or hand surgery in 2.5 percent, head and neck surgery (including ophthalmic surgery) in 9.0 percent, gynecologic surgery other than hysterectomy in 28.2 percent, other bone surgery in 6.6 percent, and other types of general surgery in 11.7 percent. The baseline characteristics were similar among the patients randomly assigned to each intervention; more detailed information can be found in Table S1 of the Supplementary Appendix (available with the full text of this article at www.nejm.org).

Overall, 1731 of 5161 patients (34 percent) had postoperative nausea and vomiting. This reflects the average incidence among all 64 possible combinations of interventions, which ranged from 59 percent among patients who were given volatile anesthesia, nitrous oxide, fentanyl, and no antiemetics (26 of 44 of these patients had nausea and vomiting) to 17 percent among patients who received propofol, nitrogen, remifentanil, ondansetron, dexamethasone, and droperidol (17 of 102 of these patients had nausea and vomiting). Nausea occurred in 1617 patients (31 percent) and vomiting in 734 (14 percent). Among the patients who had symptoms, the median and mean ratings for the maximal nausea level were 5 and 5.7, respectively, and the median and mean numbers of emetic episodes were 1 and 1.5, respectively. According to bivariate analyses, each antiemetic reduced the incidence of postoperative nausea and vomiting by about 26 percent, propofol reduced it by about 19 percent, and nitrogen reduced it by about 12 percent (Table 1). The rates of hypotension, use of intraoperative vasoconstrictors, and shivering were similar with each antiemetic. Propofol was associated with less frequent use of intraoperative vasoconstrictors (15 percent) than were volatile anesthetics (20 percent, P=0.001). The use of remifentanil rather than fentanyl did not significantly reduce the incidence of postoperative nausea and vomiting, but it was associated with increased use of intraoperative vasoconstrictors (21 percent, vs. 13 percent with fentanyl; P<0.001) and an increased incidence of shivering (6.7 percent, vs. 3.3 percent with fentanyl; P<0.001).

Increasing the number of antiemetics administered reduced the incidence of postoperative nausea and vomiting from 52 percent when no antiemetics were used to 37 percent, 28 percent, and 22 percent when one, two, and three antiemetics, respectively, were administered (Fig. 2). This corresponds to a 26 percent reduction in the relative risk of nausea and vomiting for each additional antiemetic used (95 percent confidence interval, 23 percent to 30 percent). Furthermore, there were no significant differences among the antiemetics (chi-square= 0.01, 2 df; P=1.00) or among any pair of antiemetics (chi-square=0.42, 2 df; P=0.81).

The effects of the anesthetic interventions and their combinations were explored in the 4086 patients who were randomly assigned with respect to all six interventions. The average incidence of postoperative nausea and vomiting was 41 percent among those given a volatile anesthetic and nitrous oxide, 34 percent among those given a volatile anesthetic and nitrogen, 32 percent among those given propofol and nitrous oxide, and 29 percent among
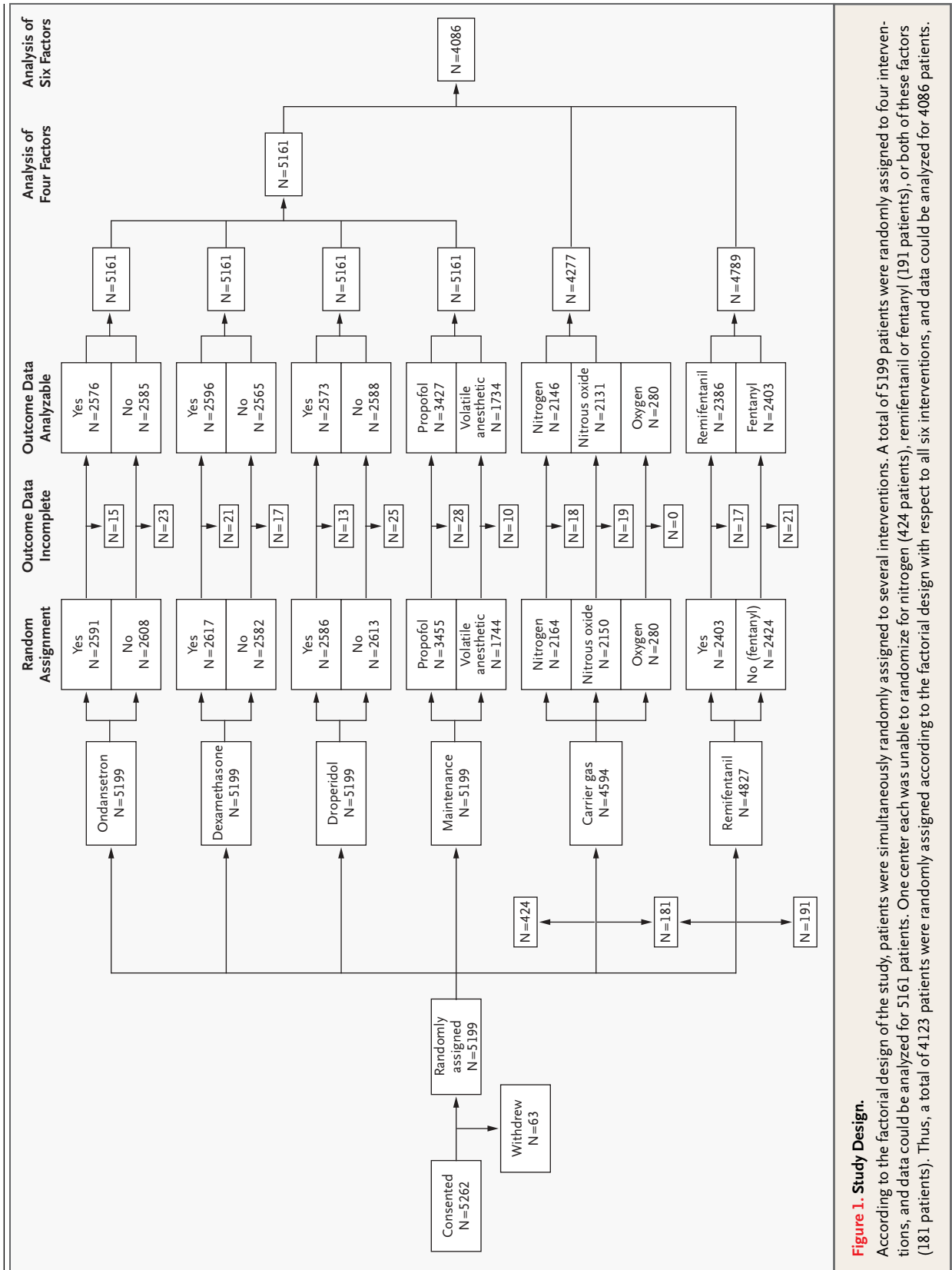
Figure 1. Study Design.

According to the factorial design of the study, patients were simultaneously randomly assigned to several interventions. A total of 5199 patients were randomly assigned to four interventions, and data could be analyzed for 5161 patients. One center each was unable to randomize for nitrogen (424 patients), remifentanil or fentanyl (191 patients), or both of these factors (181 patients). Thus, a total of 4123 patients were randomly assigned according to the factorial design with respect to all six interventions, and data could be analyzed for 4086 patients.

Table 1. Risk of Postoperative Nausea and Vomiting According to Patients' Randomly Assigned Interventions.				
Intervention	Received Intervention		Percent Relative Risk (95% CI)*	P Value†
	Yes	No		
	no. with PONV/total no. (%)‡			
Ondansetron (vs. no ondansetron)	735/2576 (28.5)	996/2585 (38.5)	−26.0 (−31.5 to −19.9)	<0.001
Dexamethasone (vs. no dexamethasone)	739/2596 (28.5)	992/2565 (38.7)	−26.4 (−31.9 to −20.4)	<0.001
Droperidol (vs. no droperidol)	742/2573 (28.8)	989/2588 (38.2)	−24.5 (−30.2 to −18.4)	<0.001
Propofol (vs. inhalational anesthetic)	1066/3427 (31.1)	665/1734 (38.4)	−18.9 (−25.0 to −12.3)	<0.001
Nitrogen as carrier gas (vs. nitrous oxide)	668/2146 (31.1)	755/2131 (35.4)	−12.1 (−19.3 to −4.3)	0.003
Remifentanil (vs. fentanyl)	827/2386 (34.7)	792/2403 (33.0)	5.2 (−2.9 to 13.8)	0.21

* CI denotes confidence interval.
† P values were calculated by the chi-square test.
‡ The numbers shown are the numbers of patients who had postoperative nausea, vomiting, or both (PONV) divided by the total numbers of patients randomly assigned to the specified intervention for whom complete outcome data could be analyzed. The data are based on all 5161 randomly assigned patients who completed the study, with the exceptions of the data for carrier gas (4277 patients) and for remifentanil versus fentanyl (4789 patients).

those given propofol and nitrogen. Figure 3 shows these incidences broken down according to the number of antiemetics. There was no significant interaction between propofol and nitrogen (chi-square=0.94, 2 df, by the likelihood ratio test; P=0.33). Although the type of volatile anesthetic (isoflurane, sevoflurane, or desflurane) was not a randomized factor, it had no significant effect on the incidence of postoperative nausea and vomiting in a multivariate model (P=0.30). The incidence of postoperative nausea and vomiting was 31 percent among the patients who received 80 percent oxygen in nitrogen and 24 percent among those who received 30 percent oxygen in nitrogen (P=0.07).

Multivariate logistic analyses of data from all 5161 patients and of data from the 4086 patients assigned with respect to all six treatments are shown in Table 2. This analysis found no significant interactions among the treatments. When the interactions between treatments and potentially confounding factors (e.g., the type of surgery) were analyzed, only one significant interaction was detected: an interaction between droperidol and sex (P=0.003). Droperidol significantly reduced the risk of postoperative nausea and vomiting among women, but not among men: 910 of the 2106 women who did not receive droperidol had nausea or vomiting (43 percent), as compared with 662 of the 2101 women who did receive this agent (32 percent) (odds ratio, 0.61; 95 percent confidence interval, 0.53 to 0.69; P<0.001), and the effect was independent of menstrual-cycle phase or whether menopause had oc-

curred; in contrast, 79 of the 482 men who did not receive droperidol had nausea or vomiting (16 percent), as compared with 80 of the 472 men who did receive this agent (17 percent) (odds ratio, 1.04; 95 percent confidence interval, 0.74 to 1.46; P=0.82).

The results based on analyses of data from 4086 patients remained essentially unchanged when data from all 5161 patients were considered or when potential confounders were included in the statistical models (Table 2). Detailed results for the 4086 patients in the 64 groups are given in Table S2 of the Supplementary Appendix. Given the finding that total intravenous anesthesia or the use of any antiemetic independently reduced the risk of postoperative nausea and vomiting by about 26 percent, the incidence of postoperative nausea and vomiting for five different initial risks was calculated for as many as four interventions (Table 3).

DISCUSSION

The large enrollment and the factorial design of our trial allowed simultaneous evaluation of the antiemetic efficacy of three antiemetic interventions and three anesthetic interventions and of all possible combinations of two or three interventions. All the tested antiemetics appeared to be similarly effective. Ondansetron and other 5-hydroxytryptamine type 3 antagonists are considered relatively safe, but they are more expensive than droperidol and dexamethasone. However, low-dose droperidol can cause dysphoria,[28,29] and the Food and Drug Administration

recently added a "black box" warning to the drug's labeling to indicate that it may be associated with torsade de pointes; however, there is little evidence that antiemetic doses trigger this condition.[30] No studies have identified complications associated with the antiemetic dose of dexamethasone, although even meta-analyses may have insufficient power to detect rare complications.[31] The combination of low cost and apparent safety makes dexamethasone at a dose of 4 mg an attractive first-line agent for prophylaxis against postoperative nausea and vomiting.

Bivariate analysis indicated that substituting propofol for a volatile anesthetic reduced the risk of postoperative nausea and vomiting by about 19 percent, whereas substituting nitrogen for nitrous oxide reduced the risk by about 12 percent. Combining these two anesthetic management strategies (i.e., total intravenous anesthesia) thus reduced the risk by about as much as any single antiemetic. In contrast, the use of remifentanil instead of fentanyl did not significantly reduce the risk of nausea and vomiting.

The relative risk reduction associated with each intervention was apparently independent for a wide range of absolute risks. Thus, interventions that reduce the relative risk to a similar extent will provide the greatest absolute risk reduction in patients most likely to have postoperative nausea and vomiting. For example, a single intervention in a patient with an 80 percent risk of postoperative nausea and vomiting will reduce the risk to 59 percent; the absolute risk reduction is 21 percent, which translates into a number needed to treat of about five to prevent nausea and vomiting in one patient. Conversely, the absolute risk reduction in a patient with a baseline risk of 10 percent is only about 3 percent; this corresponds to a number needed to treat of about 40, which would probably not justify the expense and risk of prophylactic treatment. The efficacy of an intervention thus depends critically on patients' baseline risk.

Interestingly, there were no significant interactions among the antiemetic interventions, among the anesthetic interventions, or among the antiemetics and the anesthetics. The resulting relative risk of nausea and vomiting associated with a combination of interventions can thus be directly calculated as the product of the individual relative risks. As a consequence, the absolute risk reduction provided by a second or third intervention is less than that provided by the initial intervention (irrespective
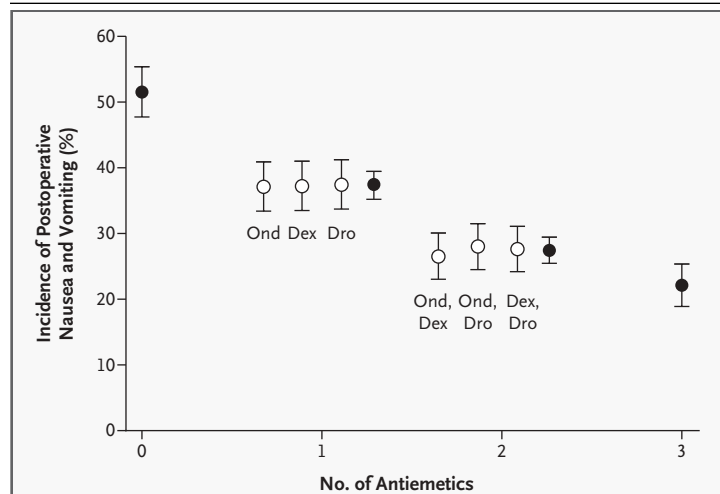

Figure 2. Incidence of Postoperative Nausea and Vomiting Associated with the Various Combinations of Antiemetic Drugs.

The data shown represent outcomes in 5161 patients. Solid circles represent the average value for each number of prophylactic antiemetics, and open symbols the incidence for each antiemetic or combination of antiemetics. Ond denotes ondansetron, Dex dexamethasone, and Dro droperidol. I bars represent 95 percent confidence intervals.
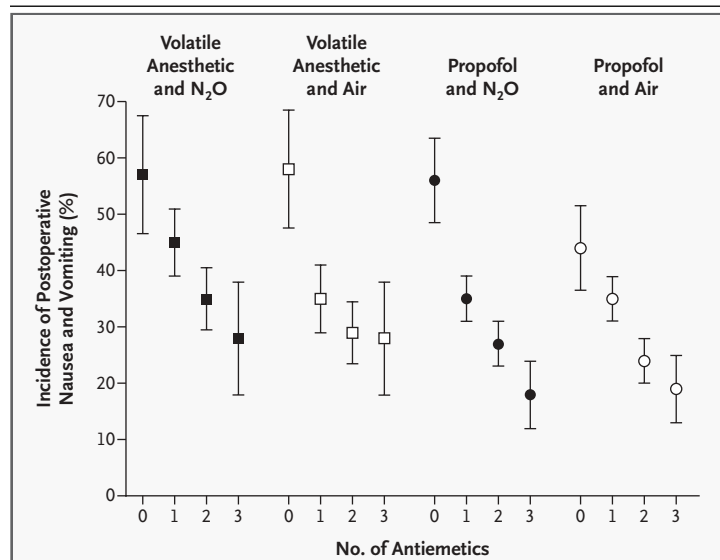

Figure 3. Incidence of Postoperative Nausea and Vomiting According to the Combinations of Anesthetic Strategies and the Number of Antiemetic Treatments Given.

The data shown represent outcomes in 4086 patients. Because assignment to remifentanil did not contribute significantly to the risk of postoperative nausea and vomiting, data pertaining to remifentanil are not shown. Although the graph suggests that there is an interaction between nitrogen (air) and propofol in patients who received no antiemetic agents, statistical analyses did not confirm this impression. I bars represent 95 percent confidence intervals.

Table 2. Results of Multiple Logistic-Regression Analysis and Odds Ratios for Postoperative Nausea and Vomiting.*

Variable	Patients Assigned with Respect to Four Interventions (N=5161)†		Patients Assigned with Respect to Six Interventions (N=4086)†	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Intervention				
Ondansetron	0.56 (0.50–0.64)	<0.001	0.56 (0.48–0.65)	<0.001
Dexamethasone	0.57 (0.50–0.65)	<0.001	0.57 (0.49–0.66)	<0.001
Droperidol	0.58 (0.51–0.67)	<0.001	0.56 (0.48–0.66)	<0.001
Propofol	0.69 (0.60–0.79)	<0.001	0.71 (0.61–0.83)	<0.001
Carrier gas				
Nitrogen (30% oxygen)	0.81 (0.70–0.93)	0.003	0.83 (0.72–0.97)	0.02
Nitrogen (80% oxygen)	0.99 (0.70–1.40)	0.96		
Remifentanil	0.96 (0.84–1.10)	0.56	0.94 (0.81–1.09)	0.39
Covariate				
Female sex	3.13 (2.33–4.20)	<0.001	2.87 (2.08–3.95)	<0.001
Interaction of droperidol and male sex	1.85 (1.26–2.72)	0.002	1.97 (1.29–3.00)	0.002
Nonsmoking	1.57 (1.32–1.87)	<0.001	1.57 (1.29–1.91)	<0.001
History of postoperative nausea and vomiting or motion sickness	1.70 (1.49–1.95)	<0.001	1.80 (1.54–2.09)	<0.001
Operation				
Hernia repair	1.04 (0.65–1.67)	0.87	1.08 (0.66–1.78)	0.75
Cholecystectomy	1.49 (1.08–2.06)	0.015	1.44 (1.01–2.05)	0.04
Hysterectomy	1.78 (1.35–2.35)	<0.001	1.94 (1.43–2.63)	<0.001
Thyroid surgery	1.22 (0.86–1.72)	0.27	1.23 (0.85–1.78)	0.27
Breast surgery	0.74 (0.48–1.17)	0.20	0.76 (0.46–1.24)	0.27
Orthopedic surgery	0.91 (0.67–1.24)	0.55	0.91 (0.65–1.29)	0.60
Head and neck surgery	1.08 (0.71–1.65)	0.72	0.88 (0.55–1.42)	0.61
Other gynecologic surgery	0.91 (0.69–1.19)	0.48	0.98 (0.73–1.32)	0.91
Duration of anesthesia (per hr)	1.20 (1.12–1.28)	<0.001	1.15 (1.06–1.24)	0.001
Use of postoperative opioids	2.14 (1.75–2.61)	<0.001	2.01 (1.59–2.53)	<0.001

* The data are presented as odds ratios, which describe the effects of the interventions or covariates as compared with the effects when the intervention or covariate is absent. CI denotes confidence interval.
† Analyses were adjusted for the study center as a potentially confounding factor.

of which combination is chosen). A 70 percent reduction in the relative risk of postoperative nausea and vomiting is thus the best that can be expected, even when total intravenous anesthesia is used in combination with three antiemetics.

Because each tested antiemetic agent and the use of total intravenous anesthesia reduced the relative risk of nausea and vomiting to a similar extent, the logical sequence is to use the least expensive or safest intervention first. Additional interventions that cost more or that are associated with a greater chance of adverse effects will further reduce the ab-

solute risk, but to a lesser extent than will the initial intervention. Combining prophylactic interventions therefore markedly increases costs and the likelihood of adverse effects while providing progressively less additional absolute benefit. Multiple interventions should thus generally be reserved for patients at high risk for postoperative nausea and vomiting or those in whom nausea and vomiting would be especially dangerous.

In analyses based on the entire study population, droperidol decreased the risk of postoperative nausea and vomiting as much as did the other anti-

emetics, but when sex was considered, no significant benefit was found in men. Such a finding has not been described in previous studies, presumably because many studies have been restricted to women and because studies that included both sexes were too small to detect the interaction. Estrogen or other hormonal factors seem unlikely to be the cause, since the effectiveness of droperidol was independent from menstrual-cycle phase and menopause (data not shown). It is possible that dopamine is a more important trigger in women than in men. It is also possible that the lack of efficacy of droperidol in men is simply a spurious finding resulting from multiple testing.

It is well known that the incidence of postoperative nausea and vomiting varies considerably according to the type of surgery conducted. However, with the exception of hysterectomy and possibly cholecystectomy, the relative risk was similar for all types of surgery when corrected for major risk factors including sex, nonsmoking status, a history of postoperative nausea and vomiting, and the use of postoperative opioids. As a consequence, risk models that include the type of surgery[1,32] do not provide greater predictive power than a simplified model.[18,19] Since no interactions were detected between the interventions and the type of surgery, it is not necessary to repeat studies of postoperative nausea and vomiting for various types of surgery.[14,33]

Management techniques such as total intravenous anesthesia cannot be used once postoperative nausea and vomiting have begun. Dexamethasone, similarly, prevents postoperative nausea and vomiting only when given near the beginning of surgery, probably by reducing surgery-induced inflammation.[34] Moreover, "rescue" treatments are ineffective when the same drug has already been used prophylactically.[35] Postoperative treatment options are thus limited when compared with the broader range of prophylactic options, suggesting that prophylaxis may be preferable to the treatment of established postoperative nausea and vomiting. A reasonable treatment strategy would be to use dexamethasone and total intravenous anesthesia as first-line and second-line methods of prophylaxis against post-

operative nausea and vomiting and to reserve serotonin antagonists as a rescue treatment.

Table 3. Estimated Incidence of Postoperative Nausea and Vomiting as a Function of Baseline Risk, on the Basis of the Assumption That Each Intervention Reduces the Relative Risk by 26 Percent.

Baseline Risk (No Intervention)*	Estimated Incidence of Postoperative Nausea and Vomiting			
	One Intervention	Two Interventions	Three Interventions	Four Interventions
	percent			
10%	7	5	4	3
20%	15	11	8	6
40%	29	22	16	12
60%	44	33	24	18
80%	59	44	32	24

* The baseline risk levels of 10 percent, 20 percent, 40 percent, 60 percent, and 80 percent reflect the presence of 0, 1, 2, 3, and 4 risk factors, respectively, according to a simplified risk score.[17]

APPENDIX

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