Severe Nausea and Vomiting in the Evaluation of Nitrous Oxide in the Gas Mixture for Anesthesia II Trial

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ABSTRACT

Background: The Evaluation of Nitrous oxide in the Gas Mixture for Anesthesia II trial randomly assigned 7,112 noncardiac surgery patients to a nitrous oxide or nitrous oxide–free anesthetic; severe postoperative nausea and vomiting (PONV) was a prespecified secondary end point. Thus, the authors evaluated the association between nitrous oxide, severe PONV, and effectiveness of PONV prophylaxis in this setting.

Methods: Univariate and multivariate analyses of patient, surgical, and other perioperative characteristics were used to identify the risk factors for severe PONV and to measure the impact of severe PONV on patient outcomes.

Results: Avoiding nitrous oxide reduced the risk of severe PONV (11 *vs.* 15%; risk ratio [RR], 0.74 [95% CI, 0.63 to 0.84]; $P < 0.001$), with a stronger effect in Asian patients (RR, 0.55 [95% CI, 0.43 to 0.69]; interaction $P = 0.004$) but lower effect in those who received PONV prophylaxis (RR, 0.89 [95% CI, 0.76 to 1.05]; $P = 0.18$). Gastrointestinal surgery was associated with an increased risk of severe PONV when compared with most other types of surgery ($P < 0.001$). Patients with severe PONV had lower quality of recovery scores (10.4 [95% CI, 10.2 to 10.7] *vs.* 13.1 [95% CI, 13.0 to 13.2], $P < 0.0005$); severe PONV was associated with postoperative fever (15 *vs.* 20%, $P = 0.001$). Patients with severe PONV had a longer hospital stay (adjusted hazard ratio, 1.14 [95% CI, 1.05 to 1.23], $P = 0.002$).

Conclusions: The increased risk of PONV with nitrous oxide is near eliminated by antiemetic prophylaxis. Severe PONV, which is seen in more than 10% of patients, is associated with postoperative fever, poor quality of recovery, and prolonged hospitalization. **(ANESTHESIOLOGY 2016; 124:1032-40)**

NITROUS oxide is a well-recognized risk factor for postoperative nausea and vomiting (PONV),[1–3] particularly in more extensive surgical procedures in which exposure to nitrous oxide is prolonged.[3] Most episodes of PONV are transient and perhaps insignificant; in contrast, persistent or recurrent PONV has distinct clinical importance.[4,5] However, most studies characterizing *any* PONV or the effectiveness of antiemetic regimens have focused on minor and ambulatory surgery. In this study, we focused on protracted and/or repeat episodes of PONV occurring up to 3 days after surgery.

We recently completed the Evaluation of Nitrous oxide in the Gas Mixture for Anesthesia (ENIGMA) II trial, which confirmed the cardiovascular safety of nitrous oxide in 7,112 at-risk patients having major noncardiac surgery in

What We Already Know about This Topic

- Nitrous oxide is a known risk factor for postoperative nausea and vomiting (PONV), but its role in severe (persistent or recurrent) PONV is less clear
- The risk factors for severe PONV were examined by a secondary analysis of data from the Evaluation of Nitrous oxide in the Gas Mixture for Anesthesia II trial that randomized subjects undergoing noncardiac surgery to receive nitrous oxide or nitrous oxide–free anesthetic

What This Article Tells Us That Is New

- Nitrous oxide increased the risk of severe postoperative nausea and vomiting (PONV), more so in Asian subjects; the effect was eliminated by pretreatment with an antiemetic
- Severe PONV was associated with fever, poor quality of recovery, and increased hospital stay, indicating that its prevention is clinically important

This article is featured in "This Month in Anesthesiology," page 1A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has an audio podcast.

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45 participating centers from 10 countries. The incidence of severe PONV was recorded prospectively as a prespecified secondary end point, and we demonstrated the higher rates of PONV in those receiving nitrous oxide.[6] Furthermore, we demonstrated that antiemetic prophylaxis could mitigate this risk.[6] Therefore, we explored the risk of severe PONV in those receiving a nitrous oxide or nitrous oxide–free anesthetic according to the prespecified subgroups, and we calculated the incidence, risk factors, and effectiveness of PONV prophylaxis for severe PONV in patients who participated in the ENIGMA-II trial.

Our primary hypothesis was that there was an association between severe PONV and patient outcomes, including quality of recovery (QoR), fever, wound infection, and hospital stay.

Materials and Methods

ENIGMA-II trial was registered at ClinicalTrials.gov (number: NCT00430989; principal investigator: P.S.M.; date of registration: January 31, 2007). The trial protocol was approved by the institutional review board at each site (sponsor site: Alfred Health Ethics Committee), and written informed consent was obtained from participating patients. Protocol details have been published.[6,7] Briefly, we enrolled patients aged 45 yr or older with known or suspected coronary artery disease who were scheduled to have general anesthesia for surgery lasting at least 2 h. Patients having cardiac surgery or requiring one-lung ventilation or in whom nitrous oxide was contraindicated in the opinion of the attending anesthesiologist (*e.g.*, current bowel obstruction, history of severe PONV), were excluded.

Randomization was performed using a computer-generated code, accessed *via* an automated telephone voice recognition service. Treatment assignment was stratified by site using permuted blocks. For patients assigned to nitrous oxide, anesthesiologists were asked to give nitrous oxide at an inspired concentration of 70% in 30% oxygen; for patients assigned to no nitrous oxide, anesthesiologists were asked to use an air–oxygen mixture at an inspired oxygen concentration of 30%. In either case, the designated gas was started shortly after induction of anesthesia and tracheal intubation or laryngeal mask insertion and was continued until completion of surgery.

The choice of anesthetic, analgesic, and antiemetic drugs was left to the discretion of the attending anesthesiologist. Attending anesthesiologists were aware of group assignment, but allocation was concealed from the surgeons, patients, and staff responsible for postoperative data collection and outcome assessment.

Measurements

Preoperative demographic characteristics and details of patient medical and surgical history were recorded. Asian ethnicity was implied for all patients enrolled in Hong Kong, Malaysia, and Singapore study sites. We calculated a modified PONV risk score based on the validated criteria[8,9] that included sex (female = 1, male = 0), age (less than 50 yr = 1, more than or equal to 50 yr = 0), smoking status (nonsmoker = 1, smoker = 0), and use of postoperative opioids (yes = 1, no = 0); the latter criterion was scored as 1 in all patients receiving intraoperative morphine, and so scores ranged from 1 (low risk) to 4 (high risk).

Fever was defined as any recorded temperature more than or equal to 38°C within 3 days of surgery. Postoperative wound infection was defined by the Centers for Disease Control and Prevention description of surgical site infection (*i.e.*, purulent drainage, or positive microbial culture from the incision, or documented wound infection in medical record) within 30 days of surgery.[10]

The primary outcome measure was severe PONV. This was assessed at 24 h after surgery by a face-to-face interview, and data were confirmed with medical record review. Severe PONV was defined as two or more episodes of nausea and/or expulsion of gastric contents, at least 6 h apart, or requiring treatment with at least three doses of at least two different classes of antiemetic medication in any 24-h period during the 3 days after surgery. We did not collect data for less severe PONV (mild or transient nausea, single episode of vomiting, or single or repeat doses of same antiemetic therapy). On day 1 after surgery, patients also rated their postoperative QoR using a validated 9-item scale score (QoR score, 0 = worst recovery to 18 = excellent recovery).[11]

Statistical Analyses

Statistical analyses were conducted according to intention-to-treat principles. Data are presented as mean ± SD, median (interquartile range), or n (%). Nitrous oxide and nitrous oxide–free groups were compared with unadjusted risk ratios (RRs) and 95% CIs using binary regression with a logarithmic link, with the no-nitrous oxide group as the reference category. We compared the baseline characteristics

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of patients who suffered severe PONV up to 3 days after surgery with those who did not using chi-square or Wilcoxon rank sum tests, as appropriate.

Risk factors for severe PONV were determined using multivariable logistic regression models, including separately those who received PONV prophylaxis or who did not in order to ascertain the risk factor–treatment interaction and to inform clinical practice in either circumstance. In these regression models, the dependent variable was severe PONV on postoperative day 1. The 17 independent variables were prespecified and included age, sex, American Society of Anesthesiologists physical status, body mass index, country, presence of diabetes mellitus, coronary artery disease, regular use of folate/multivitamins or vitamin B_{12} injection, smoking habits, ethnicity, surgical types, duration of anesthesia, intraoperative exposure to nitrous oxide, propofol infusion, regional block, bispectral index monitoring, and avoidance of morphine administration. Model fit was assessed using area under the receiver operating characteristic curve.

The associations between severe PONV and postoperative fever, wound infection, and adverse events were determined using logistic regression. We compared QoR scores between patients with and without severe PONV using the Wilcoxon rank sum test. The impact of severe PONV on length of hospital stay was assessed using a Cox proportional hazards model.

We determined the efficacy of various prophylactic strategies for severe PONV by calculating the relative risk for severe PONV using a log binomial model. To adjust for the lack of randomization of prophylactic strategies, which led to imbalances between different treatment groups, analyses were adjusted using a propensity score approach.[12] The balance of baseline covariates between treatment groups was assessed using the standardized difference, the difference between the percentage (categorical or binary variables) or mean (continuous variables) between groups, divided by the SD, and expressed as a percentage.[12] Standardized differences more than 10% in absolute value are taken to be indicative of meaningful imbalances between groups, and inverse probability of treatment weighting was used to account for the differences between groups.

Inverse probability of treatment weighting is a propensity score–based approach, with treatment probabilities estimated using a propensity score model. In the case of categorical treatments, a multinomial logistic regression model was used. These models contained baseline characteristics and were selected iteratively to ensure balance between treatment groups as assessed by the standardized difference, according to recommendations.[12] Each patient was weighted by the estimated probability of receiving the treatment that they actually received. A key assumption required for the validity of propensity score–based approaches is that all patients have a positive probability of receiving each treatment.[13] Hence, patients with estimated propensity scores higher or lower than those of patients in any other treatment group were excluded from analyses to ensure the comparability of patients across treatment groups; this resulted in 2,257 exclusions for this secondary analysis.

We considered two classifications of prophylactic PONV interventions: (1) classification by number of antiemetic drugs administered (with patients classified as receiving 0, 1, or 2 or more drugs) and (2) classification by type of PONV intervention (classified as patients receiving no antiemetics, dexamethasone, 5-hydroxytryptamine$_3$ [5-HT$_3$] receptor antagonists, or both dexamethasone and 5-HT$_3$ receptor antagonists). Other antiemetic combinations were not tested because there were few patients receiving such combinations.

All analyses were conducted using Stata 12 software (Stata Corporation, USA). All P values were two sided, with $P < 0.05$ considered to be statistically significant.

Results

Nitrous Oxide and Severe PONV

Patient demographic and perioperative characteristics of those given nitrous oxide or a nitrous oxide–free anesthetic are reported in table 1. There was a small (0.1%) amount of missing PONV outcome data, mostly because of critical illness or early deaths. Patients assigned to the nitrous oxide group were more likely to receive PONV prophylaxis ($P < 0.001$). Avoiding nitrous oxide reduced the risk of severe PONV (11 *vs.* 15%; RR, 0.74 [95% CI, 0.63 to 0.84]; $P < 0.0001$). The emetogenic effect of nitrous oxide was stronger in Asian patients (interaction $P = 0.004$; RR, 1.89 [95% CI, 1.08 to 2.33], $P < 0.001$) and in those receiving intraoperative morphine (RR, 1.72 [95% CI, 1.41 to 2.13], $P < 0.001$; fig. 1). Avoiding nitrous oxide had a smaller effect in non-Asian patients (RR, 0.84 [95% CI, 0.72 to 0.97]). As previously reported,[6] avoiding nitrous oxide had a nonsignificant effect on the risk of PONV if antiemetic prophylaxis was used (RR, 0.89 [95% CI, 0.76 to 1.05], $P = 0.18$).

Figure 1 reports the results of prespecified subgroup analyses of the impact of eliminating nitrous oxide on severe PONV. The protective effect of PONV prophylaxis in those exposed to nitrous oxide was most apparent in Asian patients (further details in the Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/B260).

Risk Factors for Severe PONV

A total of 884 patients (12.4%) had severe PONV within 3 days of surgery. Table 2 reports the comparison of baseline characteristics in patients who did or did not suffer severe PONV; further details are provided in Supplemental Digital Content 1 (tables 2 and 3, http://links.lww.com/ALN/B260), for which the multivariate logistic regression models for severe PONV had areas under the receiver operating characteristic curve of 0.71 (for patients with PONV prophylaxis) and 0.72 (for patients without PONV prophylaxis). Female patients, nonsmokers, gastrointestinal surgery patients, and those having surgery more than 2 h *and* receiving nitrous oxide were more likely to suffer severe PONV whether or not they received prophylactic antiemetics (fig. 2). Asian patients were not at an increased risk of

Table 1. Patient and Perioperative Characteristics*

Characteristic	Nitrous Oxide (N = 3,495)	No Nitrous Oxide (N = 3,516)
Age (yr), mean (SD)	69.2 ± 9.8	69.5 ± 9.7
Age ≥ 60 yr, n (%)	2,861 (82)	2,922 (83)
Female sex, n (%)	1,253 (36)	1,299 (37)
Body weight (kg), mean (SD)	78.3 (20.1)	77.7 (19.1)
Race, n (%)		
White	2,587 (74)	2,630 (75)
Asian/other	908 (26)	886 (25)
ASA physical status, n (%)		
1 or 2	1,083 (31)	1,120 (32)
3 or 4	2,412 (69)	2,395 (69)
Nausea and vomiting risk score, n (%)		
1	476 (14)	414 (12)
2	1,882 (54)	1,945 (55)
3	1,100 (32)	1,121 (32)
4	29 (0.8)	33 (0.9)
Preexisting medical conditions, n (%)		
Hypertension	2,941 (84)	2,994 (85)
Coronary artery disease	1,257 (36)	1,309 (37)
Heart failure	268 (7.7)	276 (7.8)
Previous myocardial infarction	733 (21)	768 (22)
Peripheral vascular disease	1,201 (34)	1,213 (35)
Previous stroke or TIA	637 (18)	627 (18)
Current smoker (≤ 6 wk)	686 (20)	622 (18)
Diabetes	1,310 (38)	1,270 (36)
Type of surgery, n (%)		
Vascular	1,348 (39)	1,369 (39)
Gastrointestinal	714 (20)	695 (20)
Orthopedic	483 (14)	481 (14)
Neurosurgery (spinal)	280 (8.0)	280 (8.0)
Urology (renal)	289 (8.3)	312 (8.9)
Gynecology	166 (4.7)	151 (4.3)
Ear, nose, throat, or faciomaxillary	102 (2.9)	101 (2.9)
Plastics/other	117 (3.3)	127 (3.6)
Antiemetic prophylaxis	2,088 (60)	1,934 (55)
Elective surgery, n (%)	3,357 (96)	3,370 (96)
Duration of surgery (h), median (IQR)	2.6 (1.9–3.7)	2.6 (1.9–3.6)
Duration of anesthesia (h), median (IQR)	3.2 (2.4–4.4)	3.2 (2.4–4.4)

Postoperative nausea and vomiting (PONV) risk score was calculated as follows: patient sex (female = 1, male = 0), age (< 50 yr = 1, ≥ 50 yr = 0), intraoperative morphine (= 1), and smoking status (nonsmoker = 1, smoker = 0).

*Most of these data, and further details, have been reported previously.[6]

ASA = American Society of Anesthesiologists; IQR = interquartile range; TIA = transient ischemic attack.

PONV, despite being less likely to receive PONV prophylaxis (Supplemental Digital Content 1, table 3, http://links.lww.com/ALN/B260).

Impact of Severe PONV

Patients with severe PONV had lower QoR scores compared with those who did not (10.4 [95% CI, 10.2 to 10.7] *vs.* 13.1 [95% CI, 13.0 to 13.2], $P < 0.0005$). The absolute difference in QoR score, adjusted for age, sex, American Society of Anesthesiologists physical status, use of nitrous oxide, and duration of surgery, was 2.45 (95% CI, 2.20 to 2.70).

Severe PONV was an independent predictor of postoperative fever (5 *vs.* 20%; adjusted odds ratio, 1.44 [95% CI, 1.17 to 1.77]; $P = 0.001$). However, it was not associated with wound infection (adjusted odds ratio, 1.20 [95% CI, 0.92 to 1.57]; $P = 0.19$) and other adverse events (adjusted odds ratio, 1.20 [95% CI, 0.97 to 1.48]; $P = 0.093$). Nevertheless, patients with severe PONV had a longer hospital stay (median [interquartile range], 7.0 [4.9 to 12.1] days) compared with those who did not (6.0 [3.2 to 10.1] days; adjusted hazard ratio, 1.14 [95% CI. 1.05 to 1.23]; $P = 0.002$; fig. 3).

Prophylactic Interventions for Severe PONV

The PONV risk score identified those at higher risk of severe PONV (table 3). Patients at higher risk of PONV were more likely to receive antiemetic prophylaxis (table 4).

Asian patients were less likely to receive PONV prophylaxis (286 of 1,398 [21%]) when compared with non-Asian patients (3,680 of 5,585 [66%]). This generally did not increase their risk of PONV, except in those receiving nitrous oxide (Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/B260).

A total of 2,227 (32%) patients were given dexamethasone, 2,728 (39%) were given 5-HT_3 receptor antagonists, and 418 (6%) were given droperidol or haloperidol. Thirty-seven percent of patients were given single-drug PONV prophylaxis, 18% were given dual prophylaxis, and 1% were given triple prophylaxis. There was no measurable superior effect of single-drug prophylaxis using dexamethasone, 5-HT_3 receptor antagonist, or droperidol/haloperidol on the rates of severe PONV. Similarly, combinations of antiemetic interventions were not associated with reduced risk of severe PONV, whether or not analyses were adjusted using a propensity score (Supplemental Digital Content 1, tables 2 to 8, http://links.lww.com/ALN/B260).

Discussion

In this preplanned secondary analysis of the ENIGMA-II trial, we found that severe PONV occurred in 12.4% of patients having major noncardiac surgery. Female patients, nonsmokers, gastrointestinal surgery patients, and those having surgery more than 2 h in duration were more likely to suffer severe PONV whether or not they received prophylactic antiemetics. PONV has been regarded by some as a minor inconvenience, primarily because PONV does not necessarily indicate diminished patient satisfaction or functional impairment.[14,15] However, our analysis showed that patients with severe PONV had poorer QoR, with a QoR score difference of 2.45 (95% CI, 2.20 to 2.70), which exceeds the direct effect of PONV (maximum 2 point difference) on the QoR score itself, suggesting that strategies to avoid severe PONV are clinically important.

Our subgroup analyses demonstrate that the emetogenic effects of nitrous oxide occurred in a broad range of patient groups and surgeries, suggesting that similar effects are likely

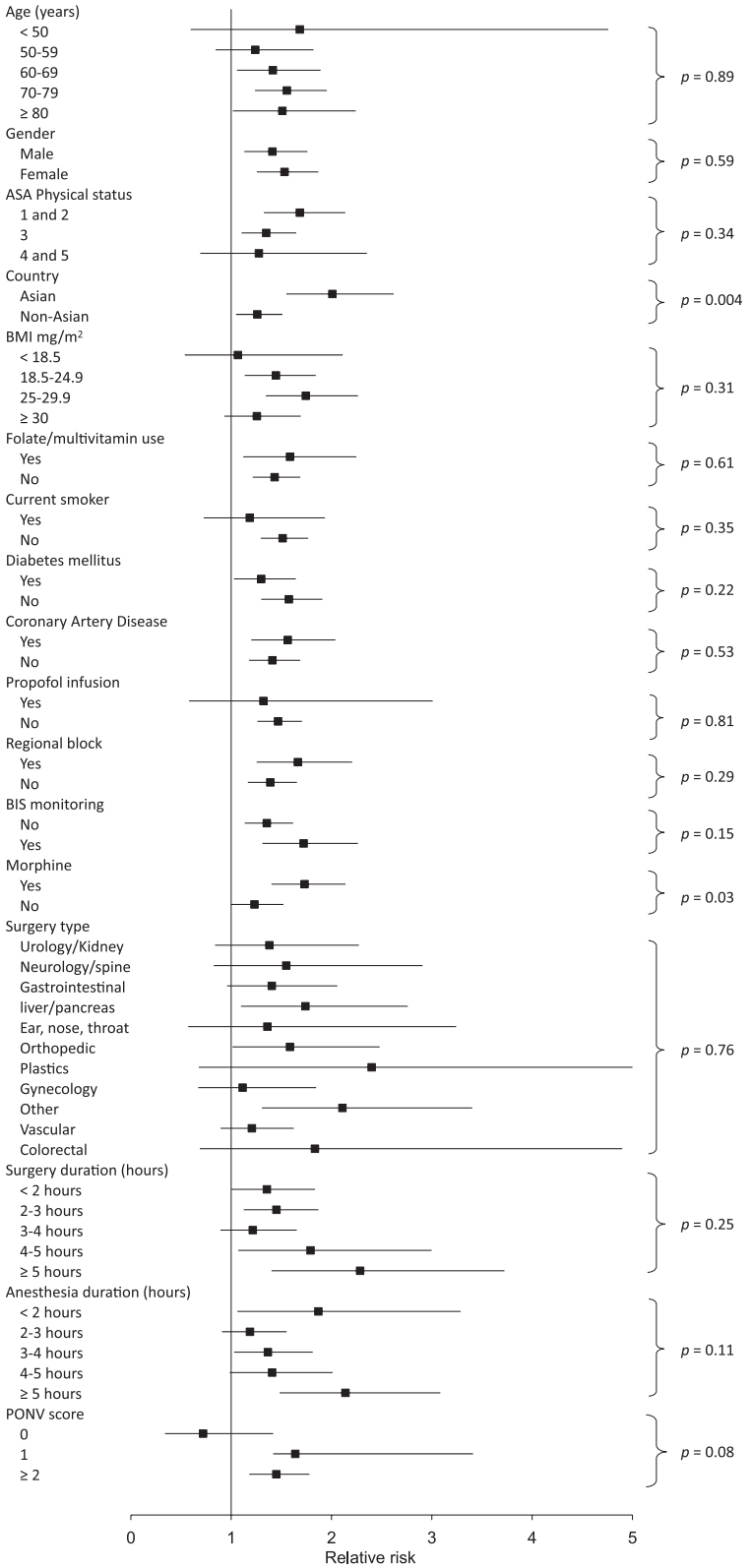

Fig. 1. Relative risk (*bars* indicate 95% CI) for severe postoperative nausea and vomiting (PONV) associated with the use of nitrous oxide in selected subgroups. The reported *P* values refer to tests of interaction. ASA = American Society of Anesthesiologists; BIS = bispectral index; BMI = body mass index.

Table 2. Risk Factors for Severe PONV Adjusted for All Listed Covariables, for All Patients

	Severe PONV			
	n/N	%	OR (95% CI)	*P* Value
PONV prophylaxis and nitrous oxide				
No nitrous oxide and no PONV prophylaxis	153/1,585	9.7	1.00 (reference)	
Nitrous oxide and no PONV prophylaxis	234/1,405	16.7	2.00 (1.60–2.51)	< 0.001
No nitrous oxide and PONV prophylaxis	225/1,904	11.8	1.65 (1.03–2.64)	0.037
Nitrous oxide and PONV prophylaxis	270/2,054	13.1	1.82 (1.14–2.90)	0.012
PONV prophylaxis and age (yr)				
< 60 and no PONV prophylaxis	43/449	9.6	1.00 (reference)	
60–69 and no PONV prophylaxis	111/806	13.8	1.54 (1.05–2.28)	0.028
70–79 and no PONV prophylaxis	166/1,250	13.3	1.27 (0.88–1.85)	0.20
≥ 80 and no PONV prophylaxis	67/485	13.8	1.21 (0.79–1.86)	0.39
< 60 and PONV prophylaxis	106/752	14.1	1.31 (0.92–1.87)	0.13
60–69 and PONV prophylaxis	126/1,130	11.2	1.08 (0.77–1.52)	0.64
70–79 and PONV prophylaxis	200/1,542	13.0	1.07 (0.79–1.47)	0.65
≥ 80 and PONV prophylaxis	63/534	11.8	Omitted	
Female	463/2,526	18.3	2.13 (1.81–2.50)	< 0.001
ASA physical status				
1 or 2	328/2,188	15.0	1.00 (reference)	
3	500/4,273	11.7	0.96 (0.80–1.15)	0.65
4 or 5	54/487	11.1	1.01 (0.72–1.41)	0.97
Asian	258/1,392	18.5	1.05 (0.82–1.34)	0.71
BMI categories (kg/m^2)				
< 18.5	34/184	18.5	1.00 (reference)	
18.5–24.9	318/2,255	14.1	0.84 (0.55–1.27)	0.40
25–29.9	303/2,418	12.5	0.88 (0.57–1.33)	0.53
≥ 30	227/2,091	10.9	0.67 (0.44–1.04)	0.078
Folate/multivitamin	166/1,265	13.1	0.99 (0.82–1.20)	0.91
Vitamin B_{12} injections	19/200	9.5	0.66 (0.40–1.09)	0.10
Nonsmoker	785/5,670	13.8	1.62 (1.27–2.05)	< 0.001
Diabetes	344/2,551	13.5	0.95 (0.81–1.11)	0.51
Coronary artery disease	286/2,542	11.3	1.09 (0.92–1.29)	0.31
Propofol maintenance	31/221	14.0	1.27 (0.85–1.91)	0.24
Regional LA block	283/1,890	15.0	1.28 (1.07–1.53)	0.006
BIS monitoring	289/2,789	10.4	0.85 (0.72–1.00)	0.049
Morphine	430/3,252	13.2	1.01 (0.85–1.20)	0.94
Surgery type				
Gastrointestinal*	322/1,376	23.4	1.00 (reference)	
Renal/bladder	81/591	13.7	0.60 (0.45–0.79)	< 0.001
Neurology/spine	44/554	7.9	0.32 (0.23–0.46)	< 0.001
Ear-nose-throat	21/202	10.4	0.43 (0.26–0.70)	0.001
Orthopedic	93/960	9.7	0.34 (0.26–0.46)	< 0.001
Plastics	11/95	11.6	0.52 (0.27–1.00)	0.049
Gynecology	75/314	23.9	0.74 (0.54–1.01)	0.060
Vascular	215/2,710	7.9	0.36 (0.29–0.44)	< 0.001
Other	20/146	13.7	0.56 (0.34–0.93)	0.026
Anesthesia duration (h)				
< 2	68/826	8.2	1.00 (reference)	
2–3	255/2,144	11.9	1.63 (1.22–2.18)	0.001
3–4	222/1,758	12.6	1.76 (1.31–2.37)	< 0.001
4–5	154/1,057	14.6	2.08 (1.52–2.85)	< 0.001
≥ 5	183/1,163	15.7	1.94 (1.42–2.64)	< 0.001

Interaction terms between postoperative nausea and vomiting (PONV) prophylaxis and nitrous oxide (interaction $P < 0.001$) and PONV prophylaxis and age category (interaction $P = 0.087$) were included. These were the only significant (at $P < 0.10$) interactions.

*Includes hepatobiliary-pancreatic-and colorectal surgery.

ASA = American Society of Anesthesiologists; BIS = bispectral index; BMI = body mass index; LA = local anesthetic; OR = odds ratio.

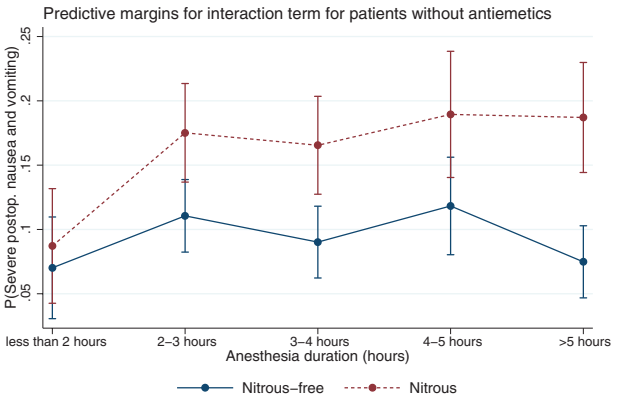

Fig. 2. Predictive probability of severe postoperative nausea and vomiting (PONV) for patients without PONV prophylaxis, for each combination of anesthetic duration and treatment group (nitrous oxide–free or nitrous oxide anesthetic).

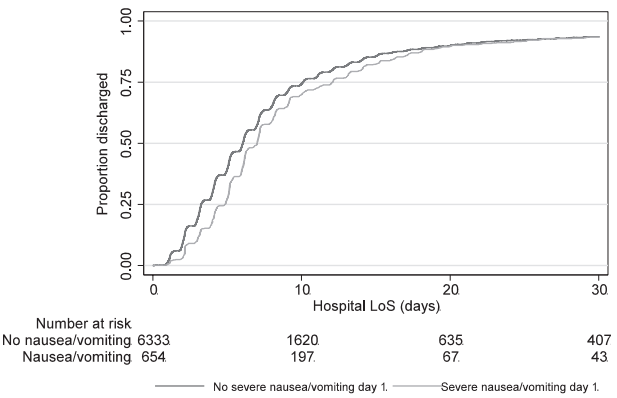

Fig. 3. Kaplan–Meier estimate of the time-to-discharge function (hospital length of stay [LoS]), comparing patients with and without severe postoperative nausea and vomiting up to 30 days after surgery (Wilcoxon rank sum test, $P < 0.0001$).

Table 3. Number (%) of Patients with Severe PONV, According to PONV Risk Score

PONV Risk Score	No Severe PONV, n (%)	Severe PONV, n (%)	Total n
1	840 (94)	50 (5.6)	890
2	3,413 (89)	406 (11)	3,819
3	1,801 (81)	416 (19)	2,217
4	50 (81)	12 (19)	62
Total	6,104 (87)	884 (13)	6,988

Chi-square test $P < 0.0005$. Postoperative nausea and vomiting (PONV) risk score was calculated as follows: patient sex (female = 1, male = 0), age (< 50 yr = 1, ≥ 50 yr = 0), intraoperative morphine (= 1), and smoking status (nonsmoker = 1, smoker = 0).

to occur in other settings. However, although eliminating nitrous oxide from the anesthetic gas mixture decreased the risk of severe PONV by one third, the absolute reduction was only 4% (a *number needed to treat* of 25), which is of questionable clinical importance. Furthermore, pretreatment with one or more common antiemetics, such as dexamethasone or a 5-HT_3 receptor antagonist, eliminated the effect of nitrous oxide on severe PONV. Based on these results, we believe that concern about severe PONV is not a valid reason to avoid nitrous oxide. We also demonstrated a higher risk of severe PONV with increasing time of exposure to nitrous oxide when surgery is greater than 2 h in duration. The impact of duration of exposure is consistent with a recent pooled analysis of PONV studies evaluating nitrous oxide.[3]

Table 4. Number (%) of Patients with Any Antiemetic Prophylaxis, According to PONV Risk Score

PONV Risk Score	No Antiemetic, n (%)	Any Antiemetic, n (%)	Total n
1	453 (51)	436 (49)	889
2	1,720 (45)	2,107 (55)	3,827
3	844 (38)	1,375 (62)	2,219
4	10 (16)	51 (84)	61
Total	3,027 (43)	3,969 (57)	6,996

Chi-square test $P < 0.0005$. Postoperative nausea and vomiting (PONV) risk score was calculated as follows: patient sex (female = 1, male = 0), age (< 50 yr = 1, ≥ 50 yr = 0), intraoperative morphine (= 1), and smoking status (nonsmoker = 1, smoker = 0).

Although this study confirms the emetogenic properties of nitrous oxide, the mechanism is still debated and may well be multifactorial. Anesthetic drugs, particularly opioids, are commonly implicated in PONV, but genetic and emotional predisposition[16] of patients and the underlying inflammatory response to surgery[17] all contribute to PONV. PONV, by itself, may aggravate the inflammatory response to surgery and impair wound healing.[18]

The strengthened association of nitrous oxide with severe PONV among people of Asian ethnicity is a new finding and is of practical importance. Previous studies have shown that people of Asian descent have increased nausea and vomiting after selected types of chemotherapy[19] and an increased susceptibility to motion sickness,[20] possibly associated with an increase in vasopressin concentrations.[20] Therefore, anesthesiologists should consider people of Asian descent at a higher risk of severe PONV when using nitrous oxide. We also found that Asian patients had greater risk of PONV on univariate testing (Supplemental Digital Content 1, table 2, http://links.lww.com/ALN/B260), but this largely disappeared after adjustment of other variables (especially nonsmoking status) and was not an independent risk (table 2). Nevertheless, Asian patients were less likely to receive PONV prophylaxis, and this should be rectified in future.

Our study found that gastrointestinal surgery of at least 2 h in duration was an independent risk factor for severe PONV. Although some types of surgery have been implicated as risk factors for PONV, only laparoscopic and gynecologic surgeries are currently identified in the most recent guidelines.[1] Anatomically, intraoperative manipulation of gastrointestinal tract enhances serotonin release from the enterochromaffin cells and might increase the risk of severe PONV.[21] Our findings provide strong support for routine PONV prophylaxis in all patients undergoing gastrointestinal surgery that is expected to last at least 2 h.

We found that severe PONV was associated with postoperative fever. Although this does not imply a causal relationship, both postoperative fever and severe PONV may serve as indicators for impending complications. Increased levels of cytokines may be a common cause for both,[22] and often this will be related to the amount of tissue damage from the surgery.[23] More importantly, patients with severe PONV had a longer hospital stay, suggesting that severe PONV has both functional and cost consequences.

Limitations and Strengths

We did not include a history of PONV or motion sickness in our risk models. We have not adjusted for the multiple comparisons and although this was a preplanned secondary analysis of the ENIGMA-II trial, it is likely that some statistically significant findings may be spurious. We could not identify a statistically significant association between nitrous oxide and wound infection, but the point estimate indicated a 20% increased risk, and so it is possible that we missed a true effect because of inadequate study power for this uncommon complication.

We did not study lesser degrees of PONV in which symptoms did not require any treatment or resolved with a single antiemetic drug administration. In contrast to previous studies,[9] we were unable to demonstrate additive antiemetic effects of propofol-based anesthesia, dexamethasone, 5-HT_3 receptor antagonists, and haloperidol or droperidol in ENIGMA-II trial patients. Consistent with this, there was no significant difference in severe PONV whether one or more prophylactic antiemetics were given. We offer two explanations for these findings. First, patients were not randomly assigned to the use of antiemetic prophylaxis, and propensity-based methods may not account for residual confounding. Second, the recommended dosage of common antiemetics may only prevent less severe symptoms. In a cluster-randomized trial that evaluated the implementation of a PONV prediction model, additional prophylactic antiemetics did not reduce the incidence of PONV over and above using a single antiemetic.[24]

The main strengths of our study are that we included 7,112 patients from 45 sites in 10 countries and achieved complete follow-up in 99.9% of patients. We have focused on severe PONV, using criteria that are known to be clinically important.[4] The subgroup findings suggest that the results are likely to be generalizable to other surgical populations.

Conclusions

Nitrous oxide increases the risk of severe PONV by only a small percentage, and the increased risk is essentially eliminated by antiemetic drug prophylaxis. Concern about severe PONV thus does not appear to be a valid reason to avoid nitrous oxide. Nitrous oxide–induced severe PONV was more likely to occur in Asian patients. Severe PONV was more likely in those undergoing gastrointestinal surgery. Severe PONV, which is seen in more than 10% of patients, is associated with postoperative fever, poor QoR, and prolonged hospitalization.

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Competing Interests

Dr. Paech has received funding from MSD Schering-Plough Pty Ltd., Macquarie Park, New South Wales, Australia. The other authors declare no competing interests.

Reproducible Science

Full protocol available from Dr. Myles: p.myles@alfred.org.au. Raw data available from Dr. Myles: p.myles@alfred.org.au.

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