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Risk factors for severe postoperative nausea and vomiting in a randomized trial of nitrous oxide-based *vs* nitrous oxide-free anaesthesia

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Background. Refractory postoperative nausea and vomiting (PONV) requiring repeated treatment with antiemetic drugs is a miserable experience for the patient that may substantially increase the cost of care. As risk stratification may aid in prophylaxis and treatment, we explored risk factors for severe PONV in patients enrolled in a large international, randomized controlled trial (the ENIGMA trial).

Methods. Two thousand and fifty patients, aged $\geq$18 yr and undergoing surgery anticipated to exceed 2 h in duration, were recruited. Patients were randomized to nitrous oxide (N_2O)-based or N_2O-free anaesthesia. Choice of other anaesthetic, analgesic, and antiemetic drugs was left to the discretion of the anaesthetist. Anaesthetic depth was adjusted according to clinical judgement and, if available, bispectral index (BIS) monitoring. Severe PONV was defined as: (i) two or more episodes of expulsion of gastric contents at least 6 h apart; (ii) received at least three doses of antiemetic medication for treatment of PONV, within 24 h of surgery; or both. We used logistic regression, and classification and regression tree analysis, to define risk factors for severe PONV.

Results. Three hundred and thirty-three (16.6%) patients experienced severe PONV. Age $<$55 yr, female sex, abdominal surgery, N_2O administration, absence of BIS monitoring, and longer duration of anaesthesia were predictors of severe PONV [area under receiver operating characteristic curve=0.70 (95% confidence interval: 0.67–0.73)].

Conclusions. Severe PONV was common and risk factors for it were similar to those reported in other studies that included all patients reporting nausea, vomiting, or both.

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Transient nausea and vomiting in the early postoperative period are certainly troublesome and undesirable complications of anaesthesia.[1 2] However, refractory postoperative nausea and vomiting (PONV) requiring repeated treatment with antiemetic drugs is a miserable experience for the patient that may substantially increase the cost of care.[2]

In many studies of PONV, the primary endpoint is defined as one or more episodes of nausea, vomiting, or both in the postoperative period.[3–9] Therefore, patients with transient or mild symptoms are combined with patients suffering from more severe PONV. In order to define risk factors and develop preventative strategies for *severe* PONV, an analysis focusing on patients with severe PONV is required.

Some of the risk factors for PONV are well established.[10] However, when combined into risk scores or models, these factors do not predict all the cases of PONV.[10] It is important therefore to seek further epidemiological, clinical, and genetic factors that increase the likelihood of PONV.[10] We believe that this is especially important in relation to severe PONV, because these patients are likely to benefit most from risk reduction strategies and prophylactic antiemetics.[2 11]

We recently completed an international, multi-centred randomized trial of nitrous oxide (N_2O)-based *vs* N_2O-free anaesthesia in 2050 adult patients presenting for surgery anticipated to last at least 2 h (the ENIGMA trial).[12] The incidence of severe nausea and vomiting in the first 24 h after surgery was prospectively reported as a secondary endpoint of the trial. In this paper, we explore the risk factors of severe PONV in the ENIGMA trial patients.

Methods

With institutional review board approval at each site and written informed patient consent, we recruited 2050 patients to this randomized controlled trial. The protocol for the trial was described in detail elsewhere.[12] Briefly, eligible patients were aged 18 yr or older, and were scheduled to receive general anaesthesia for surgery that included a skin incision and that was anticipated to exceed 2 h. Patients undergoing cardiac surgery or thoracic surgery requiring one-lung ventilation, or in whom N_2O was contraindicated in the opinion of the anaesthetist (e.g. past history of severe postoperative emesis and current bowel obstruction), were excluded. The primary hypothesis of the ENIGMA trial was that avoidance of N_2O in the gas mixture for anaesthesia may decrease the duration of hospital stay. The current paper presents an analysis of one of the secondary outcomes of the trial. This secondary analysis was prospectively planned.

Procedures

Randomization was achieved using a computer-generated code, accessed *via* an automated telephone service, and occurred after consent had been obtained. For patients in the N_2O-based group, anaesthetists were advised to administer 70% N_2O with 30% oxygen. For patients in the N_2O-free group, anaesthetists were advised to administer 80% oxygen with 20% nitrogen. Randomized gas mixtures were used after induction of anaesthesia and airway instrumentation, and until completion of surgery. In both groups, a range of inspired oxygen concentrations (25–100%) was allowed if the anaesthetist had a strong preference, medical air was unavailable, or if clinically indicated (e.g. haemoglobin oxygen saturation was inadequate). In particular, anaesthetists could administer 100% oxygen during induction of anaesthesia and after completion of surgery, and could prescribe oxygen therapy in the recovery room and postoperative surgical ward.

Choice of other anaesthetic, analgesic, and antiemetic drugs was left to the discretion of the attending anaesthetist. Anaesthetic depth was adjusted according to clinical judgement and, if available, bispectral index (BIS) monitoring (Version 3.4, A-2000 monitor, Aspect Medical Systems Inc., Norwood, MA, USA). Choice of antibiotic prophylaxis was according to institutional practice and anaesthetists were advised to avoid intraoperative hypothermia ($<35.5^{\circ}C$).

Attending anaesthetists were aware of group identity, but this was concealed from the surgeons (using drapes or cardboard to screen the anaesthesia machine), patients, and staff responsible for postoperative data collection and outcome assessment. Postoperative management, including analgesia and antiemetics, was at the discretion of the patients' carers.

Measurements

Preoperative demographic characteristics and details of patient medical and surgical history were recorded. A past history of PONV or motion sickness and postoperative opioid use were not recorded.

Severe PONV was defined as: (i) two or more episodes of expulsion of gastric contents at least 6 h apart; (ii) received at least three doses of antiemetic medication for treatment of PONV, within the first 24 h after surgery; or both. Severe PONV was assessed at 24 h post-surgery by an interview and medical record review.

Statistical analyses

All randomized patients were considered as comprising the intention-to-treat population for all primary and secondary analyses. Continuous data were graphed to assess their distribution. Data were summarized using mean (SD) (symmetrically distributed data), median (range) (interquartile range) (skewed data), and number (%) (categorical data). Groups were compared using unpaired, two-tailed *t*-tests (symmetrically distributed data), Wilcoxon rank-sum tests (skewed data), χ^2 tests (categorical data), or log rank tests (survival data). Because of the expected possibility of interactions between two or more covariates, including effect modifiers, we chose to explore the confounding effect of those variables found to have a significant ($P<0.20$) association with severe PONV in multivariate logistic regression models. We thus developed a parsimonious model of independent predictors of risk of

severe PONV. We used receiver operating characteristic (ROC) analysis on our logistic regression model. These statistical analyses were conducted using Stata 8.2 (Stata Corporation, College Station, TX, USA).

In addition, we applied a recursive partitioning or classification and regression tree analysis (CART).[13] Whereas logistic regression is used to define overall relationships between potential risk factors and outcomes, CART is used to examine local or subgroup relationships. For example, CART, or similar procedures, has been used to identify high-risk groups for harmful alcohol use[14] and patients at high risk of atrial fibrillation after cardiac surgery.[15]

We used the CART 6 (2006) binary tree-building procedure (Salford Systems, San Diego, CA, USA). All of the variables used in the logistic regression analysis were available for selection by CART. BIS monitoring and N_2O were entered into CART first, because a significant interaction between them was identified during logistic regression modelling. We began with the full data set (n=2012). Although CART includes cross-validation procedures, we further tested the methodology by randomly splitting the sample into a training sample to create the CART tree (n=1509; 75%) and a testing sample (n=503; 25%) to test it.[14] Both subsamples were highly similar on the composition of the outcome variable. The classification accuracy obtained for each subset was compared using a χ^2 test, if not significantly different, the two samples were combined and the tree reconstructed on the total sample. Finally, the final subgroups (or 'terminal nodes') of the CART tree were entered into a logistic regression analysis, adjusting for the effects of possible risk factors available to, but not chosen by, CART (i.e. age <45 yr and abdominal surgery).[14]

All reported P-values are two-sided and not adjusted for multiple comparisons.[16 17]

Results

Of the 2050 randomized patients, 2012 patients were included in the intention-to-treat analyses of the ENIGMA trial.[12] Three hundred and thirty-three (16.6%) of these patients experienced severe PONV in the first 24 h after surgery.

Patients aged <55 yr experienced a higher rate of severe PONV than older patients (Table 1). The age effect remained significant, despite a higher incidence of smoking in younger patients (84% *vs* 74%; P<0.0001). However, fewer younger patients underwent abdominal surgery (50% *vs* 62%; P<0.0001) and durations of anaesthesia were shorter in younger patients [2.9 (0.5–17.5) *vs* 3.4 (0.5–12.4) h; P<0.0001]. There were no statistically significant differences in the rates of propofol maintenance (16% *vs* 12%; P=0.064) or BIS monitoring (19% *vs* 22%; P=0.137) between younger and older patients.

Table 1 Baseline characteristics of patients with and without severe PONV (n=2012). Data are presented as mean (SD) (normally distributed data) or number (%) (categorical data). PONV, postoperative nausea and vomiting; ASA, American Society of Anesthesiologists

Characteristic	PONV (n=333)	No PONV(n=1679)	P-value
Age (yr)	53 (18–89)	56 (18–99)	0.0197
Weight (kg)	66 (18)	66 (21)	0.5903
Sex (female)	208 (62)	751 (45)	<0.0001
ASA physical status			
I	76 (23)	339 (20)	
II	186 (56)	919 (55)	
III/IV	71 (21)	421 (25)	0.273
Chinese race	130 (39)	574 (34)	0.090
Non-smoking status	283 (85)	1311 (78)	0.005
Surgery			
General	166 (50)	754 (45)	
Neurosurgery	34 (10)	261 (15)	
Urology	44 (13)	213 (13)	
Orthopaedic	125 (8)	166 (10)	
Gynaecology	40 (12)	107 (6)	
Other	24 (7)	178 (11)	<0.0001
Abdominal surgery	225 (68)	915 (54)	<0.0001

Women experienced a higher rate of severe PONV than men. Women in this trial were younger [53 (16) *vs* 57 (16) yr; P<0.0001], healthier (ASA III/IV: 22% *vs* 27%; P=0.003), and more likely to be non-smokers (86% *vs* 73%; P<0.0001) than men. The effect of female sex persisted in older women: the incidence of PONV was 23% in women *vs* 14% in men aged <55 yr (P<0.0001), and 20% in women and 10% in men aged ≥55 yr (P<0.0001).

There was a trend towards a higher rate of severe PONV in Chinese patients than non-Chinese patients. Forty-one per cent of Chinese patients were female compared with 51% of non-Chinese patients (P<0.0001). Chinese patients were more likely to have abdominal surgery (77% *vs* 46%; P<0.0001) and surgery lasting more than 3 h (88% *vs* 38%; P<0.0001) than non-Chinese patients.

N_2O-based anaesthesia was associated with a higher rate of severe PONV than N_2O-free anaesthesia (Table 2). Volatile anaesthetic maintenance was not associated with a higher rate of severe PONV than propofol maintenance. Propofol maintenance was administered to 13% of women and 13% of men, but was used more often in patients undergoing neurosurgery than in patients undergoing other types of surgery (21% *vs* 12%; P<0.0001). Propofol maintenance was used in 13% of patients in the N_2O-based group and 19% of patients in the N_2O-free group (P<0.001).

BIS-monitored patients experienced a lower rate of severe PONV than non-BIS monitored patients. BIS monitoring was used in 42% of patients maintained with propofol and 18% of patients maintained with volatile anaesthetics (P<0.0001). In the patients maintained with propofol, BIS monitoring was used in 68% of patients who received N_2O and 47% of patients who did not receive N_2O (P=0.003). BIS-monitored patients received lower doses of volatile agents [MAC-equivalents: 0.58 (0.24)% *vs* 0.82 (0.45)%; P<0.0001] and propofol [target

Table 2 Intraoperative characteristics of patients with and without severe PONV (n=2012). Data are presented as mean (SD) (normally distributed data); median [range (inter-quartile range)] (skewed data) or number (%) (categorical data). PONV, postoperative nausea and vomiting; $F_{I_{O_2}}$, fraction of inspired oxygen; ICU, intensive care unit

Characteristic	PONV (n=333)	No PONV (n=1679)	P-value
Nitrous oxide	229 (69)	786 (47)	<0.0001
$F_{I_{O_2}}$ (%) (quartiles)			
≤30	64 (19)	166 (10)	
31–40	155 (47)	585 (35)	
41–80	40 (12)	315 (19)	
>80	74 (22)	613 (37)	<0.0001
Propofol maintenance	39 (12)	228 (13)	0.359
Intraoperative morphine (mg)			
0.1–5.0	18 (8)	150 (14)	
5.1–10.0	110 (50)	536 (51)	
10.1–15.0	59 (27)	252 (24)	
>15.0	32 (14)	106 (10)	0.029
Intraoperative antiemetic	114 (34)	584 (35)	0.848
BIS monitoring	52 (16)	367 (22)	0.010
Duration of anaesthesia (h)			
<2.5	86 (26)	525 (31)	
2.5–3.4	84 (25)	452 (27)	
3.5–4.4	53 (16)	264 (16)	
≥4.5	110 (33)	438 (26)	0.047

concentration: 2.95 (0.50) *vs* 3.39 (0.85) μg ml^{-1}; P<0.0001] for maintenance than patients who were not BIS-monitored. BIS-monitored patients opened their eyes after discontinuation of anaesthesia more rapidly than patients who were not BIS-monitored [7 (0–124) *vs* 12 (0–183) min; P<0.0001].

Antiemetics were more likely to be administered to younger patients than older patients (39% *vs* 31%; P<0.0001), women than men (41% *vs* 29%; P<0.0001), non-Chinese than Chinese patients (15% *vs* 45%; P<0.0001), and patients receiving volatile anaesthetic agents than those receiving propofol maintenance (36% *vs* 26%; P=0.02). However, antiemetics were less likely to be administered to patients having abdominal surgery than patients having other types of surgery (40% *vs* 31%; P<0.0001). There was no significant difference in antiemetic use in the N_2O-based and N_2O-free groups (35% *vs* 34%) or in non-smokers and smokers (35% *vs* 34%).

Age <55 yr, female sex, abdominal surgery, N_2O administration, absence of BIS monitoring, and longer duration of anaesthesia were predictors of severe PONV in our multivariate logistic regression model (Table 3)

Table 3 Predictors of severe PONV (n=2012). PONV, postoperative nausea and vomiting; $F_{I_{O_2}}$, fraction of inspired oxygen. Pseudo-R^2 for logistic regression model=0.0764

Characteristic	Patients, n(%)	PONV, n(%)	Univariate OR (95% CI)	P-value	Multivariate OR (95% CI)	P-value
Age (yr)						
≥55	1078 (54)	156 (14)	1.00		1.00	
<55	934 (46)	177 (19)	1.38 (1.09–1.75)	0.007	1.35 (1.05–1.72)	0.019
Sex						
Male	1053 (52)	125 (12)	1.00		1.00	
Female	959 (48)	208 (22)	2.06 (1.61–2.62)	<0.0001	2.07 (1.60–2.66)	<0.0001
Chinese race						
No	1308 (65)	203 (16)	1.00		—	
Yes	704 (35)	130 (18)	1.23 (0.97–1.57)	0.090	—	—
Non-smoking status						
No	418 (21)	50 (12)	1.00		—	
Yes	1594 (79)	283 (18)	1.59 (1.15–2.19)	0.005	—	—
Abdominal surgery						
No	872 (43)	108 (12)	1.00		1.00	
Yes	1140 (57)	225 (20)	1.74 (1.36–2.23)	<0.0001	1.78 (1.37–2.32)	<0.0001
Nitrous oxide						
No	997 (50)	104 (10)	1.00		1.00	
Yes	1015 (50)	229 (23)	2.50 (1.95–3.21)	<0.0001	2.04 (1.55–2.70)	<0.0001
$F_{I_{O_2}}$ (%) (quartiles)						
≤30	230 (11)	64 (28)	1.00		—	
31–40	740 (37)	155 (21)	0.69 (0.49–0.96)	0.030	—	—
41–80	355 (19)	40 (11)	0.33 (0.21–0.51)	<0.0001	—	—
>80	687 (34)	74 (11)	0.31 (0.21–0.46)	<0.0001	—	—
Intraoperative morphine (mg)						
0.1–5	168 (13)	18 (11)	1.00		—	
5.1–10	646 (51)	110 (17)	1.71 (1.01–2.91)	0.047	—	—
10.1–15	311 (25)	59 (19)	1.95 (1.11–3.43)	0.120	—	—
>15	138 (11)	32 (23)	2.52 (1.34–4.72)	0.004	—	—
BIS monitoring						
No	1593 (79)	281 (18)	1.00		1.00	
Yes	419 (21)	52 (12)	0.66 (0.48–0.91)	0.011	0.34 (0.19–0.61)	<0.0001
Duration of anaesthesia (h)						
<2.5	611 (30)	86 (14)	1.00		1.00	
2.5–3.4	536 (27)	84 (16)	1.13 (0.82–1.57)	0.448	1.31 (0.94–1.83)	0.115
3.5–4.4	317 (16)	53 (17)	1.23 (0.84–1.78)	0.285	1.42 (0.95–2.12)	0.089
≥4.5	548 (27)	110 (20)	1.53 (1.13–2.09)	0.007	1.82 (1.30–2.55)	<0.0001
Nitrous oxide×BIS interaction					2.46 (1.22–4.96)	0.012

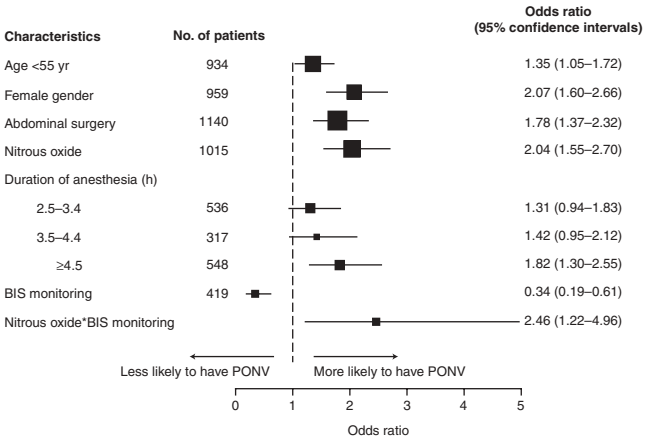

Fig 1 Multivariate odds ratios (95% CIs) for PONV for preoperative and intraoperative predictors.

(Fig. 1). An interaction term between N_2O and BIS monitoring was significant. The ROC area for the logistic regression model was 0.70 [95% confidence interval (CI): 0.67–0.73].

There was no significant difference between the training and the testing subsets in terms of the incidence of vomiting (16.7% *vs* 16.1%; P=0.763) or classification performance of the CART tree (P=0.411) and so the two subsets were combined.

The results of the CART recursive partitioning subgroup analysis are shown in Figure 2. The reference group in the CART analysis was the BIS-monitored group who did not receive N_2O (5.8% incidence of PONV). Addition of the terminal nodes generated by the CART model to our logistic regression model did not significantly change the area under the ROC curve [0.70 (95% CI: 0.67–0.73);

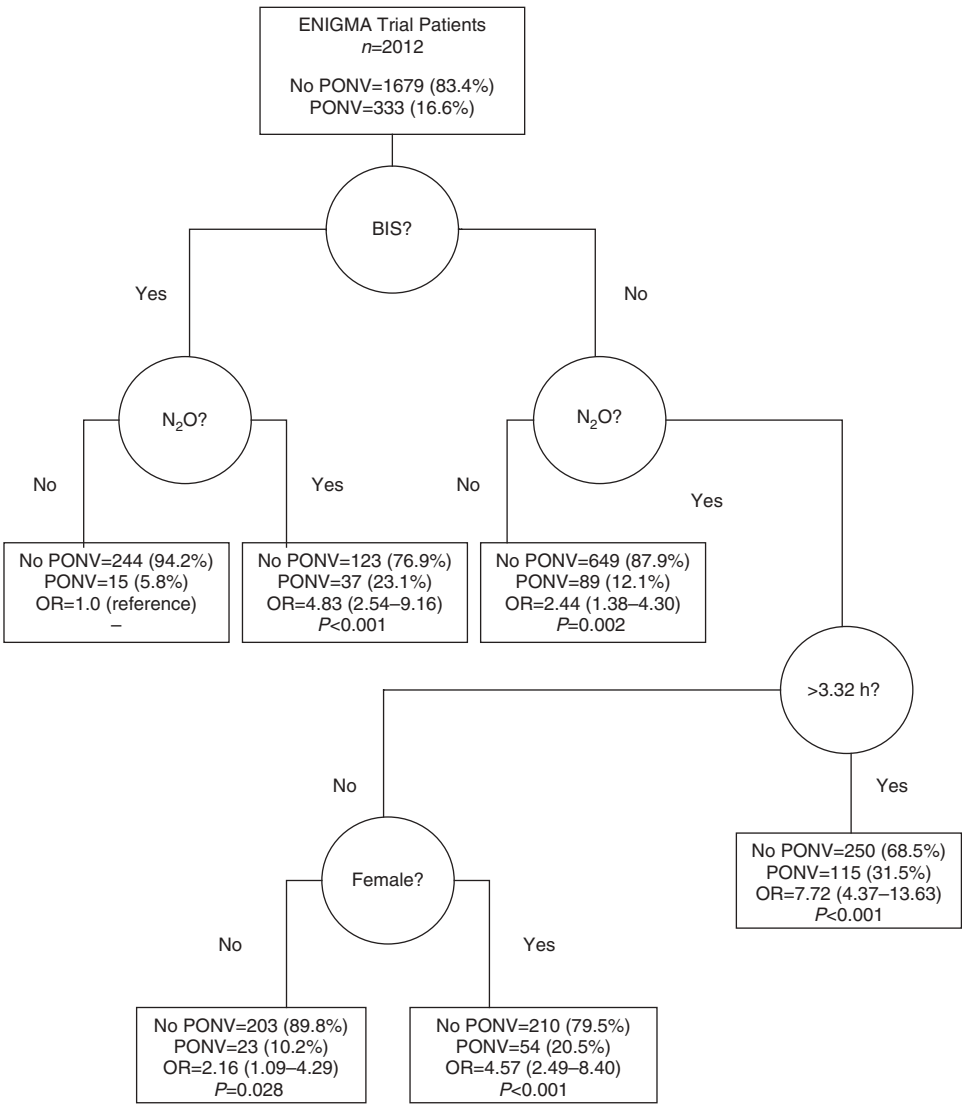

Fig 2 Recursive partitioning/CART analysis of factors predicting severe PONV. BIS monitoring and N_2O were entered into CART first, because a significant interaction between them was identified. CART splits the variable 'duration of anaesthesia' at 3.32 h. Odds ratios (OR) (95% CIs and P-values) are reported from analysis that were adjusted for age <55 yr and abdominal surgery (factors that CART did not include in the model). The subgroup of patients with the lowest risk of PONV (BIS-monitored and N_2O-free) served as the reference group.

P=0.1436 compared with the original logistic regression model].

Patients with severe PONV spent more time in the recovery room [95 (IQR: 67–130) *vs* 85 (IQR: 64–120) min; P=0.045] than those without severe PONV. The rates of major complications (32% *vs* 30%) and hospital lengths of stay [7.3 (IQR: 4.9–12.2) *vs* 7.0 (IQR: 4.0–11.1) days] were similar in patients with and without severe PONV.

Discussion

Severe PONV within 24 h of surgery was a common occurrence in the ENIGMA trial. This provided an excellent opportunity to assess risk factors and develop a model applicable to patients having major non-ambulatory surgery expected to last more than 2 h.

Our multivariate logistic regression model included several proven risk factors for PONV: female sex,[3–9 18–21] younger age,[4 6 18 21] abdominal surgery,[7 8 21] N_2O administration,[6 8 22] and longer duration of anaesthesia.[4 6 8 9 18–20] Previous studies defined PONV as one or more episode of nausea, vomiting, or both—our study proves that these risk factors are predictive of *severe* PONV as well. The generalizability of our results is high, as our study was conducted at 19 centres in Australia, New Zealand, Hong Kong, Singapore, Saudi Arabia, and the UK and included a broad range of adult patients aged up to 99 yr.[10]

Our model included one independent risk factor (absence of BIS monitoring) that has not been included in previous risk models. Our result is consistent with a meta-analysis of 11 randomized trials that reported that a pooled odds of PONV in BIS-monitored patients compared with routine-care patients of 0.77 (95% CI: 0.56–0.99; P=0.04), although the overall risk reduction was small (37.5% incidence of PONV in routine-care patients *vs* 31.5% in BIS-monitored patients).[23] The effect of BIS monitoring is probably mediated through a reduction in anaesthetic dose,[10] an effect that was also reconfirmed in our study.

Several widely reported risk factors, including non-smoking status[5 6 8 19 20 24] and higher dose intraoperative opioid administration,[3 6 7 18 19] were predictive in univariate but not multivariate analyses in our study. In addition, the incidence of severe PONV was similar in patients maintained with propofol and volatile anaesthetics, conflicting with previous reports.[25 26]

These differences may be attributed to the fact that all anaesthetic interventions apart from N_2O and oxygen administration were made at the discretion of the anaesthetist and were not randomized. Propofol maintenance was administered to more patients having neurosurgery (a risk factor in some studies)[10] and more patients who were randomized to N_2O,[6 8 22] but on the other hand, propofol-maintained patients were more likely to be monitored with BIS[23] and to receive antiemetics.[8] Anaesthetists may have selected the type of anaesthetic maintenance, opioid dose, antiemetic use, and monitoring based on their assessment of factors we did not record in our study, such as a past history of PONV or motion sickness.

Oxygen concentration was not a predictor of severe PONV in our study. An apparent effect in the univariate analyses was due to confounding by administration of N_2O to patients receiving lower inspired concentrations of oxygen. This result confirms a recent meta-analysis of previous randomized controlled trials.[27]

Genetic factors other than gender almost certainly play a role in the aetiology of PONV;[10] however, reports about the influence of ethnicity have been conflicting so far.[21 28] In our study, a higher incidence of severe PONV in Chinese patients than other patients could be explained by the higher rate of abdominal surgery, less frequent use of anti-emetics, and the longer duration of surgery in Chinese patients.

Our multivariate logistic regression model had an ROC value of 0.70. The model includes six risk factors (three preoperative and three intraoperative) and an interaction term between N_2O administration and BIS monitoring. This ROC area is in the same range as those reported for other risk scores and models,[3–6 19 20] reflecting the imperfect prediction of risk scores and models for PONV.[10] Simplified risk scores are easy to apply, but have the disadvantage of giving equal weighting to a small number of risk factors. Models are harder to calculate clinically, but can account for subcategories of predictor variables (such as multiple categories for duration of anaesthesia) and can weight factors differentially. New models such as ours may aid in the refinement of existing simplified risk scores or the development of new ones,[10] though it should be emphasized that several well-established risk factors were not considered for inclusion in our model.

We used the CART analysis to explore the interactions between predictors of PONV in our study and to attempt to improve the predictive power (area under ROC curve) of our model. CART is a very conservative approach because of the cross-validation involved and therefore compensates for multiple comparisons to some extent. CART provided interesting information about the odds of vomiting in subgroups of our dataset. For example, CART predicted that patients who were not BIS-monitored, who received N_2O, who had anaesthesia lasting more than 3.32 h, and who were female were ≈5 times more likely to vomit than the reference patients. However, addition of the terminal nodes (interactions) from CART did not improve the predictive power of our model. In addition, it should be noted that the number of patients in the terminal subgroups is quite small. This analysis does highlight, however, the potential utility of CART analysis in this area.

We did not record a past history of PONV or motion sickness, or postoperative opioid use in our patients, both of which are proven risk factors for PONV.[10] Our protocol

was designed before consensus guidelines for managing PONV were published[11] and PONV was not the primary endpoint of our study. The protocol also left the management of PONV entirely to the anaesthetists' discretion. Nevertheless, exclusion of these data from our analysis may have decreased the accuracy of our model or altered the factors that were included in the model, and may explain the apparent lack of effectiveness of prophylactic antiemetic drugs. Prophylactic antiemetics were more likely to be administered to patients at high risk of PONV (i.e. women and younger patients). However, the high baseline rate of antiemetic administration (25%) may be explained by the anaesthetists taking into account risk factors that we did not record (such as a past history of PONV or motion sickness, or likely postoperative opioid use). Finally, we undertook multiple comparisons which increases the chance of a type I error. Differences between the groups therefore should be treated with caution.

In conclusion, the incidence of severe PONV in the ENIGMA trial patients was 16.6%. Age $<$55 yr, female sex, abdominal surgery, N_2O administration, absence of BIS monitoring, and longer duration of anaesthesia were predictors of severe PONV in our multivariate logistic regression model. These risk factors are similar to those reported in studies that included patients reporting any nausea, vomiting, or both. Identification of risk factors for severe PONV is especially important, as these patients are likely to benefit most from risk reduction strategies and prophylactic antiemetics.

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Appendix

Members of the ENIGMA Trial Steering Group: Chairs: P.S.M. (Alfred Hospital); K.L. (Royal Melbourne Hospital); Endpoint Adjudicator: J. Tomlinson (Alfred Hospital); Biostatisticians: A.F., E. Pascoe (Monash University); Data Management: A. Saldukas (Alfred Hospital); Project Coordinator: J. Hunt (Alfred Hospital).

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