2016-05-02

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

Myles, PS

10.1097/ALN.0000000000001057
Anesthesiology
Ovid Technologies (Wolters Kluwer Health)

Severe Nausea and Vomiting in the ENIGMA-II Trial

Paul S. Myles, M.B.,B.S., M.P.H., M.D., F.C.A.I., F.A.N.Z.C.A., F.R.C.A., F.A.H.M.S.*

Matthew T.V. Chan, M.B.,B.S., Ph. D., F.A.N.Z.C.A., F.H.K.C.A.†

Jessica Kasza, B.Sc., Ph.D.‡

Michael J. Paech, M.B.,B.S., D.M., F.A.N.Z.C.A., F.F.P.M.A.N.Z.C.A., F.R.A.N.Z.C.O.G. §

Kate Leslie, M.B.,B.S., M.D., M.Epi., M.Hlth.Serv.Mt., F.A.N.Z.C.A.#

Philip J. Peyton, M.B.,B.S., M.D., Ph.D., F.A.N.Z.C.A.¥

Daniel I. Sessler, M.D.~

Guy Haller, M.D., M.Sc, Ph.D.Δ

W. Scott Beattie, M.D., Ph.D.≈

Cameron Osborne, M.B.,B.S., F.A.N.Z.C.A.¤

J. Robert Sneyd, M.B., M.Chir., M.A., M.D., F.R.C.A¶

Andrew Forbes, M.Sc., Ph.D.‡

and the ANZCA Clinical Trials Network

*Department of Anaesthesia and Perioperative Medicine, Alfred Hospital and Monash University, Melbourne, Victoria, Australia.
†Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, People's Republic of China.
‡Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia.
§School of Medicine and Pharmacology, The University of Western Australia, Perth, Australia.
#Department of Anaesthesia and Pain Management, Royal Melbourne Hospital; Anaesthesia, Perioperative and Pain Medicine Unit, and Department of Pharmacology and Therapeutics, University of Melbourne, Melbourne, Victoria, Australia.
¥Department of Surgery, Austin Hospital and University of Melbourne, Melbourne, Australia, and Institute for Breathing and Sleep, Victoria, Australia.
~Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH, US.
ΔDepartement of Anaesthesia, Intensive Care and Pharmacology, Geneva University Hospitals-University of Geneva (Switzerland) Chief Quality Officer, Departement of Anaesthesia, Intensive Care and Pharmacology, Geneva University Hospitals-University of Geneva, Switzerland.
≈Department of Anesthesia and Pain Management, University Health Network, and Department of Anesthesia, University of Toronto, Ontario, Canada.

¤ Department of Anesthesia, Perioperative and Acute Pain Management, Barwon health, Geelong, Victoria, Australia.
¶Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, UK

Address for Correspondence
Paul Myles
Department of Anaesthesia and Perioperative Medicine
Alfred Hospital
Commercial Road
Melbourne, Victoria, 3004
Australia
p.myles@alfred.org.au

Funding disclosure: The Australian National Health and Medical Research Council, and the Australian New Zealand College of Anaesthetists, and the Canadian Heart and Stroke Foundation provided funding for this work.

Word Count: Total: 2613, Abstract: **301**, Introduction: 209, Discussion: 934.

Abbreviated Title: Severe PONV and Nitrous Oxide

Registration: ClinicalTrials.gov number NCT00430989

What We Already Know about This Topic

- The major risks factors for postoperative nausea and vomiting (PONV) are female sex, history of PONV or motion sickness, non-smoker status, and use of intraoperative opioids
- Nitrous oxide increases the risk of PONV
- Laparoscopic and gynecological surgery are associated with increased risk of PONV

What This Article Tells Us That Is New

- Asians are more adversely affected by nitrous oxide-induced PONV
- Gastrointestinal surgery is a risk factor for PONV
- Longer duration of surgery is a risk factor for PONV but this can be controlled with antiemetic prophylaxis
- Severe PONV is associated with early postoperative fever, poor quality of recovery, and increased hospital stay

Abstract

Background: The ENIGMA-II trial randomly assigned 7112 noncardiac surgery patients from 45 participating centers in 10 countries to a nitrous oxide or nitrous oxide-free anesthetic; severe postoperative nausea and vomiting (PONV) was a prespecified secondary endpoint. We thus evaluated the association between nitrous oxide, severe PONV and patient outcomes, and effectiveness of PONV prophylaxis in this setting.

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

Results: A total of 884 patients (12.4%) had severe PONV within 3 days of surgery. Avoiding nitrous oxide reduced the risk of severe PONV, 11% versus 15%, risk ratio (RR) 0.74 (95% CI: 0.63-0.84), $P < 0.001$, with a stronger effect in Asians, RR 0.53 (95% CI: 0.43-0.93). Avoidance of nitrous oxide did not significantly reduce PONV in those who received PONV prophylaxis, RR 0.89 (95% CI: 0.76-1.05), $P = 0.18$. Gastrointestinal surgery was associated with increased risk of severe PONV when compared to most other types of surgery ($P < 0.001$). Patients with severe PONV had lower quality of recovery scores compared with those who did not, 10.4 (95% CI: 10.2-10.7) versus 13.1 (95% CI: 13.0-13.2), $P < 0.0005$. Severe PONV was associated with postoperative fever (15% vs. 20%, $P = 0.001$) but not wound infection or other adverse events. Patients with severe PONV had a longer hospital stay, adjusted hazard ratio 1.14 (95% CI: 1.05-1.23), $P = 0.002$.

Conclusion: The increased risk of PONV seen with nitrous oxide is essentially eliminated by antiemetic prophylaxis. Severe PONV was more likely in Asian patients

and in those undergoing gastrointestinal surgery. Severe PONV, which is seen in over 10% of patients, is associated with postoperative fever, poor quality of recovery, and prolonged hospitalization.

Introduction

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 characterising *any* PONV or the effectiveness of anti-emetic regimens have focused on minor and ambulatory 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 7112 at-risk patients having major noncardiac surgery in 45 participating centers from 10 countries. The incidence of severe PONV was recorded prospectively as a prespecified secondary endpoint, and we demonstrated higher rates of PONV in those receiving nitrous oxide.[6] Furthermore, we demonstrated that anti-emetic prophylaxis could mitigate this risk.[6] We therefore explored the risk of severe PONV in those receiving a nitrous oxide or nitrous oxide-free anesthetic according to prespecified subgroups, and we calculated the incidence, risk factors and effectiveness of PONV prophylaxis for severe PONV in patients who participated in ENIGMA II.

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

Methods

The ENIGMA-II trial protocol was approved by institutional review board at each site and written informed consent was obtained from participating patients. Protocol details have been published.[6,7] Briefly, we enrolled patients ≥45 years with known or suspected coronary artery disease who were scheduled to have general anesthesia for surgery lasting at least two hours. 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 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, Malaysian and Singapore study sites. We calculated a modified PONV risk score based on validated criteria,[8,9] that included gender (female = 1, male = 0), age (<50 years = 1, ≥50 years = 0), smoking status (non-smoker = 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 (lower risk) to 4 (high risk).

The primary outcome measure was severe PONV. This was assessed at 24 hours 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 six hours apart; or requiring treatment with at least three doses of at least two different classes of anti-emetic medication in any 24 h period during the three 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 anti-emetic therapy). On day 1 after surgery patients also rated their postoperative quality of recovery using a validated 9-item scale score (QoR Score, 0 = worst recovery to 18 = excellent recovery).[10]

Statistical Analyses

Statistical analyses were conducted according to intention-to-treat principles. Data are presented as mean ± standard deviation (SD), median (interquartile range [IQR]) or number (%). Nitrous oxide and nitrous oxide-free groups were compared with unadjusted risk ratios (RR) and 95% confidence intervals (CI) using binary regression with a logarithmic link, with the no-nitrous oxide group as the reference category. We compared the baseline characteristics of patients who suffered severe PONV on day 1 after surgery with those who did not using χ^2 or Wilcoxon rank sum tests, as appropriate.

Risk factors for severe PONV were determined using multivariable logistic regression models, including separately for those who received PONV prophylaxis or 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, gender, American Society of Anesthesiologists physical status, body mass index, 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 (temperature ≥38°C), wound infection, and adverse events were determined using logistic regression. We

compared quality of recovery 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 binary logistic regression model. To adjust for the lack of randomisation of prophylactic strategies, which led to imbalances between different treatment groups, analyses were adjusted using a propensity score approach.[11]

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 anti-emetic combinations were not tested since there were few patients receiving such combinations.

All analyses were conducted using Stata 12 software (Stata Corporation, College Station, TX, 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. Patient 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% versus 15%, RR 0.74 (95% CI: 0.63-0.84), P <0.0001. The emetogenic effect of nitrous oxide was stronger in Asians, RR 1.89 (95% CI: 1.08-2.33), P < 0.001, and in those receiving intraoperative morphine, RR 1.72 (95% CI: 1.41-2.13), P < 0.001 – see Figure 1. As previously reported,[6] the emetogenic effect of nitrous oxide became nonsignificant if PONV prophylaxis was used, RR 0.89 (95% CI: 0.76-1.05), 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 (Web Supplement Table 1).

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 Web Supplement Table 2, 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, non-smokers, gastrointestinal surgery patients, and those having surgery more than 2

hours *and* receiving nitrous oxide were more likely to suffer severe PONV whether or not they received prophylactic antiemetics (Figure 2).

Impact of Severe PONV

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

Severe PONV was an independent predictor of postoperative fever (5% versus 20%, adjusted odds ratio 1.44 [95% CI: 1.17-1.77]; P = 0.001). However, it was not associated with wound infection (adjusted odds ratio 1.20 [95% CI: 0.92-1.57]; P = 0.19) and other adverse events (adjusted odds ratio 1.20 [95% CI: 0.97-1.48]; P = 0.093). Nevertheless, patients with severe PONV had a longer hospital stay, median (IQR) 7.0 (4.9-12.1) days, compared with those who did not, 6.0 (3.2-10.1) days, adjusted hazard ratio 1.14 (95% CI: 1.05-1.23), P = 0.002 (Figures 3 and 4).

Prophylactic Interventions for Severe PONV

The PONV risk score identified those at highest risk of severe PONV (Table 3). Patients at higher risk of PONV were more likely to receive anti-emetic prophylaxis (Table 4).

Asian patients were less likely to receive PONV prophylaxis (286 of 1398 [21%]) when compared to non-Asian patients (3680 of 5585, [66%]). This generally did not increase their risk of PONV, except in those receiving nitrous oxide (Web Supplement Table 1).

A total of 2,227 (32%) patients were given dexamethasone, 2,728 (39%) were given a 5-HT_3 receptor antagonists, and 418 (6%) were given droperidol or haloperidol. 37% 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 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 (Web Supplements Tables 2-7).

Discussion

In this pre-planned secondary analysis of the ENIGMA II trial, we found that severe PONV occurred in 12.4% of patients having major noncardiac surgery. Female patients, non-smokers, gastrointestinal surgery patients, and those having surgery more than two hours 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.[12,13] However, our analysis showed that patients with severe PONV had poorer quality of recovery, with a QoR score

difference of 2.45 (95% CI: 2.20-2.70), 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 similar effects are likely to occur in other settings. However, although eliminating nitrous oxide from the anesthetic gas mixture lowered 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 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 hours in duration. The impact of duration of exposure is consistent with a recent pooled analysis of PONV studies evaluating nitrous oxide.[3]

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 patient genetic and emotional predisposition,[14] and the underlying inflammatory response to surgery[15] all contribute. PONV, of itself, may aggravate the inflammatory response to surgery and impair wound healing.[16]

The strengthened association of nitrous oxide and severe PONV among people of Asian ethnicity is a new finding and of practical importance. Previous studies have shown that people of Asian descent have increased nausea and vomiting after selected types of chemotherapy[17] and an increased susceptibility to motion sickness,[18] possibly associated with an increase in vasopressin concetrations.[18] Anesthesiologists should therefore 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 (Web Supplement Table 2), but this largely disappeared after adjustment of other variables (esp. non-smoking status) and was not an independent risk (Table 2).

Our study found that gastrointestinal surgery of at least 2 hours 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 surgery 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.[19] Our findings provide strong support for routine PONV prophylaxis in all patients undergoing gastrointestinal surgery expected to last at least 2 hours.

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,[20] and often this will be related to the amount of tissue damage from the surgery.[21] 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 have not adjusted for the multiple comparisons and so 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 we missed a true effect because of inadequate study power for this uncommon complication.

In contrast to previous studies,[9] we were unable to demonstrate additive antiemetic effects of propofol-based anesthesia, dexamethasone, $5HT_3$ 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. Firstly, patients were not randomly assigned to the use of antiemetic prophylaxis and propensity-based methods may not account for residual confounding. Secondly, 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 anti-emetic.[22]

The main strengths of our study are that we included 7112 patients from 45 sites in 10 countries and achieved complete follow-up in 99.9% of patients. We have focussed 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, which is seen in over 10% of patients, is associated with postoperative fever, poor quality of recovery, and prolonged hospitalization.

References

1. Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, Watcha M, Chung F, Angus S, Apfel CC, Bergese SD, Candiotti KA, Chan MT, Davis PJ, Hooper VD, Lagoo-Deenadayalan S, Myles P, Nezat G, Philip BK, Tramer MR: Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2014; 118: 85-113
2. Leslie K, Myles PS, Chan MT, Paech MJ, Peyton P, Forbes A, McKenzie D: Risk factors for severe postoperative nausea and vomiting in a randomized trial of nitrous oxide-based vs nitrous oxide-free anaesthesia. Br J Anaesth 2008; 101: 498-505
3. Peyton PJ, Wu CY: Nitrous oxide-related postoperative nausea and vomiting depends on duration of exposure. Anesthesiology 2014; 120: 1137-45
4. Myles PS, Wengritzky R: Simplified postoperative nausea and vomiting impact scale for audit and post-discharge review. Br J Anaesth 2012; 108: 423-9
5. Gan T, Sloan F, Dear G, El-Moalem H, Lubarsky D: How much are patients willing to pay to avoid postoperative nausea and vomiting. Anesth Analg 2001; 92: 393-400
6. Myles PS, Leslie K, Chan MT, Forbes A, Peyton PJ, Paech MJ, Beattie WS, Sessler DI, Devereaux PJ, Silbert B, Schricker T, Wallace S, investigators ATGftE-I: The safety of addition of nitrous oxide to general anaesthesia in at-risk patients having major non-cardiac surgery (ENIGMA-II): a randomised, single-blind trial. Lancet 2014; 384: 1446-54
7. Myles PS, Leslie K, Peyton P, Paech M, Forbes A, Chan MT, Sessler D, Devereaux PJ, Silbert BS, Jamrozik K, Beattie S, Badner N, Tomlinson J, Wallace S: Nitrous oxide and perioperative cardiac morbidity (ENIGMA-II) Trial: rationale and design. Am Heart J 2009; 157: 488-494 e1
8. Apfel C, Laara E, Koivuranta M, Greim C, Roewer N: A simplified risk score for predicting postoperative nausea and vomiting. Anesthesiology 1999; 91: 693-700
9. Gan T: Risk factors for postoperative nausea and vomiting. Anesth Analg 2006; 102: 1884-98
10. Myles P, Hunt J, Nightingale C, Fletcher H, Beh T, Tanil D, Nagy A, Rubinstein A, Ponsford J: Development and psychometric testing of a quality of recovery score after general anesthesia and surgery in adults. Anesth Analg 1999; 88: 83-90
11. Williamson EJ, Forbes A: Introduction to propensity scores. Respirology 2014; 19: 625-35
12. Fisher DM: The "big little problem" of postoperative nausea and vomiting: do we know the answer yet? Anesthesiology 1997; 87: 1271-3
13. Fisher D: Surrogate outcomes: they don't get it. Anesth Analg 2009; 109: 994
14. Joy Lin YM, Hsu CD, Hsieh HY, Tseng CC, Sun HS: Sequence variants of the HTR3A gene contribute to the genetic prediction of postoperative nausea in Taiwan. J Hum Genet 2014; 59: 655-60
15. Ma W, Wang K, Du J, Luan J, Lou G: Multi-dose parecoxib provides an immunoprotective effect by balancing T helper 1 (Th1), Th2, Th17 and regulatory T cytokines following laparoscopy in patients with cervical cancer. Mol Med Rep 2015; 11: 2999-3008
16. Williams KS: Postoperative nausea and vomiting. Surg Clin North Am 2005; 85: 1229-41, xi
17. Bourdeanu L, Frankel P, Yu W, Hendrix G, Pal S, Badr L, Somlo G, Luu T: Chemotherapy-induced nausea and vomiting in Asian women with breast cancer

receiving anthracycline-based adjuvant chemotherapy. J Support Oncol 2012; 10: 149-54
18. Stern RM, Hu S, Uijtdehaage SH, Muth ER, Xu LH, Koch KL: Asian hypersusceptibility to motion sickness. Hum Hered 1996; 46: 7-14
19. Gan TJ: Mechanisms underlying postoperative nausea and vomiting and neurotransmitter receptor antagonist-based pharmacotherapy. CNS Drugs 2007; 21: 813-33
20. Yamashita K, Gon Y, Shimokawa T, Nunomura S, Endo D, Miyata N, Hashimoto S, Van Lint J, Ra C: High affinity receptor for IgE stimulation activates protein kinase D augmenting activator protein-1 activity for cytokine producing in mast cells. Int Immunopharmacol 2010; 10: 277-83
21. Dauleh MI, Rahman S, Townell NH: Open versus laparoscopic cholecystectomy: a comparison of postoperative temperature. J R Coll Surg Edinb 1995; 40: 116-8
22. Kappen TH, Moons KG, van Wolfswinkel L, Kalkman CJ, Vergouwe Y, van Klei WA: Impact of risk assessments on prophylactic antiemetic prescription and the incidence of postoperative nausea and vomiting: A Cluster-randomized Trial. Anesthesiology 2013; 120:343-54

Table 1. Patient and perioperative characteristics.

Characteristic	Nitrous Oxide (N=3495)	No Nitrous Oxide (N=3516)
Age, years – mean (SD)	69.2 ± 9.8	69.5 ± 9.7
Age >50 years – no. (%)	3,391 (97)	3,349 (96)
Female sex – no. (%)	1253 (36)	1299 (37)
Body weight, kg – mean (SD)	78.3 (20.1)	77.7 (19.1)
Race – no. (%)		
White	2,587 (74)	2,630 (75)
Asian/other	908 (26)	886 (25)
ASA physical status – no.(%)		
1 or 2	1,083 (31)	1,120 (32)
3 or 4	2,412 (69)	2,395 (69)
Nausea and vomiting risk score – no. (%)		
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)
Pre-existing medical conditions – no.(%)		
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 weeks)	686 (20)	622 (18)
Diabetes	1,310 (38)	1,270 (36)
Type of surgery – no.(%)		
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– no.(%)	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)

ASA = American Society of Anesthesiologists. TIA = transient ischemic attack. ACE = angiotensin converting enzyme. PONV = postoperative nausea and vomiting

PONV risk score calculated as: patient sex (female = 1, male = 0), age (< 50 years = 1, ≥ 50 years = 0), intraoperative morphine (= 1), and smoking status (non-smoker = 1, smoker = 0).

Table 2. Risk factors for severe postoperative nausea and vomiting (PONV) adjusted for all listed covariables. Interaction terms between nitrous oxide and anesthetic duration included in both models. P value for interaction in the PONV prophylaxis group was 0.56, for the No PONV prophylaxis group 0.40.

Variable	PONV Prophylaxis (n=3,970)				No PONV Prophylaxis (n=3,041)			
	Severe PONV n/N	%	OR (95% CI)	P value	Severe PONV n/N	%	OR (95% CI)	P value
Age categories (years)								
<60	106/752	14.1	1.00 (ref)		43/449	9.6	1.00 (ref)	
60-69	126/1130	11.2	0.83 (0.62-1.10)	0.20	111/806	13.8	1.54 (1.04-2.28)	0.030
70-79	200/1542	13.0	0.80 (0.61-1.06)	0.12	166/1250	13.3	1.29 (0.88-1.88)	0.19
≥80	63/534	11.8	0.75 (0.52-1.08)	0.12	67/485	13.8	1.23 (0.79-1.91)	0.37
Female	287/1608	17.8	2.18 (1.76-2.72)	<0.001	176/918	19.2	2.11 (1.65-2.70)	<0.001
ASA Physical status								
1 or 2	163/1030	15.8	1.00 (ref)		165/1158	14.2	1.00 (ref)	
3	302/2623	11.5	0.79 (0.62-1.00)	0.047	198/1650	12.0	1.23 (0.94-1.61)	0.14
4 or 5	30/305	9.8	0.71 (0.45-1.11)	0.13	24/182	13.2	1.58 (0.93-2.66)	0.090
Asian	63/286	22.0	0.90 (0.62-1.32)	0.60	195/1106	17.6	1.22 (0.86-1.74)	0.26
BMI categories (kg/m^2)								
<18.5	12/68	17.6	1.00 (ref)		22/116	19.0	1.00 (ref)	
18.5-24.9	155/1984	14.3	0.84 (0.43-1.68)	0.63	163/1171	13.9	0.82 (0.48-1.38)	0.45
25-29.9	172/1403	12.3	0.82 (0.41-1.64)	0.58	131/1015	12.9	0.93 (0.54-1.60)	0.79
≥30	156/1403	11.1	0.62 (0.31-1.25)	0.18	71/688	10.3	0.71 (0.39-1.28)	0.25
Folate/multivitamin	104/808	12.9	0.92 (0.72-1.18)	0.53	62/457	13.6	1.12 (0.82-1.54)	0.46
Vitamin B_{12} injections	13/118	11.0	0.82 (0.44-1.51)	0.52	6/82	7.3	0.45 (0.19-1.09)	0.077
Non-smoker	440/3250	13.5	1.68 (1.22-2.31)	0.001	345/2420	14.3	1.51 (1.05-2.18)	0.028
Diabetes	189/1361	13.9	1.09 (0.88-1.35)	0.41	155/1190	13.0	0.81 (0.64-1.02)	0.074
Coronary artery disease	174/1542	11.3	1.15 (0.92-1.42)	0.22	112/1000	11.2	0.98 (0.75-1.26)	0.85
Propofol maintenance	22/125	17.6	1.76 (1.07-2.92)	0.027	9/96	9.4	0.75 (0.36-1.57)	0.45

Regional LA block	173/1094	15.8	1.34 (1.07-1.68)	0.012	110/796	13.8	1.16 (0.87-1.54)	0.32
BIS monitoring	183/1725	10.6	0.85 (0.68-1.05)	0.12	106/1064	10.0	0.84 (0.64-1.10)	0.21
Morphine	210/1699	12.4	1.01 (0.81-1.26)	0.91	220/1553	14.2	0.92 (0.69-1.23)	0.56
Surgery type								
Gastrointestinal*	160/645	24.8	1.00 (ref)		162/731	22.2	1.00 (ref)	
Renal/bladder	39/346	11.3	0.45 (0.30-0.67)	<0.001	42/245	17.1	0.80 (0.54-1.19)	0.28
Neurology/spine	28/416	6.7	0.26 (0.17-0.41)	<0.001	16/138	11.6	0.50 (0.28-0.90)	0.021
Ear-nose-throat	14/135	10.4	0.39 (0.21-0.71)	0.002	7/67	10.4	0.46 (0.20-1.06)	0.068
Orthopedic	56/540	10.4	0.37 (0.26-0.54)	<0.001	37/420	8.8	0.31 (0.20-0.48)	<0.001
Plastics	10/67	14.9	0.67 (0.33-1.38)	0.28	1/28	3.6	0.14 (0.02-1.05)	0.056
Gynecology	52/213	24.4	0.71 (0.48-1.05)	0.086	23/101	22.8	0.74 (0.43-1.27)	0.27
Vascular	121/1498	8.1	0.35 (0.27-0.47)	<0.001	94/1212	7.8	0.35 (0.26-0.48)	<0.001
Other	15/98	15.3	0.57 (0.31-1.05)	0.071	5/48	10.4	0.48 (0.18-1.26)	0.14
Anesthesia duration and nitrous oxide								
No nitrous oxide								
<2 hours	18/273	6.6	1.00 (ref)		11/156	7.1	1.00 (ref)	
2-3 hours	64/610	10.5	1.94 (1.11-3.38)	0.019	51/462	11.0	1.69 (0.84-3.39)	0.14
3-4 hours	63/480	13.1	2.50 (1.42-4.38)	0.001	35/389	9.0	1.33 (0.64-2.75)	0.44
4-5 hours	31/237	13.1	2.50 (1.33-4.70)	0.004	31/284	10.9	1.83 (0.87-3.84)	0.109
≥5 hours	49/304	16.1	2.86 (1.59-5.16)	<0.001	25/294	8.5	1.08 (0.50-2.30)	0.85
Nitrous oxide								
<2 hours	26/242	10.7	1.86 (0.98-3.53)	0.059	13/155	8.4	1.28 (0.54-3.01)	0.57
2-3 hours	78/697	11.2	2.00 (1.16-3.44)	0.013	62/375	16.5	3.00 (1.50-5.99)	0.002
3-4 hours	68/532	12.8	2.54 (1.46-4.44)	0.001	56/357	15.7	2.78 (1.38-5.59)	0.004
4-5 hours	48/305	15.7	2.92 (1.62-5.27)	<0.001	44/231	19.0	3.32 (1.61-6.85)	0.001
≥5 hours	50/278	18.0	2.95 (1.63-5.31)	<0.001	59/287	20.6	3.27 (1.62-6.60)	0.001

*includes hepatobiliary-pancreatic-and colorectal surgery.

PONV = postoperative nausea and vomiting; ASA = American Society of Anesthesiologists; LA = local anesthetic; BIS = bispectral index.

Table 3. Number (%) of patients with severe postoperative nausea and vomiting (PONV), according to PONV risk score. χ^2 test P<0.0005.

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

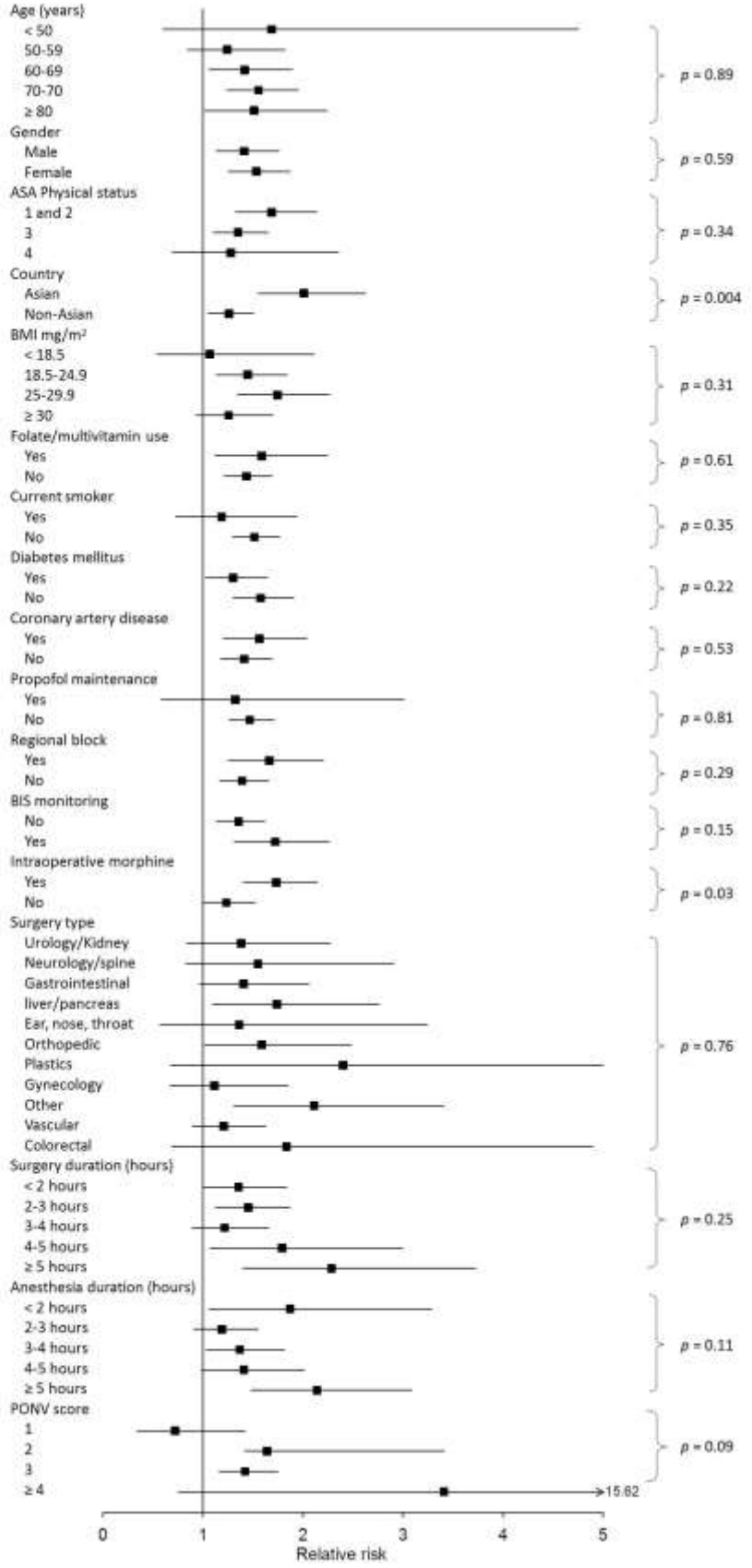
PONV risk score calculated as: patient sex (female = 1, male = 0), age (<50 years = 1, ≥50 years = 0), intraoperative opioid (= 1), and smoking status (non-smoker = 1, smoker = 0).

Table 4. Number (%) of patients with any antiemetic prophylaxis, according to postoperative nausea and vomiting (PONV) risk score. χ^2 test P <0.0005.

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

PONV risk score calculated as: patient sex (female = 1, male = 0), age (< 50years = 1, ≥50 years = 0), intraoperative opioid (= 1), and smoking status (non-smoker = 1, smoker = 0).

Figure 1. Relative risk (bars indicate 95% CI) for severe postoperative nausea and vomiting associated with use of nitrous oxide in selected subgroups.



ASA = American Society of Anesthesiologists. BMI = body mass index; BIS = bispectral index

Figure 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).

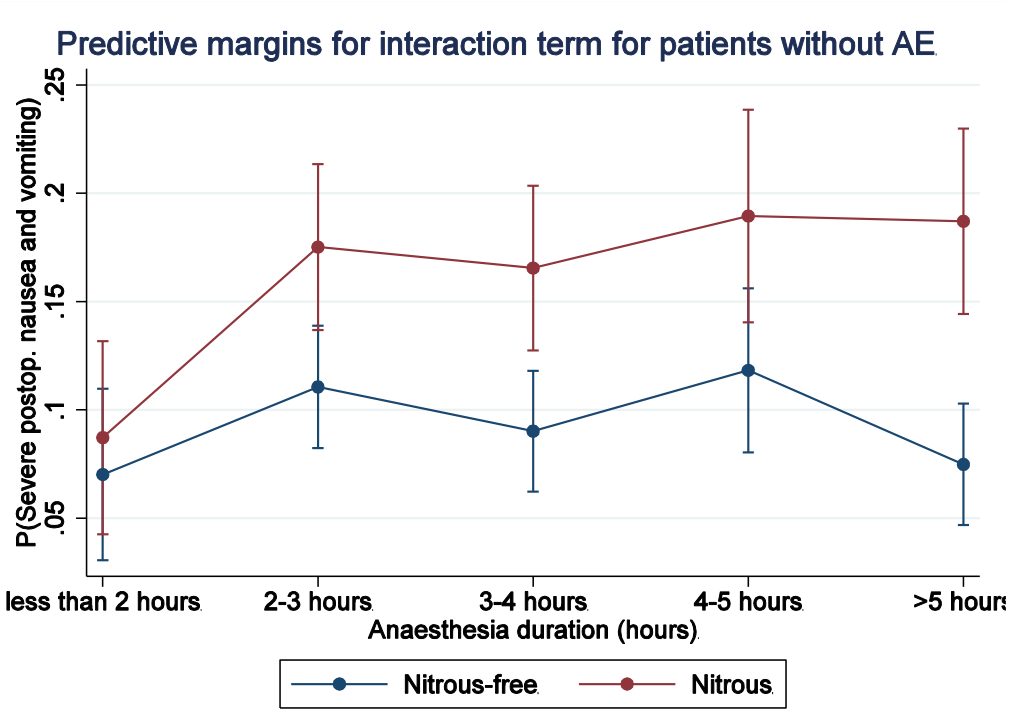


Figure 3. Kaplan-Meier estimate of the time-to-discharge function, comparing those with and without severe postoperative nausea and vomiting at up to 30 days after surgery (Wilcoxon test P < 0.0001).

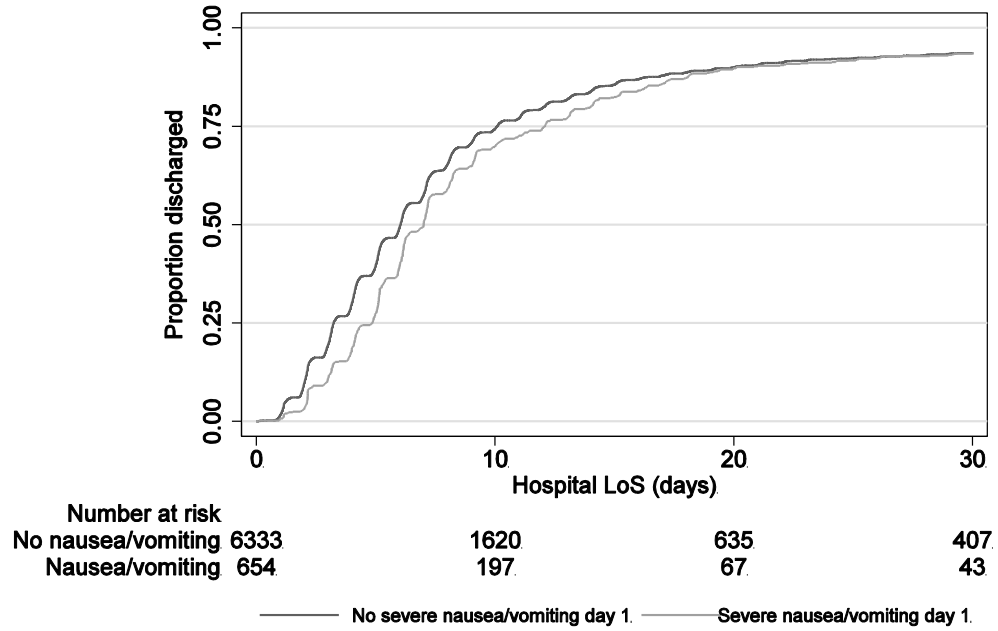


Figure 4. Cox model estimates of time to discharge (censored at 30 days) for patients with and without severe postoperative nausea and vomiting, adjusted for age, American Society of Anesthesiologists physical status, and duration of surgery. Estimated hazard ratio for those with severe nausea and vomiting, 1.14 (95% CI: 1.05-1.23), P=0.002.