Nitrous Oxide–related Postoperative Nausea and Vomiting Depends on Duration of Exposure

Philip J. Peyton, M.D., Ph.D., M.B.B.S., F.A.N.Z.C.A., Christine Yx Wu, M.B.B.S.

ABSTRACT

Background: Inclusion of nitrous oxide in the gas mixture has been implicated in postoperative nausea and vomiting (PONV) in numerous studies. However, these studies have not examined whether duration of exposure was a significant covariate. This distinction might affect the future place of nitrous oxide in clinical practice.

Methods: PubMed listed journals reporting trials in which patients randomized to a nitrous oxide or nitrous oxide–free anesthetic for surgery were included, where the incidence of PONV within the first 24 postoperative hours and mean duration of anesthesia was reported. Meta-regression of the log risk ratio for PONV with nitrous oxide (lnRR $PONV_{N2O}$) *versus* duration was performed.

Results: Twenty-nine studies in 27 articles met the inclusion criteria, randomizing 10,317 patients. There was a significant relationship between lnRR $PONV_{N2O}$ and duration (r^2 = 0.51, P = 0.002). Risk ratio PONV increased 20% per hour of nitrous oxide after 45 min. The number needed to treat to prevent PONV by avoiding nitrous oxide was 128, 23, and 9 where duration was less than 1, 1 to 2, and over 2 h, respectively. The risk ratio for the overall effect of nitrous oxide on PONV was 1.21 (CIs, 1.04–1.40); P = 0.014.

Conclusions: This duration-related effect may be *via* disturbance of methionine and folate metabolism. No clinically significant effect of nitrous oxide on the risk of PONV exists under an hour of exposure. Nitrous oxide–related PONV should not be seen as an impediment to its use in minor or ambulatory surgery. **(ANESTHESIOLOGY 2014; 120:1137-45)**

POSTOPERATIVE nausea and vomiting (PONV) is a common and distressing complication of anesthesia and surgery, particularly in the setting of inhalational anesthesia.[1] Inclusion of nitrous oxide in the administered gas mixture has been implicated as a causative factor in PONV in numerous studies and reviews.[2–4] Avoidance of nitrous oxide has been recommended as a strategy to reduce the risk of PONV after general anesthesia.[5] This is likely to have contributed to the decline in the popularity of nitrous oxide as an agent of choice among anesthesiologists over the last 10 to 20 yr.

A recent meta-analysis showed that, whereas the risk ratio (RR) for PONV was increased by 20% where nitrous oxide was used, there was significant heterogeneity among included studies.[4] In particular, there is considerable disparity among the findings of the few large randomized controlled trials on the subject.

A possible reason for this that has not been examined by previous reviewers is the effect on PONV of duration of exposure to nitrous oxide. Published studies and reviews on nitrous oxide and PONV have treated their relationship as an all-or-nothing phenomenon and have not examined whether duration of exposure to nitrous oxide was a significant covariate in the incidence of PONV. This distinction might have important implications for the future place of nitrous oxide in clinical practice, as well as raise questions about the underlying mechanism of nitrous oxide–induced PONV.

What We Already Know about This Topic

- The inclusion of nitrous oxide as a component of inhalational anesthesia has been observed to increase the likelihood of postoperative nausea and vomiting

What This Article Tells Us That Is New

- Duration of exposure to nitrous oxide less than 1 h has little effect on the rate of postoperative nausea and vomiting
- The risk ratio for postoperative nausea and vomiting increases approximately 20% per hour after the first 45 min of exposure to nitrous oxide

We conducted an updated literature review and meta-regression analysis to determine whether duration of exposure to nitrous oxide in published randomized trials was related to the incidence of PONV.

Materials and Methods

In line with Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines, a primary search was performed using an electronic database in the form of PubMed with the search terms "nitrous oxide and nausea," "vomiting," or "PONV." The study protocol restricted the search to published English-language articles in PubMed listed journals reporting trials in adults, which prospectively allocated patients by randomization to groups receiving a nitrous

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oxide or nitrous oxide–free anesthetic for surgery, where the incidence of PONV within the first 24 postoperative hours was reported in each group, and where the mean or median duration of anesthesia (or duration of surgery if this was not presented) was reported or could be estimated from the data presented. No restriction was placed on the date of publication. A further search was done of the bibliographies of articles sourced from this primary search, and published reviews and meta-analyses. Data in sourced articles were scrutinized by both authors and logged to Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA) for collation. PONV for the purposes of our analysis was defined as the need for antiemetic rescue treatment where this was specifically reported by a study, otherwise as the reported incidence of nausea with or without vomiting.

Heterogeneity in study design complicated pooling of the data from these studies, with the potential for confounding of results. Many studies did not state explicitly in their methods, how the presence of PONV was defined or how it was measured. For this reason, the definition above was considered to be the most robust one to use for the purposes of the current analysis, as it was reported by a majority of studies including all the larger studies. A large number of studies deliberately randomized patients to an additional intervention other than inclusion or exclusion of nitrous oxide, which might be expected to affect the incidence of PONV, for example, propofol *versus* nitrous oxide or nitrous oxide–volatile agent; opioid *versus* nitrous oxide; or antiemetic *versus* no antiemetic prophylaxis.[6–23] In general, PONV was a secondary endpoint in these studies. Some of these studies involved multiple treatment groups receiving different combinations of induction and maintenance anesthesia drugs, where only some of these treatment groups were suitable for direct comparison.[7–9,11,12]

The flow diagram for inclusion and exclusion of studies is shown in figure 1. After exclusion of studies listed above with confounding randomization protocols, a total of 32 randomized studies in 30 published articles met the inclusion criteria, randomizing 10,577 patients in total. Three of these articles, studying a total of 117 patients, reported a zero incidence of PONV in one or more groups and were unable to be included, as the mathematical weighting applied to such comparisons is zero in meta-analytic models.[7,24,25] The studies included in the analysis are listed in table 1.[7–9,11,12,26–48]

In one article involving two large studies of 935 and 483 patients, respectively, who were randomized to a nitrous oxide or nitrous oxide–free anesthetic on a background of intravenous propofol anesthesia, the duration of anesthesia was not stated. However, it was possible to estimate this from the study protocol for intravenous propofol administration, as the total propofol dose received was recorded in each group.[26] With this exception the data required for the analysis were available from the publications. In one article involving a study of 60 patients, contact was attempted with the authors for more detailed data but this was not successful.[43]

Statistical Analysis

The dependent variable in the meta-regression model was the RR for each study of the effect of nitrous oxide on the incidence of PONV (RR $PONV_{N2O}$), *versus* duration of anesthesia as the independent variable. A random-effects model with inverse variance weighting of the log risk ratio (lnRR $PONV_{N2O}$) was used in STATA 12 statistical software (Stata Corp., College Station, TX), using the method of moments based on DerSimonian and Laird.[49] A clinically significant increase in the incidence of PONV due to nitrous oxide was considered to 10% (RR $PONV_{N2O}$ of 1.1).

In addition, the number needed to treat to prevent PONV by avoiding nitrous oxide, and the associated RR $PONV_{N2O}$ and CIs, were calculated after stratifying included studies into three groups, where duration of anesthesia was less than 1 h, 1 to 2 h, and greater than 2 h, respectively. The overall effect of nitrous oxide on the RR for PONV, irrespective of duration, was also assessed by meta-analysis of all studies included in the primary analysis, using a random-effects

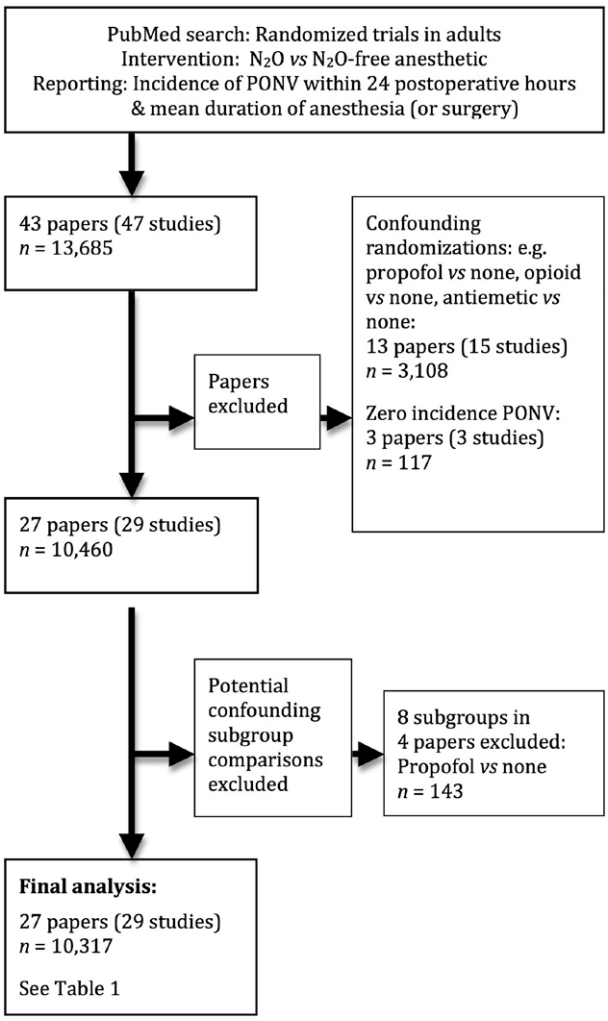

Fig. 1. The flow diagram indicating the exclusion and inclusion of studies in the meta-regression and meta-analysis. N_2O = nitrous oxide; PONV = postoperative nausea and voming.

Table 1. List of Eligible Included Studies

	Anesthetic				PONV/*n* (% Incidence)	
First Author and Ref	Non-N_2O Group	N_2O Group	Type of Surgery	Duration (min)	Non-N_2O Group	N_2O Group
Lonie[27]	Fent-Enf	N_2O-Fent-Enf	Gynecological laparoscopy	39	20/46 (43)	20/41 (49)
Korttila[28]	Fent-Iso	N_2O-Fent-Iso	Abdominal hysterectomy	102	25/55 (45)	30/55 (55)
Melnick[29]	Iso	N_2O-Iso	Minor gynecology	13	1/28 (3)	8/32 (25)
Muir[30]	Morph-Enf	N_2O-Morph-Enf	Nonbody cavity	73	67/181 (37)	67/178 (38)
Muir[30]	Morph-Iso	N_2O-Morph-Iso	Nonbody cavity	78	62/186 (33)	65/173 (38)
Bloomfield[31]	Iso ± Sufent	N_2O-Iso ± Sufent	Extraabdominal	96	5/31 (16)	11/32 (34)
Sengupta[32]	Fent-Iso	N_2O-Fent-Iso	DC laparoscopy	23	10/31 (32)	13/33 (39)
Hovorka[33]	Fent-Iso	N_2O-Fent-Iso/Enf	Gynecological laparoscopy	38	26/50 (52)	53/100 (53)
Eger[34]	Iso ± Fent	N_2O-Iso ± Fent	Various	178	63/137 (46)	64/133 (48)
Scheinin[35]	Fent-Iso	N_2O-Fent-Iso	Colonic	266	5/20 (25)	5/20 (25)
Ranta[36]	Fent-Iso	N_2O-Fent-Iso	Upper abdominal	121	12/24 (50)	13/26 (50)
Wrigley[8]	Fent-Des	N_2O-Fent-Des	DC orthopedic	29	3/13 (23)	6/14 (43)
Rapp[9]	Fent-Des	N_2O-Fent-Des	Orthopedic	53	9/22 (41)	10/24 (42)
Taylor[37]	Fent-Iso	N_2O-Fent-Iso	Laparoscopic cholecystectomy	87	13/24 (53)	9/26 (35)
Akhtar[38]	Prop	N_2O-Prop	Gynecology/urology	10	2/50 (4)	6/50 (12)
Graham[11]	Fent-Des	N_2O-Fent-Des	Gynecological laparoscopy	24	11/15 (27)	4/15 (73)
Jensen[39]	Fent-Iso	N_2O-Fent-Iso	Laparoscopic cholecystectomy	165	10/23 (43)	11/19 (58)
Lebenbom-Mansour[12]	Fent-Des	N_2O-Fent-Des	Orthopedic	86	2/16 (12)	7/14 (50)
Pedersen[40]	Fent-Iso	N_2O-Fent-Iso	Abdominal hysterectomy	95	6/19 (32)	5/17 (29)
Sukhani[41]	Prop	N_2O-Prop	Gynecological laparoscopy	81	5/36 (14)	2/34 (6)
Bloomfield[42]	Iso-Alfent	N_2O-Iso-Alfent	Extraabdominal	139	12/60 (20)	26/59 (44)
Vanacker[43]	Fent-Des	N_2O-Fent-Des	Breast	120	6/30 (20)	17/30 (57)
Arellano[26]	Fent-Prop	N_2O-Fent-Prop	Minor gynecology	13	22/467 (5)	9/468 (2)
Arellano[26]	Fent-Prop	N_2O-Fent-Prop	Gynecological laparoscopy	31	70/241 (29)	63/242 (26)
Apfel[44]	Various	N_2O-various	Various	108	638/2,050 (31)	721/2,036 (35)
Fleischmann[45]	Iso-Remi	N_2O-Iso-Remi	Colonic resection	202	26/206 (13)	39/208 (19)
Myles[46]	Various	N_2O-Various	Major surgery	222	102/1,015 (10)	229/997 (23)
El-Galley[47]	Fent-Iso	N_2O-Fent-Iso	Donor laparscopic nephrectomy	138	4/16 (25)	6/12 (50)
Mraovic[48]	Fent-Sevo	N_2O-Fent-Sevo	Gynecological laparoscopy	73	7/46 (15)	20/91 (22)

Alfent = alfentanil; DC = day case/ambulatory surgery; Des = desflurane; Enf = enflurane; Fent = fentanyl; Iso = isoflurane; Morph = morphine; N_2O = nitrous oxide; PONV = postoperative nausea and vomiting; Prop = propofol; Remi = remifentanil; Sevo = sevoflurane; Sufent = sufentanil.

model in STATA, using the method of DerSimonian and Laird,[49] and calculation of an overall RR $PONV_{N2O}$, with the estimate of heterogeneity being taken from the I^2 of Higgins *et al.*[50] I^2 values of over 50% are generally considered to indicate substantial heterogeneity.

Two covariates were also considered, which might have a confounding influence on the relationship between nitrous oxide–induced PONV and duration of anesthesia. The first of these was patient sex, which was examined due to the presence of several studies involving day-stay gynecological surgery of relatively short duration. Second, the likelihood that an older patient group might undergo major surgery of longer duration was also considered. The relationship of these to both duration of anesthesia and lnRR $PONV_{N2O}$ was assessed by regression modeling, and the meta-regression was repeated with patient sex (quantified as the proportion of males in each study), and the mean age of the patients in each study included as covariates with duration of anesthesia. For all statistical analyses, a P value of 0.05 or less was considered to indicate statistical significance.

Results

In total the meta-regression analysis contained data from 10,317 randomized patients (N_2O n = 5,179, no-N_2O n = 5,138). There was a significant relationship between lnRR $PONV_{N2O}$

and duration of exposure to nitrous oxide (r^2 = 0.51, P = 0.002). This is shown in figure 2 as a bubble plot. The RR $PONV_{N2O}$ exceeded 1.1 at t = 75 min. The slope of the relationship was equivalent to the positive risk of PONV increasing by 20% per hour of exposure to nitrous oxide after 45 min.

The RR for the overall effect of nitrous oxide on PONV, independent of duration, was 1.21 (CIs, 1.04–1.40), P = 0.014. Figure 3 shows the forest plot for this meta-analysis. Substantial heterogeneity among the published studies in lnRR $PONV_{N2O}$ was confirmed (χ^2 = 84.3, df = 28, I^2 = 66.8%, P < 0.001).

Where duration of anesthesia was less than 1 h, the number needed to treat to prevent PONV from avoidance of nitrous oxide was 128. Where duration of anesthesia was 1 to 2 h, the number needed to treat was 24 and where duration of anesthesia was over 2 h, the number needed to treat was 9. This and the accompanying RR $PONV_{N2O}$ for each of the three time periods is summarized in table 2.

There was a statistically significant relationship between duration of anesthesia and both sex (the proportion of males in each study, r^2 = 0.61, P < 0.001) and the mean age of study patients (r^2 = 0.68, P < 0.001). A statistically significant relationship was found between lnRR $PONV_{N2O}$ and patient age (r^2 = 0.26, P = 0.023) but there was no significant relationship between lnRR $PONV_{N2O}$ and sex (P = 0.09). On repeating the meta-regression incorporating age and sex as independent covariates a significant relationship was still found between lnRR $PONV_{N2O}$ and duration of anesthesia (r^2 = 0.49, P = 0.023).

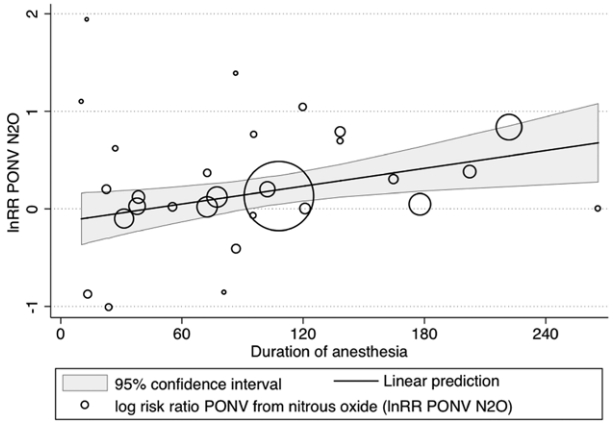

Fig. 2. The relationship between the log risk ratio for postoperative nausea and vomiting from nitrous oxide (lnRR $PONV_{N2O}$) and duration of exposure to nitrous oxide (N_2O), as a bubble plot. The meta-regression line of best fit (linear prediction) and upper and lower 95% CIs are shown. Bubble size is inversely proportional to the standard error of the log risk ratio in each study.

Discussion

Our data demonstrate that the increase in PONV seen with nitrous oxide administration is highly dependent on duration of exposure, and any emetogenic effect of nitrous oxide is insignificant up to at least 1 h of exposure. This has important implications for the place of nitrous oxide in clinical practice. Minor operations of brief duration typically take place in the setting of high turnover, day stay, or ambulatory surgery, where the pharmacokinetic and pharmacodynamic advantages of nitrous oxide are most useful, with its analgesic, minimum alveolar concentration–sparing and second gas effects, and rapid washout.[51–54] Furthermore, a common practice is commencement of nitrous oxide toward the end of longer surgery to "wash out" maintenance volatile agent and promote rapid emergence.[54] Our findings suggest that nitrous oxide–related PONV should not be seen as an impediment to its use in these contexts.

While the contribution of nitrous oxide to PONV is widely accepted and confirmed in several reviews,[1–5] this literature includes many small underpowered studies, with varying findings and significant heterogeneity. Our findings help to reconcile these results, and the opposing findings of the few large randomized trials. In the earliest of these, the study by Muir *et al.*[30] showed no effect of nitrous oxide on the rate of PONV in a total of 718 patients receiving inhalational anesthesia with enflurane or isoflurane undergoing nonbody cavity surgery with a mean duration of approximately 75 min. Arellano *et al.*[26] found no effect of nitrous oxide on the rate of PONV in 483 patients receiving propofol anesthesia for ambulatory gynecological laparoscopy. We estimated the mean duration of anesthesia to be approximately 32 min in this study. Both these studies were adequately powered to detect a clinically important effect on PONV from nitrous oxide, with baseline rates of PONV of 35 and 23%, respectively.

The largest randomized study in this field was by Apfel *et al.*[44] who conducted a multifactorial study of the effectiveness of several interventions to reduce PONV. One of these interventions was nitrous oxide *versus* nitrogen in air, involving over 4,000 patients. The mean duration of anesthesia was 108 min and the risk reduction in PONV from avoiding nitrous oxide was 12%.

More recently, Myles *et al.*[46] found that nitrous oxide increased the rate of severe PONV by more than two-fold in patients undergoing a wide range of major surgery in the ENIGMA (Evaluation of Nitrous oxide In the Gas Mixture for Anaesthesia) 1 trial, involving approximately 2,000 patients with a mean anesthetic duration of slightly over 3 ½ h. This study was potentially confounded by asymmetry between the control and nitrous oxide groups in the delivered inspired oxygen concentration (F_{IO_2}) and rate of usage of propofol, both of which have been suggested to affect PONV.[55–57] However, recent meta-analysis has concluded that a high F_{IO_2} is not protective against PONV.[58] Furthermore, a *post hoc* multivariate analysis of the contributing factors to PONV in the ENIGMA 1 trial by Leslie *et al.*[59] showed that after adjustment for differing rates of propofol administration, the multivariate odds ratio for PONV with nitrous oxide was still 2.04.

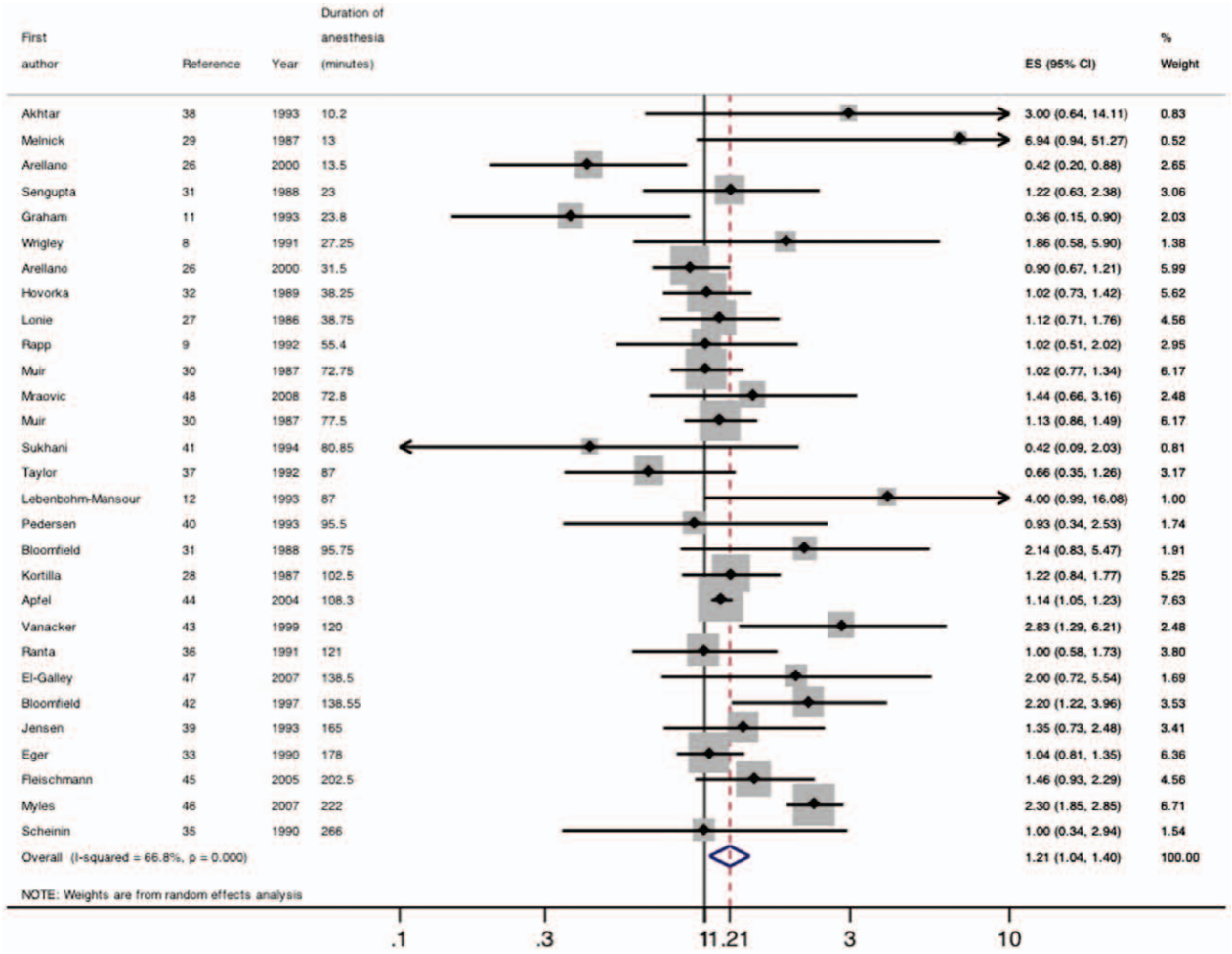

Fig. 3. Forest plot showing the results of meta-analysis of the overall effect of nitrous oxide on the risk of postoperative nausea and vomiting during the first 24 postoperative hours. *Boxes* indicate study weighting on random effects modeling. *Diamonds* and *bars* are mean and 95% confidence limits (CI) for the risk ratio or effect size for each study, and the *large diamond* indicates the overall risk ratio and 95% confidence limits.

Table 2. Stratification of Risk by Duration

Duration of Anesthesia	N Studies	n Total No-N_2O Groups	n Total N_2O Groups	NNT	RR $PONV_{N2O}$	RR $PONV_{N2O}$ 95% CIs
0–1 h	10	963	1,019	128	1.04	0.87–1.25
1–2 h	11	2,674	2,686	23	1.14*	1.05–1.27
>2 h	8	1,501	1,474	9	1.72*	1.48–1.98

The NNT to prevent PONV by avoiding N_2O and the RR and 95% CIs for postoperative nausea or vomiting from using N_2O (RR $PONV_{N2O}$). Studies are stratified into three groups, based on duration of anesthesia.

* Statistically significant, $P < 0.05$.

NNT = number needed to treat; N_2O = nitrous oxide; PONV = postoperative nausea and vomiting; RR = risk ratio.

Limitations

While it was possible in our analysis to eliminate the comparisons between studies and subgroup where confounding factors were present such as randomization to propofol, opioid or antiemetic in one treatment arm, there are some features inherent to nitrous oxide anesthesia, which cannot be avoided. Complete double blinding of an intervention such as inclusion of nitrous oxide in the gas mixture is difficult, although almost all studies specified that postoperative care and data collection was done by blinded observers. Due to its minimum alveolar concentration–sparing effect, data from control and treatment groups generally showed differences in the dose or concentration of accompanying anesthetics. These included volatile agents, which have their own emetic properties, and propofol, which has antiemetic properties.[1,56,57] These effects cannot be separated from the

intrinsic effect of nitrous oxide in clinical practice. Similarly, nitrous oxide use precludes administration of a high F_{IO_2}. Among the articles included here there was heterogeneity of F_{IO_2} in the non–nitrous oxide groups. While previous research suggested that a high F_{IO_2} in the absence of nitrous oxide is protective against PONV, subsequent meta-analysis has failed to confirm a significant effect, and this was ignored in the current analysis.[55,58]

Alternatively, the effect of duration of anesthesia on nitrous oxide–induced PONV may instead simply reflect of the invasiveness and magnitude of the surgery. It has been well demonstrated that PONV is related to duration of surgery and anesthesia regardless of the presence of nitrous oxide, which may reflect a number of physiological disturbances that are exaggerated by prolonged or major surgery, such as increased fluid and electrolyte disturbances, more prolonged exposure to volatile agents, or increased need for opioid analgesics.[1,59–61] However, a specific mechanism is still required to explain how major surgery might specifically increase nitrous oxide–induced PONV, given that the delivered concentration of nitrous oxide is not dependent on magnitude of surgery in usual clinical practice. Similar considerations apply to patient age and sex,[1,5,59–61] but including these factors as covariates did not invalidate the statistically significant relationship between nitrous oxide–induced PONV risk and duration found in our analysis.

Mechanisms

A number of possible mechanisms for nitrous oxide–induced nausea and vomiting have been suggested. These include an action on central opioid and dopaminergic receptors,[62,63] diffusion of nitrous oxide into the middle ear cavity,[64] and bowel distension.[65] However, only the last of these is consistent with our findings. Due to its relatively low solubility in blood and tissues, partial pressures of nitrous oxide approach equilibration rapidly in well perfused tissues such as the brain, which is one of the reasons for its usefulness for inhalational analgesia in conscious patients, such as in obstetrics. Similarly, rapid increases in middle ear pressures have been demonstrated in animal models and humans after commencement of nitrous oxide, approaching a peak within 20 to 30 min,[14,64,66] which does not explain the progressive increase in nitrous oxide–related PONV across the studies in our analysis. It is interesting that no studies report concurrent symptoms of dizziness or vertigo to suggest that otic disturbances are the cause of any accompanying PONV. Meta-analysis has shown that the degree of bowel distension with nitrous oxide anesthesia is related to duration of anesthesia, with an odds ratio of 2.09 for each additional hour of exposure.[65] However, whereas bowel distension has been shown to be related to postoperative pain,[67] causation of PONV has been merely assumed by previous commentators, and not proven.

The progressive rise in PONV we have demonstrated with longer exposure parallels the metabolic derangements produced by nitrous oxide, which are related to its known inhibition of methionine synthetase activity. This raises the possibility that nitrous oxide–induced PONV has a similar origin. Nitrous oxide irreversibly oxidizes the cobalt atom on vitamin B12–dependent methionine synthetase, which sits at the center of two interdependent cyclic metabolic pathways, the S-adenosyl methionine cycle and the folate cycle. The S-adenosyl methionine cycle generates methyl donor groups from methionine for a range of vital synthetic functions, producing homocysteine as an intermediate metabolite. The degree of inactivation of methionine synthetase activity is related to duration of exposure, with a half time of approximately 45 min in humans.[68] Several studies have shown that ongoing exposure to nitrous oxide in patients leads to progressive increases in plasma homocysteine levels after approximately an hour of anesthesia, which, it is postulated, may lead to cardiovascular complications.[69–78] Acute increase of plasma homocysteine levels, such as are produced in the methionine loading test to investigate endothelial dysfunction, commonly causes nausea in subjects at a rate similar to that observed in the perioperative studies in this meta-analysis.[79,80]

The associated disturbance of folate metabolism could also contribute to nausea and vomiting with nitrous oxide. Animal and human data demonstrate that nitrous oxide exposure leads to rapid depletion of intracellular folate levels in major organs, accompanied by a rise in plasma folate, due to the cell's inability to take up and use plasma folate.[69,81,82] Gastrointestinal symptoms such as nausea and vomiting are a common manifestation of intracellular folate depletion due to methotrexate treatment or dietary deficiency, and can be treated with folate supplementation.[83–88]

Nitrous oxide–induced intracellular folate depletion and homocysteine increase may be associated with PONV *via* a similar mechanism. Myles *et al.*[46] could find no evidence that patients taking routine preoperative folate or vitamin B supplementation had less PONV in the ENIGMA 1 trial. However, data from recent trials of the effectiveness of folate/ vitamin B supplementation to prevent nitrous oxide–induced homocysteine increase provide strong support for this hypothesis.[74,75] Five hundred patients undergoing nitrous oxide anesthesia for major noncardiac surgery lasting over 2 h were randomized to receive folate/vitamin B or placebo by Nagele *et al.*[75] Patients who received folate had much lower rates of PONV (1.2 *vs.* 5.2%, $\chi^2 = 6.46$, $P = 0.011$). This hypothesis and the effectiveness of folate prophylaxis are worthy of further study in prospective randomized controlled trials with nitrous oxide–related PONV as the primary endpoint.

Nitrous oxide–induced PONV needs to be considered in the broader context of toxicity related to methionine synthetase inhibition by nitrous oxide. Interference with folate production and DNA synthesis and consequent immunosuppression is considered to contribute to an increased incidence of wound and pulmonary complications, and possibly to cardiovascular complications, studied in the ENIGMA trials.[46,78] However, this research has investigated the use of nitrous

oxide in major surgery with prolonged administration. With the exception of established contraindications such as pneumothorax, which have a different mechanism, evidence of toxicity with briefer administration of nitrous oxide, including PONV, is lacking. Nitrous oxide–related PONV is clinically insignificant up to at least 1 h of exposure and should not be seen as an impediment to nitrous oxide use for limited periods of time, such as in minor or ambulatory surgery.

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Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Peyton: Department of Anaesthesia, Austin Health, Heidelberg 3084, Melbourne, Australia. phil.peyton@austin.org.au. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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