Avoidance of Nitrous Oxide for Patients Undergoing Major Surgery

A Randomized Controlled Trial

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Background: Nitrous oxide is widely used in anesthesia, often administered at an inspired concentration around 70%. Although nitrous oxide interferes with vitamin B_{12}, folate metabolism, and deoxyribonucleic acid synthesis and prevents the use of high inspired oxygen concentrations, the consequences of these effects are unclear.

Methods: Patients having major surgery expected to last at least 2 h were randomly assigned to nitrous oxide–free (80% oxygen, 20% nitrogen) or nitrous oxide–based (70% N_2O, 30% oxygen) anesthesia. Patients and observers were blind to group identity. The primary endpoint was duration of hospital stay. Secondary endpoints included duration of intensive care stay and postoperative complications; the latter included severe nausea and vomiting, and the following major complications: pneumonia, pneumothorax, pulmonary embolism, wound infection, myocardial infarction, venous thromboembolism, stroke, awareness, and death within 30 days of surgery.

Results: Of 3,187 eligible patients, 2,050 consenting patients were recruited. Patients in the nitrous oxide–free group had significantly lower rates of major complications (odds ratio, 0.71; 95% confidence interval, 0.56–0.89; $P = 0.003$) and severe nausea and vomiting (odds ratio, 0.40; 95% confidence interval, 0.31–0.51; $P < 0.001$), but median duration of hospital stay did not differ substantially between groups (7.0 vs. 7.1 days; $P = 0.06$). Among patients admitted to the intensive care unit postoperatively, those in the nitrous oxide–free group were more likely to be discharged from the unit on any given day than those in the nitrous oxide group (hazard ratio, 1.35; 95% confidence interval, 1.05–1.73; $P = 0.02$).

Conclusions: Avoidance of nitrous oxide and the concomitant increase in inspired oxygen concentration decreases the incidence of complications after major surgery, but does not significantly affect the duration of hospital stay. The routine use of nitrous oxide in patients undergoing major surgery should be questioned.

> ◆ This article is accompanied by an Editorial View. Please see: Hopf HW: Is it time to retire high-concentration nitrous oxide? ANESTHESIOLOGY 2007; 107:200–1.

> 🌐 Additional material related to this article can be found on the ANESTHESIOLOGY Web site. Go to http://www.anesthesiology.org, click on Enhancements Index, and then scroll down to find the appropriate article and link. Supplementary material can also be accessed on the Web by clicking on the "ArticlePlus" link either in the Table of Contents or at the top of the Abstract or HTML version of the article.

NITROUS oxide has achieved remarkable longevity as an anesthetic, having been in widespread, worldwide use

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since 1844. However, the low toxicity of modern anesthetic agents, the accumulating evidence about the adverse effects of nitrous oxide,[1-4] and the potential benefits of high inspired concentrations of oxygen[5-7] provide compelling reasons to question the continued use of nitrous oxide in anesthesia.

Many of the adverse effects of nitrous oxide result from the irreversible inhibition of vitamin B_{12}, which inhibits methionine synthase, folate metabolism, and deoxyribonucleic acid synthesis.[1,2] This mechanism explains reports of megaloblastic anemia and neurologic toxicity with prolonged nitrous oxide administration,[8,9] and a possible increased risk of teratogenicity, immunodeficiency, and impaired wound healing.[1,10,11] In addition, inactivation of methionine synthase is associated with increased plasma homocysteine concentrations,[12,13] which may increase the risk of postoperative cardiovascular complications.[12] Nitrous oxide impairs cerebral blood flow–activity coupling[4] and worsens air space conditions (pneumothorax, air embolism) and bowel distension.[2,3] Finally, nitrous oxide is a proven risk factor for postoperative nausea and vomiting,[14,15] which is a common, troublesome, and costly complication of anesthesia.[16]

As a weak anesthetic, nitrous oxide is often administered as 70% of the inspired gas mixture, thereby limiting the inspired concentration of oxygen that can be delivered. Supplemental oxygen during surgery potentially reduces the risk of wound infection[6,7] and nausea and vomiting,[5] both of which are important contributors to duration of hospital stay and cost of care.

Despite the adverse effects that may result directly from nitrous oxide or from the restriction of inspired oxygen concentration, the use of nitrous oxide in patients undergoing surgery remains near-routine.[17] The aim of this randomized controlled trial, therefore, was to evaluate whether avoidance of nitrous oxide in the gas mixture for anesthesia, an intervention that avoids potential nitrous oxide toxicity and in addition allows an increase in the inspired oxygen fraction, could decrease the duration of hospital stay after surgery and reduce postoperative complications, compared with a nitrous oxide–based anesthetic regimen, in adult patients presenting for major surgery. We chose a pragmatic trial design, aiming to include a variety of anesthetic regimens and hospital settings, because we wanted to measure the effectiveness of removing nitrous oxide from the anesthetic regimen in routine clinical practice.[18-20]

Materials and Methods

Patients

Patients eligible to take part in this study were aged 18 yr or older, were scheduled to undergo general anesthesia for surgery that included a skin incision and that was anticipated to exceed 2 h, and were expected to be in the hospital for at least 3 days after surgery. Patients undergoing cardiac surgery, or thoracic surgery requiring one-lung ventilation, were excluded. Patients were also excluded if the anesthesiologist considered that nitrous oxide was contraindicated (e.g., a history of postoperative emesis or if the anesthesiologist wanted to use supplemental oxygen for colorectal surgery). This was a multicenter trial with 19 participating sites around the world (see appendix). The protocol was approved by the institutional review board at each site. Written informed consent was obtained from each participant.

A preliminary estimate of sample size was based on a clinically important reduction in mean duration of hospital stay from 4.0 days to 3.5 days (SD = 3 days), based on our previous research,[21] for which a study with a type I error of 0.05 and a type II error of 0.1 would require approximately 800 patients per group with two-sided significance testing. We planned to include 2,000 patients in this study to allow for dropouts and the possibility of requiring nonparametric tests for the skewed duration of stay data. With a sample size of 2,000, a decrease in the rate of wound infection from 14% to 10% can be detected with 77% power.

Procedures

A study Protocol and Procedures Manual was available to all staff, and each site's research staff were trained and given 24-h access to the study coordinating center. The case report form documented all planned interventions, process variables, and outcomes. Patients were randomly assigned to receive either nitrous oxide–free or nitrous oxide–based general anesthesia, using a computer-generated code, accessed via an automated telephone voice recognition service. Treatment assignment was stratified by site and elective/emergency status of the surgery, using permuted blocks.

For patients assigned to nitrous oxide–free anesthesia, anesthesiologists were advised to administer a gas mixture of 80% oxygen with 20% nitrogen. However, a range of inspired oxygen concentration (25–100%) was allowed if the anesthesiologist had a strong preference, if medical air was unavailable, or if clinically indicated. Given that there is some evidence that high inspired oxygen concentrations may have beneficial effects,[5-7] we planned a priori to explore this effect in secondary analyses.

For patients assigned to the nitrous oxide–based anesthesia, anesthesiologists were advised to administer a gas mixture of 70% nitrous oxide with 30% oxygen, after induction of anesthesia, and until completion of surgery. If hemoglobin oxygen saturation was inadequate, any airway and ventilatory maneuvers deemed necessary, including an increase in inspired oxygen concentration, could be used.

All patients otherwise received standard anesthetic care and monitoring. Choice of other anesthetic drugs

and intravenous fluids was at the discretion of the attending anesthesiologist. Choice of antibiotic prophylaxis was according to institutional practice. Anesthetic depth was adjusted according to clinical judgment and, if available, Bispectral Index monitoring (Aspect Medical Systems Inc., Newton, MA). Combined regional and general anesthetic techniques could be included. Anesthesiologists were advised to avoid intraoperative hypothermia ($< 35.5°C$), which is known to increase the risk of wound infection.[22] In line with normal anesthetic practice, the inspired oxygen concentration could be increased to 100% in both groups at the conclusion of anesthetic administration. All other perioperative clinical care was conducted according to local practice. This included use of oxygen therapy, typically delivered *via* a clear plastic non-Venturi mask at 4–8 l/min, in the postanesthesia care unit and postoperative surgical ward.

Attending anesthesiologists were required to have knowledge of group identity for the safe administration of anesthesia, but group identity was concealed from the surgeon using drapes or cardboard to screen the anesthesia machine. At the end of the procedure, the intraoperative case report form and documentation of group identity were faxed to the data management center and then placed in an opaque envelope by the anesthesiologist. The envelope was then sealed to ensure blinding of research staff conducting the postoperative follow-ups. The trial data management center checked each completed record for missing or illogical items within 24–48 h, with corrections verified *via* e-mail contact to the site coordinator and local study investigator. The anesthesia record was not concealed or removed from the patient's medical record, because it is our experience that the anesthetic record is not perused by surgical staff. The patient and surgical staff were not informed of the patient's group identity. All research staff, including those responsible for postoperative data collection and outcome assessment, were precluded by protocol from accessing the anesthetic record and so were blinded to group identity.

Measurements

Preoperative demographic characteristics and details of patient medical and surgical history were recorded. A brief dietary history was obtained, including whether the patient took vitamin B or folate supplements on a daily basis. The National Nosocomial Infections Surveillance System was used to define risk of wound infection.[23] The National Nosocomial Infections Surveillance System scores 1 point for each of American Society of Anesthesiologists (ASA) physical status III, IV, or V; contaminated or dirty-infected surgery; and duration of surgery (varied according to type of surgery) (total score = 0–3). The risk of postoperative nausea or vomiting was based on a modification of recently validated criteria[24]: sex (female = 1, male = 0), age (< 50 yr = 1, ≥ 50 yr = 0),

smoking status (nonsmoker = 1, smoker = 0), and intraoperative morphine administration (> 10 mg = 1, ≤ 10 mg = 0). This resulted in a score of 0 (low risk) to 4 (high risk).

Most patients (87%) were admitted to the postanesthesia care unit after surgery; those with serious medical conditions and/or undergoing extensive surgery were admitted to the intensive care unit (according to local practices). The anesthesiologist or, if delayed, the postanesthesia care unit nursing staff, recorded time of eye opening after surgery. The postanesthesia care unit nursing staff were asked to record the time of fitness for discharge, which was defined as a modified Aldrete score[25] of 9 or greater (if used), or alternatively, at the time the patient was first awake, orientated, and had stable vital signs, and pain and emesis were controlled.

All patients were seen by a research assistant on the day after surgery to assess their quality of recovery and to detect awareness.[26] If there was any evidence of any postoperative complication at this visit, or if notified by the surgical team at a later date, they were generally visited at regular intervals until hospital discharge. A 12-lead electrocardiogram was obtained before surgery and the day after surgery in all patients at risk of coronary artery disease. Any patient suspected of having coronary artery disease had blood collected on the first postoperative day after surgery for serum troponin estimation. Any other additional laboratory tests or other investigations were ordered when clinically indicated (*e.g.*, fever, chest pain, dyspnea). Therefore, the frequency of the postoperative visits was determined by the patient's clinical status. Finally, patients were contacted by phone at 30 days, and laboratory reports and the hospital record were reviewed to ascertain whether they had experienced any additional adverse outcomes.

Determination of Outcomes

To account for all the potential complications associated with nitrous oxide, we chose the duration of hospital stay as the primary endpoint of the study. This was defined as the duration from the start of surgery until actual hospital discharge. Patients transferred to another hospital were tracked until final discharge to home (or other final destination). In addition, we recorded duration of stay in the intensive care unit (ICU) for patients who were transferred immediately after surgery.

As outlined above, patients were screened for a predetermined set of postoperative complications occurring in the first 30 postoperative days. Additional laboratory testing was performed by staff who were blinded to group allocation. If any event was identified, a report with confirmatory data was sent to an attending physician with dual qualifications in anesthesia and internal medicine for verification. The adjudicator was blind to group allocation. The following criteria were used:

1. Wound infection—if associated with purulent discharge, with or without a positive microbial culture; or pathogenic organisms isolated from aseptically obtained microbial culture[27]
2. Pneumonia—radiologic infiltrate confirmed by chest x-ray or computed tomography, in association with at least one of the following: temperature greater than 38°C, leukocyte count greater than 12,000/ml, or positive sputum culture that was not heavily contaminated with oral flora or that corresponded with positive blood cultures
3. Fever—a temperature greater than 37.5°C within 24 h after surgery
4. Pulmonary atelectasis—confirmed by chest x-ray or computed tomography
5. Pneumothorax—confirmed by chest x-ray or computed tomography
6. Severe nausea and vomiting—two or more episodes of expulsion of gastric contents at least 6 h apart, or if requiring at least three doses of antiemetic medication
7. Myocardial infarction—confirmed by a typical rise and fall in cardiac enzymes (troponin or creatine kinase-MB fraction) with at least one of the following: typical ischemic symptoms, new Q-wave or ST-segment electrocardiographic changes, or coronary intervention; or pathologic findings of myocardial infarction
8. Stroke—a new neurologic deficit persisting for 24 h or longer, confirmed by neurologist assessment and/or computed tomography or magnetic resonance imaging
9. Awareness—postoperative recollection of intraoperative events, identified using a structured questionnaire,[26] at 24 h and 30 days after surgery
10. Venous thromboembolism—(a) deep venous thrombosis with typical symptoms and signs, or confirmed with venography or duplex ultrasonography; (b) pulmonary embolism confirmed by ventilation/perfusion scan, spiral computed tomography, or autopsy
11. Blood transfusion—any erythrocyte transfusion within 30 days of surgery
12. Quality of recovery at 24 h after surgery—using the validated quality of recovery score instrument,[28] a nine-item global assessment of early postoperative health status that is associated with patient satisfaction, completed on the morning after surgery. The quality of recovery score has a range of 0 (poor recovery) to 18 (excellent recovery). Collection of a preprocedure baseline score is also validated.

In addition, we formed two composite endpoints: "any respiratory complication" included pneumonia, atelectasis, pneumothorax, and pulmonary embolism; and "any major complication" included pneumonia, pneumothorax, pulmonary embolism, wound infection, myocardial infarction, venous thromboembolism, stroke, awareness, and death within 30 days of surgery.

Statistical Analyses

All patients randomly assigned to nitrous oxide–free or nitrous oxide–based anesthesia undergoing eligible surgery were considered as comprising the intention-to-treat population for all primary and secondary analyses. Analyses of the primary outcome of duration of hospital stay was performed using the log-rank test and Cox proportional hazards model with adjustment for the prespecified covariates of age, ASA physical status, and duration of anesthesia. Assessment of the requisite proportionality assumptions was performed using diagnostic residuals. Duration of ICU stay was recorded only to the nearest day and therefore was analyzed by a discrete time analog of proportional hazards regression using binary regression with a complementary log–log link function.[29] Deaths in the ICU were assigned the longest duration of stay, and analyses were repeated to adjust for the prespecified covariates listed above. Incidences of postoperative complications were analyzed using the chi-square test, with prespecified covariate adjustment performed by logistic regression. Results are expressed with hazard or odds ratios and 95% confidence intervals (CIs). The reference category for both ratios is the nitrous oxide group (being routine practice in most institutions). Therefore, a hazard ratio greater than 1 indicates a faster discharge rate in the nitrous oxide–free group compared with the nitrous oxide group, and an odds ratio less than 1 indicates a lower risk in the nitrous oxide–free group compared with the nitrous oxide group. Other secondary endpoints and differences in anesthetic procedures were assessed with *t* tests, chi-square test, or Wilcoxon rank sum test according to distributional criteria.

A multivariate analysis exploring an independent effect of inspired oxygen concentration was planned, because previous studies identified a beneficial[5–7] or detrimental[30] effect on some outcomes. Because "sicker" patients at increased risk of adverse outcomes would be expected to require a higher inspired oxygen concentration during surgery, we restricted the secondary analysis to the nitrous oxide–free group to minimize the possibility of selection (Berksonian) bias. Additional regression analyses were performed to explore the effect of possible covariate imbalance and to assess whether preoperative vitamin B_{12} or folate supplementation influenced the effects of nitrous oxide. All reported *P* values are two-sided and not adjusted for multiple comparisons.

Results

The 19 participating centers of the ENIGMA trial group recruited subjects between April 2003 and November
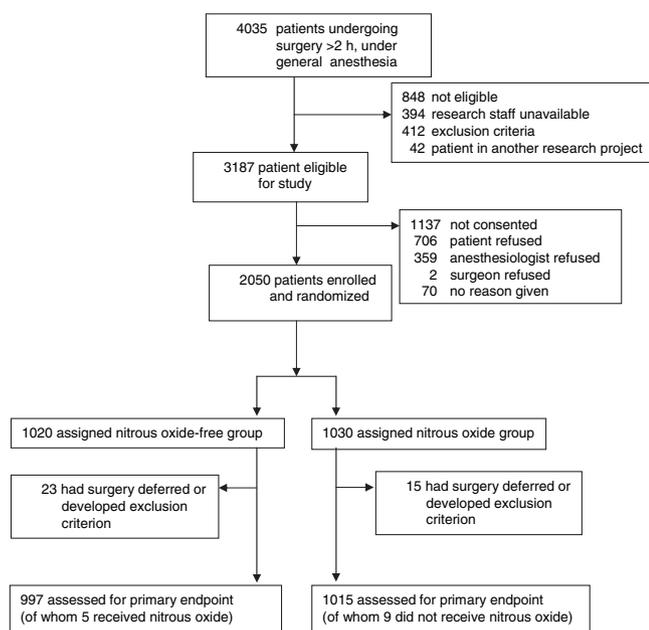
Fig. 1. Trial profile.

2004. Of 3,187 eligible patients, 2,050 surgical patients were enrolled (997 in the nitrous oxide–free group and 1,015 in the nitrous oxide group) (fig. 1). Demographic, dietary, medical, and perioperative characteristics at baseline were similar in the two groups (table 1). The median inspired oxygen concentration was 80% (interquartile range, 75-85%) for the nitrous oxide–free group and 30% (interquartile range, 30-32%) for the nitrous oxide group. There were 122 patients in the nitrous oxide–free group (12%) and 140 patients in the nitrous oxide group (14%) admitted to the ICU immediately postoperatively ($P = 0.30$). There were some differences in anesthetic drug administration as a result of removing nitrous oxide from the inspired gas mixture (table 2). Patients receiving a nitrous oxide–free anesthetic had a shorter time to eligibility to discharge from the postanesthesia care unit ($P = 0.02$) (table 2).

The median (interquartile range) duration of hospital stay was 7.0 (4.0-10.9) days in the nitrous oxide–free group and 7.1 (4.0-11.8) days in the nitrous oxide group. But the rate of hospital discharge did not differ between groups (hazard ratio, 1.09; 95% CI, 1.00-1.19; $P = 0.06$; fig. 2). There was also little evidence for nonproportionality of hazards ($P = 0.12$). The hospital discharge rate ratio was largely unaffected after adjustment for age, ASA physical status, and duration of anesthesia (hazard ratio, 1.06; 95% CI, 0.97-1.16; $P = 0.18$).

The median duration of ICU stay was 1 day in each group, but patients in the nitrous oxide–free group were more likely to be discharged on any given day (hazard ratio, 1.35; 95% CI, 1.05-1.73; $P = 0.02$; fig. 3), with little evidence for nonproportionality of hazards ($P = 0.15$). The ICU discharge rate ratio was largely unaffected after adjustment for age, ASA physical status, and

duration of anesthesia (hazard ratio, 1.44; 95% CI, 1.12-1.85, $P = 0.005$). Patients in the nitrous oxide–free group had a lower incidence of several postoperative complications, including severe nausea or vomiting, fever, wound infection, pneumonia, and atelectasis (table 3). Patients in the nitrous oxide–free group were less likely to have at least one major complication compared with patients in the nitrous oxide group (16% *vs.* 21%; odds ratio, 0.71; 95% CI, 0.56-0.89; $P = 0.003$; table 3). Selected subgroup analyses show comparable findings across a variety of clinical situations (fig. 4).

Patients in the nitrous oxide–free group had better quality of recovery scores than patients in the nitrous oxide group (mean [SD], 12.2 [3.4] *vs.* 11.9 [3.9]; difference, 0.34; 95% CI, 0.01-0.66; $P = 0.042$). This was largely unaffected after adjustment for age, ASA physical status, duration of anesthesia, sex, and preoperative quality of recovery score ($P = 0.042$).

Secondary and Exploratory Analyses

Effect of Inspired Oxygen Concentration. Data from the nitrous oxide–free group (n = 997) were analyzed to determine whether there was an independent effect of supplemental oxygen on key outcomes, after adjusting for prespecified potential confounding variables (as above). There was no measurable effect of supplemental oxygen on hospital stay ($P = 0.15$), ICU stay ($P = 0.60$), wound infection ($P = 0.40$), or severe nausea or vomiting ($P = 0.88$), but there was a reduction in fever ($P < 0.001$). Additional exploratory analyses regarding this are available on the ANESTHESIOLOGY Web site at www.anesthesiology.org.

Effect of Preoperative Folate or Vitamin B Supplementation. Three hundred eighty-nine study patients (19%) were taking vitamin B or folate supplements before surgery. Key outcomes were analyzed to determine whether the difference in outcome between the nitrous oxide–free and nitrous oxide–based groups varied according to vitamin B/folate supplementation (*via* interaction terms in Cox/logistic regression models), after adjusting for prespecified potential confounding variables (as above). There was no evidence that vitamin supplementation modified the effect of nitrous oxide on hospital stay (interaction $P = 0.14$), ICU stay ($P = 0.32$), fever ($P = 0.49$), wound infection ($P = 0.58$), severe nausea or vomiting ($P = 0.86$), any respiratory complication ($P = 0.40$), any major complication ($P = 0.26$), or quality of recovery ($P = 0.59$).

Discussion

In this study, major postoperative complications, including postoperative fever, wound infection, pneumonia, pulmonary atelectasis, and severe nausea or vomiting, were significantly reduced if nitrous oxide was

Table 1. Baseline Characteristics

Characteristic	Nitrous Oxide–free Group (n = 997)	Nitrous Oxide Group (n = 1,015)
Age, mean (SD), yr	55.8 (17)	54.6 (16)
Age > 65 yr, n (%)	325 (33)	289 (29)
Male sex, n (%)	533 (54)	520 (51)
Body weight, mean (SD), kg	71 (19)	71 (19)
Body weight ≥ 100 kg, n (%)	77 (7.2)	70 (6.9)
Risk scores, n (%) unless otherwise stated		
ASA physical status		
I	209 (21)	206 (20)
II	548 (55)	557 (55)
III	230 (23)	241 (24)
IV	10 (1.0)	11 (1.1)
PONV score, median (IQR)	2 (1–2)	2 (1–3)
0	49 (4.9)	77 (7.6)
1	318 (32)	285 (28)
2	389 (39)	397 (39)
3	220 (22)	215 (21)
4	21 (2.1)	41 (4.0)
NNISS score, median (IQR)	1 (0–2)	1 (0–2)
0	317 (32)	307 (30)
1	336 (34)	343 (34)
2	287 (29)	308 (30)
3	57 (5.7)	57 (5.6)
Emergency surgery, n (%)	40 (4.0)	41 (4.0)
Surgery with potential contamination or dirty-infected, n (%)	348 (35)	346 (34)
Preexisting medical conditions, n (%)		
Asthma	78 (7.8)	91 (9.0)
Chronic obstructive lung disease	53 (5.3)	47 (4.6)
Coronary artery disease	110 (11)	113 (11)
Current smoker	184 (19)	234 (23)
Diabetes	137 (14)	140 (14)
Hypertension	322 (32)	356 (35)
Heart failure	26 (2.6)	30 (3.0)
Anemia (including pernicious anemia)	104 (10)	126 (12)
Current infection	43 (4.3)	44 (4.3)
History of thromboembolism	29 (2.9)	27 (2.7)
History of stroke	41 (4.0)	41 (4.0)
Other	355 (36)	382 (38)
Any medical condition	799 (79)	751 (75)
Dietary factors, n (%)		
Vegan	40 (4.0)	49 (4.8)
Regular breakfast cereals	483 (49)	455 (45)
Regular fruit/vegetables	720 (72)	762 (75)
Vitamin B supplementation	166 (17)	166 (16)
Folate supplementation	61 (6.1)	80 (7.9)
Vitamin B_{12} injection	19 (1.9)	18 (1.8)
Folate or vitamin B supplementation	193 (19)	196 (19)
Prophylactic antibiotics given, n (%)	887 (89)	927 (91)
Type of surgery, n (%)		
General	472 (47)	448 (44)
Colorectal	157 (16)	142 (14)
Neurosurgery	144 (14)	151 (15)
Urology	127 (13)	130 (13)
Orthopedic	86 (8.6)	105 (10)
Gynecology	74 (7.4)	73 (7.2)
Ear, nose, throat, or faciomaxillary	40 (4.0)	50 (4.9)
Vascular	40 (4.0)	45 (4.4)
Plastics	14 (1.4)	12 (1.2)
Any abdominal	577 (58)	563 (56)
Duration of surgery, mean (SD), h	3.3 (2.0)	3.3 (2.0)
Median (IQR)	2.7 (2.0–4.1)	2.8 (1.9–4.3)
Duration of anesthesia, mean (SD), h	3.7 (2.0)	3.7 (2.0)
Median (IQR)	3.1 (2.3–4.6)	3.2 (2.3–4.8)
Preoperative quality of recovery score, mean (SD)	16.1 (2.0)	16.1 (2.0)
Median (IQR)	17 (15–18)	17 (15–18)

ASA = American Society of Anesthesiologists; IQR = interquartile range; NNISS = National Nosocomial Infections Surveillance System; PONV = postoperative nausea and vomiting.

Table 2. Comparison of Anesthetic Procedures

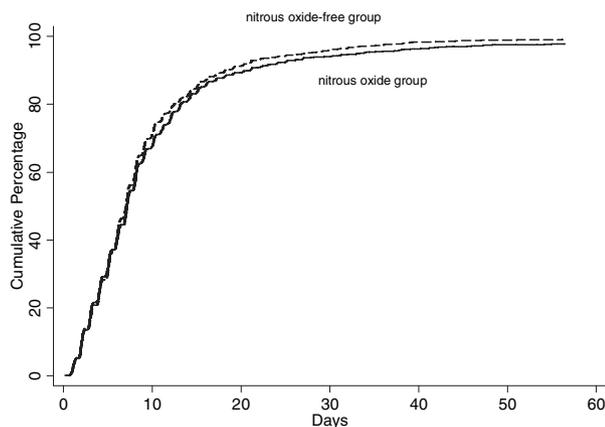| Variable	Nitrous Oxide–free Group (n = 997)	Nitrous Oxide Group (n = 1,015)	P Value
Inspired oxygen concentration, %			< 0.001
Mean (SD)	73 (17)	32 (6.4)	
Minimum	25	21	
25th centile	75	30	
50th centile	80	30	
75th centile	85	32	
Maximum	100	100	
Bispectral Index monitoring, n (%)	259 (26)	160 (16)	< 0.001
Induction agents			
Midazolam used, n (%)	513 (52)	514 (51)	0.72
Dose, median (IQR), mg	2 (2–3)	2 (2–3)	0.67
Propofol used, n (%)	942 (95)	966 (95)	0.49
Dose, median (IQR), mg	120 (100–160)	120 (100–170)	0.048
Thiopental used, n (%)	35 (3.5)	27 (2.7)	0.27
Dose, median (IQR), mg	250 (200–275)	250 (200–300)	0.25
Propofol maintenance anesthesia, n (%)	191 (19)	132 (13)	< 0.001
Mean (SD) infusion rate, mg · kg^{-1} · h^{-1}	0.18 (0.25)	0.23 (0.33)	0.39
Or mean (SD) target plasma concentration, μg/ml	3.27 (0.84)	3.09 (0.79)	0.28
Opioid dose			
Fentanyl, median (IQR), μg; n = 748, 719	100 (100–150)	100 (100–150)	0.41
Morphine, mean (SD), mg; n = 643, 620	10.9 (6.0)	10.8 (5.4)	0.72
End-tidal volatile concentration, median (IQR), MAC equivalents*	0.87 (0.61–1.06)	0.67 (0.52–0.83)	< 0.001
Prophylactic antiemetic used, n (%)	342 (34)	356 (35)	0.72
Lowest temperature intraoperatively, mean (SD), °C	35.8 (0.59)	35.8 (0.62)	0.10
For patients admitted to PACU	n = 872	n = 874	
Time to eye-opening, median (IQR), min	11 (7–17)	11 (7–18)	0.41
Time to eligibility for discharge from PACU, median (IQR), min	84 (64–120)	92 (65–125)	0.02

* Minimum alveolar concentration (MAC) is a measure of anesthetic volatile agent potency; the MACs of sevoflurane, isoflurane, and desflurane are 1.80, 1.15, and 6.0, respectively.

IQR = interquartile range; PACU = postanesthesia care unit.

avoided. However, despite the decrease in postoperative complications, we did not observe a meaningful difference in duration of hospital stay between groups. Hospital stay is often used as an outcome measure after surgery,[6,30,31] but can be affected by nonclinical factors and variable local practices. Furthermore, some postoperative complications are transient or can be readily treated and so may not affect hospital stay. This view is supported by figure 2, which indicates no apparent difference between groups within the first 7 days after

surgery, but that a difference may exist in those staying longer than 7 days, possibly because of increased postoperative complications.

The decreased risk of complications in the nitrous oxide–free group of our study could be explained by avoidance of nitrous oxide and/or administration of high inspired oxygen concentrations. We believe that, in a practical sense, this distinction is immaterial; regardless of whether the risk reduction is a result of nitrous oxide

Fig. 2. Kaplan–Meier estimates of hospital discharge. Patients in the nitrous oxide–free group were more likely to be discharged from the hospital on any given day (hazard ratio, 1.09; 95% confidence interval, 1.00–1.19; log rank P = 0.06).
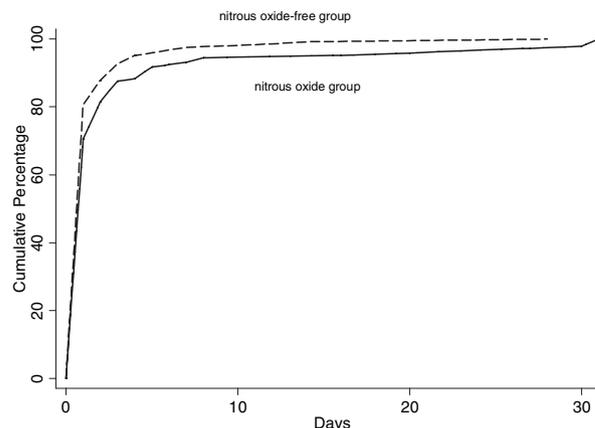
Fig. 3. Kaplan–Meier estimates of discharge from the intensive care unit. Patients in the nitrous oxide–free group were more likely to be discharged from the intensive care unit on any given day (hazard ratio 1.35; 95% confidence interval, 1.05–1.73; log rank P = 0.02).

Table 3. Postoperative Complications

Variable	Nitrous Oxide–free Group (n = 997), n (%)	Nitrous Oxide Group (n = 1,015), n (%)	Univariate Odds Ratio (95% CI)	P Value	Adjusted Odds Ratio* (95% CI)	P Value
Severe nausea or vomiting	104 (10)	229 (23)	0.40 (0.31–0.51)	< 0.001	0.40 (0.31–0.51)†	< 0.001
Wound infection	77 (7.7)	106 (10)	0.72 (0.53–0.98)	0.034	0.72 (0.52–0.98)‡	0.036
Fever	275 (28)	345 (34)	0.74 (0.61–0.89)	0.002	0.73 (0.60–0.90)	0.003
Pneumonia	15 (1.5)	30 (3.0)	0.50 (0.27–0.94)	0.031	0.51 (0.27–0.97)	0.040
Atelectasis	75 (7.5)	127 (13)	0.57 (0.42–0.77)	< 0.001	0.55 (0.40–0.75)	< 0.001
Pneumothorax	1 (0.1)	3 (0.3)	0.34 (0.01–4.23)	0.63	—	—
Myocardial infarction	7 (0.7)	13 (1.3)	0.54 (0.22–1.37)	0.20	0.58 (0.22–1.50)	0.26
Thromboembolism	16 (1.6)	10 (1.0)	1.64 (0.74–3.63)	0.22	1.60 (0.72–3.55)	0.25
Blood transfusion	188 (19)	202 (20)	0.94 (0.75–1.17)	0.55	0.96 (0.75–1.21)	0.71
Stroke	1 (0.1)	1 (0.1)	1.02 (0.01–80)	> 0.99	—	—
Awareness	0 (0.0)	2 (0.2)	—	—	—	—
Death within 30 days	3 (0.3)	9 (0.9)	0.34 (0.09–1.25)	0.10	0.33 (0.09–1.22)	0.096
Any pulmonary complication	78 (7.8)	132 (13)	0.57 (0.42–0.76)	< 0.001	0.54 (0.40–0.74)	< 0.001
Any major complication§	155 (16)	210 (21)	0.71 (0.56–0.89)	0.003	0.70 (0.55–0.89)	0.003

* Adjusted for age, American Society of Anesthesiologists physical status classification, and duration of anesthesia unless otherwise stated. † Adjusted for postoperative nausea and vomiting risk score (see text) and intraoperative antiemetic drug use. ‡ Adjusted for National Nosocomial Infections Surveillance System score (see text), lowest intraoperative temperature, and smoking status. § Any major complication includes wound infection, pneumonia, pneumothorax, myocardial infarction, thromboembolism, stroke, awareness, and death within 30 days of surgery.
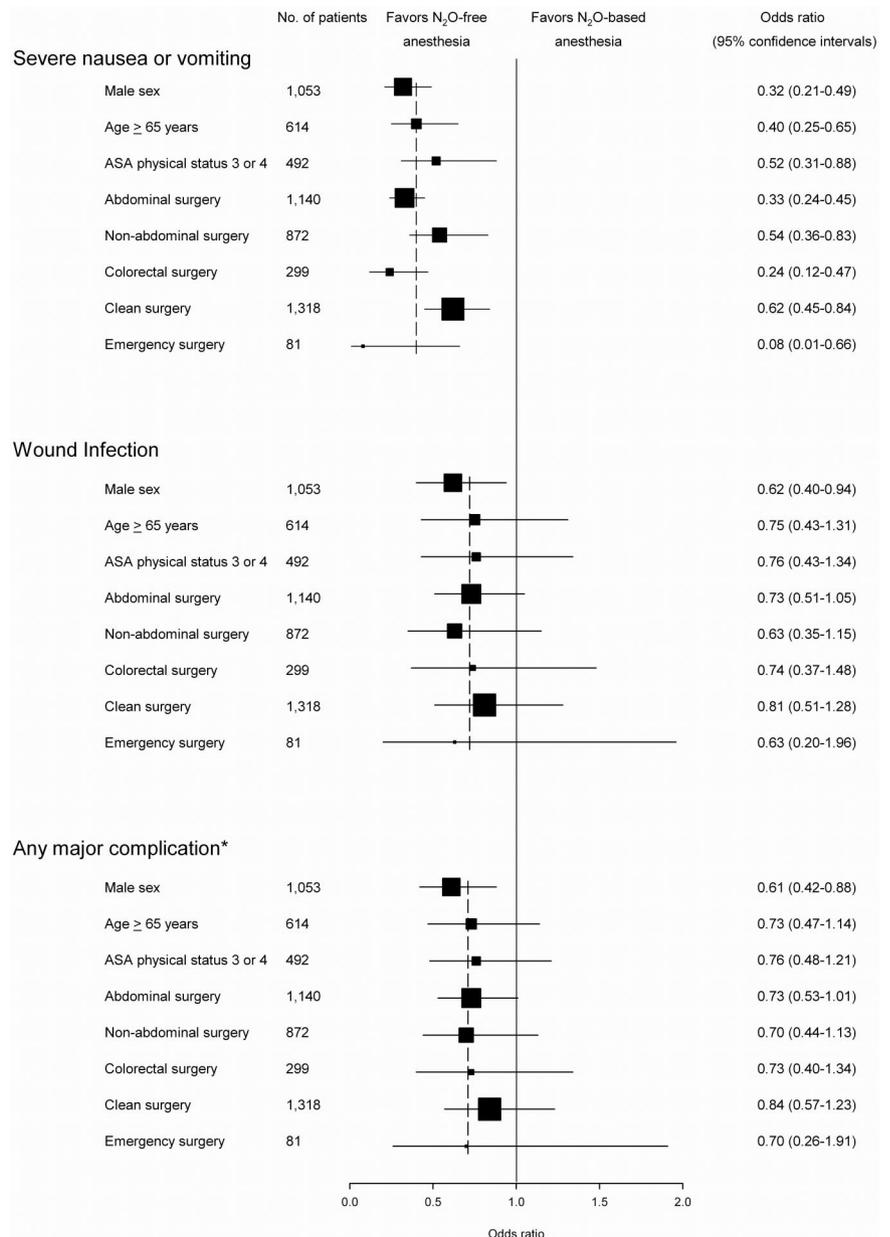
CI = confidence interval.

toxicity or direct benefits of supplemental oxygen, anesthesiologists should question the inclusion of nitrous oxide as part of their anesthetic regimen. We chose not to include a third group receiving 30% oxygen in 70% nitrogen,[32] because this combination is not often used clinically and high inspired oxygen concentrations have been reported to be beneficial.[5–7] Some anesthesiologists are concerned about absorption atelectasis occurring if nitrous oxide is avoided and high inspired oxygen concentrations are used.[32] However, nitrous oxide promotes absorption atelectasis in the lung as effectively as breathing 100% oxygen,[33] and we found a higher rate of atelectasis in the nitrous oxide group.

By allowing use of a lower or higher inspired oxygen concentration (25–100%) in the nitrous oxide–free group in our study protocol, we had an opportunity to examine our data for an independent effect of oxygen concentration. We found no evidence that oxygen concentration affected our main outcomes in the nitrous oxide–free group, but this exploratory analysis was limited by the small number (n = 156) of patients receiving inspired oxygen concentration of less than 51%. Some of the decreased adverse effects seen in the nitrous oxide–free group, therefore, could be attributed to supplemental oxygen. A recent meta-analysis could not confirm the previous suggestion of a significant reduction in nausea or vomiting with supplemental oxygen.[34]

Several recent studies have compared the effect of inspiring 80% oxygen and 30–35% oxygen on wound infection in colorectal surgery patients, but their results are conflicting. Two trials reported a beneficial effect,[6,7] whereas one reported a detrimental effect, with the rate of wound infection more than doubled in the 80% oxy-gen group.[30] Unlike the two former trials in which nitrogen (20% or 70%) made up the remainder of the inspired gas mixture,[5,6] in the latter trial, some of the patients in both groups were given nitrous oxide. This trial has been criticized,[35] but in view of the contradictory findings to date, the effect of supplemental oxygen on the risk of wound infection is unclear. A trial comparing nitrous oxide or nitrogen with an identical inspired oxygen concentration of 35% found no difference in wound infection rates, but the trial sample size was based on a doubling of the relative risk.[31]

Nausea or vomiting after surgery is rated by patients as one of the most undesirable postoperative complications.[16] Our study found a marked reduction in the rate of severe nausea or vomiting in the first 24 h after surgery in the nitrous oxide–free group. Although this is consistent with the findings from one large trial (but our effect size is larger, perhaps due to longer duration of surgery)[15] and a meta-analysis of small trials,[14] our findings have greater clinical applicability, because minor or transient nausea or vomiting was excluded and so only genuinely distressing severe nausea or vomiting was included.[16] The incidence of severe nausea or vomiting within 24 h of surgery in our study was reduced from 23% in the nitrous oxide group to 10% in the nitrous oxide–free group, giving a number needed to treat of 8. The simple intervention of removing nitrous oxide from the anesthetic regimen should therefore have a substantial impact on patient comfort after surgery.[16] Indeed, we demonstrated a subsequent improved quality of recovery in patients in whom nitrous oxide was omitted. Patients allocated to the nitrous oxide group were less likely to receive an intravenous propofol anesthetic for

Fig. 4. The risk reduction for severe nausea or vomiting, wound infection, and any complication associated with avoidance of nitrous oxide in selected subgroups, expressed as univariate odds ratio (95% confidence interval). The *vertical interrupted lines* represent the overall risk reductions for the selected outcomes in the total study population. ASA = American Society of Anesthesiologists. * Any major complication includes wound infection, pneumonia, pneumothorax, myocardial infarction, thromboembolism, stroke, awareness, and death within 30 days of surgery.

maintenance (13% *vs.* 19%); maintenance with propofol has been shown to reduce the risk of postoperative nausea and vomiting.[14] However, when we adjusted for this difference and other potential confounders in the analysis, the results remained unaffected.

Inclusion of nitrous oxide allows a dose reduction of other hypnotic agents; in our study, there was a 23% dose-reduction in volatile agent administration, but we found no significant effect on time to eye opening. In fact, patients receiving a nitrous oxide–free anesthetic were eligible for discharge from the postanesthesia care unit slightly faster than those receiving nitrous oxide. There is some concern that avoidance of nitrous oxide may also increase the risk of awareness during anesthesia.[14] This may explain the higher rate of Bispectral Index monitoring in the nitrous oxide–free group in our

study. The meta-analysis that suggested this increased risk was based on early studies, all of which were small. Widespread use of volatile agent monitoring, greater experience with intravenous maintenance techniques, and the ability to monitor anesthetic depth[36] probably discount the contemporary validity of this meta-analysis. We found no evidence in our study that avoidance of nitrous oxide increases the risk of awareness, although the trial was not powered to address this issue.

Exposure to nitrous oxide beyond a few hours will reduce methionine synthase activity by 50%[1] and can lead to clinically significant vitamin B_{12} and folate deficiency.[37] These effects may be partly avoided with large doses of vitamin B_{12} and folate.[38] Many studies have demonstrated that preoperative vitamin B or folate supplementation can increase plasma folate and decrease

homocysteine concentrations.[12,13] We found no evidence that the increased risk of adverse outcomes with nitrous oxide were mitigated by folate or vitamin B supplementation.

Subclinical adverse events (*e.g.*, asymptomatic deep venous thrombosis) may have gone undetected. Many of our postoperative complications were detected by patient interview and/or medical chart review at postoperative day 30, and some of these were dependent on laboratory or radiologic investigation. This raises the possibility of detection bias, but we believe we controlled for this by prospectively defining each complication, blinding surgical and research staff to group identity, and including a blinded endpoint adjudication process that required documentary evidence. We undertook multiple comparisons, which increases the chance of a type I error; the secondary, exploratory, and subgroup analyses should be treated cautiously. Because we chose to study patients undergoing major surgery lasting at least 2 h, the trial selected those patients who were at greatest risk of nitrous oxide–induced adverse effects.[2,12,13] Extrapolation of our findings to other situations, such as the use of nitrous oxide in minor surgery, pediatric surgery, or labor analgesia, should be avoided.

We found that a nitrous oxide–free anesthetic was associated with less myocardial infarction and death, but these were not statistically significant. However, this could be a type II error because our study was not of sufficient size to reliably address this question because these complications are rare in unselected patients. If nitrous oxide were to increase the risk of these serious postoperative complications, then this would be of marked clinical importance, and we have commenced a follow-up trial in 7,000 patients at risk of coronary artery disease (the ENIGMA II trial).§§

In conclusion, avoidance of nitrous oxide combined with supplementary oxygen in the gas mixture for anesthesia decreases the incidence of complications after major surgery but does not significantly affect duration of hospital stay. Whether the reduction in complications is due entirely to the known toxic effects of nitrous oxide, a possible beneficial effect of supplementary oxygen, or both, requires further study. In either case, the routine use of nitrous oxide in adult patients undergoing major surgery should be questioned.

§§ Available at: www.ClinicalTrials.gov (NCT00430989). Accessed April 4, 2007.

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