Section Editor: **Sorin J. Brull**

The Association Between Nitrous Oxide and Postoperative Mortality and Morbidity After Noncardiac Surgery

Alparslan Turan, MD,* Edward J. Mascha, PhD,*† Jing You, MS,*† Andrea Kurz, MD,* Ayako Shiba, MD,* Leif Saager, MD,* and Daniel I. Sessler, MD*‡

BACKGROUND: Nitrous oxide (N_2O) has been widely used in clinical anesthesia for >150 years. However, use of N_2O has decreased in recent years because of concern about the drug's metabolic side effects. But evidence that routine use of N_2O causes clinically important toxicity remains elusive. We therefore evaluated the relationship between intraoperative N_2O administration and 30-day mortality as well as a set of major inpatient postoperative complications (including mortality) in adults who had general anesthesia for noncardiac surgery.

METHODS: We evaluated 49,016 patients who had noncardiac surgery at the Cleveland Clinic between 2005 and 2009. Among 37,609 qualifying patients, 16,961 were given N_2O ("nitrous," 45%) and 20,648 were not ("nonnitrous," 55%). Ten thousand seven hundred fifty-five nitrous patients (63% of the total) were propensity score-matched with 10,755 nonnitrous patients. Matched nitrous and nonnitrous patients were compared on 30-day mortality and a set of 8 in-hospital morbidity/mortality outcomes.

RESULTS: Inhalation of N_2O intraoperatively was associated with decreased odds of 30-day mortality (odds ratio [OR]: 97.5% confidence interval, 0.67, 0.46–0.97; $P = 0.02$). Furthermore, nitrous patients had an estimated 17% (OR: 0.83, 0.74–0.92) decreased odds of experiencing major in-hospital morbidity/mortality than nonnitrous ($P < 0.001$). Among the individual morbidities, intraoperative N_2O use was only associated with significantly lower odds of having pulmonary/respiratory morbidities (OR, 95% Bonferroni-adjusted CI: 0.59, 0.44–0.78).

CONCLUSIONS: Intraoperative N_2O administration was associated with decreased odds of 30-day mortality and decreased odds of in-hospital mortality/morbidity. Aside from its specific and well-known contraindications, the results of this study do not support eliminating N_2O from anesthetic practice. (Anesth Analg 2013;116:1026–33)

Nitrous oxide (N_2O) was the first inhaled anesthetic and has been given to more than 1 billion people in >150 years of active clinical use, readily eclipsing the use of any other anesthetic. Despite its extraordinary history, there are reasons for concern. For example, prolonged administration to N_2O (i.e., days) is clearly toxic,[1] and there is weak epidemiologic evidence suggesting that environmental exposure to N_2O increased the risk of spontaneous abortion in dental assistants before effective scavenging was mandated.[2] Toxicity of N_2O is presumed to result largely from inhibition of methionine synthase,[3,4] which reduces proliferation of human peripheral blood mononuclear cells[5] and can cause megaloblastic anemia.[6,7]

Inhibition of methionine synthase by N_2O elevates homocysteine concentrations, which impair endothelial function and may worsen myocardial ischemia.[8–10] For example, Hohner et al.[11] reported that N_2O administration in high-risk vascular surgery patients increased intraoperative myocardial ischemia. Badner et al. similarly evaluated 90 patients randomized to anesthesia with or without N_2O and observed a significant increase in homocysteine concentrations and cardiovascular events.[12] Consistent with this mechanism, a (nonsignificant) trend towards increased cardiovascular complications was identified in the recent Evaluation of N_2O in Gas Mixture for Anesthesia (ENIGMA) study in which 2,050 patients were randomly assigned to N_2O or oxygen.[13]

The ENIGMA investigators also concluded that N_2O significantly increases the risk of vomiting, wound infection, and pneumonia.[13] That N_2O increases the risk of postoperative nausea and vomiting is well established, but nausea and vomiting are not life-threatening complications; furthermore, N_2O is less emetogenic than volatile anesthetics.[14] The effect of N_2O on surgical site infection is difficult to interpret since the ENIGMA trial compared N_2O to oxygen, and supplemental oxygen per se may[15,16] or may not[17] reduce wound infection risk. Similarly, high inspired oxygen concentration per se contributes to postoperative atelectasis and pulmonary complications.[18–20]

From the *Department of Outcomes Research and †Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH; and ‡Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada.

Ayako Shiba is currently affiliated with Anesthesiology Institute, Jikei University School of Medicine, Tokyo, Japan.

Accepted for publication December 1, 2011.

Funding: Supported by internal funds. None of the authors has any personal financial interest in this research.

The authors declare no conflict of interest.

This report was previously presented, in part, at the American Society of Anesthesiologists 2010.

Address correspondence to Alparslan Turan, MD, Department of Outcomes Research, Cleveland Clinic, 9500 Euclid Avenue/P77, Cleveland, OH 44195. Address e-mail to turana@ccf.org.

DOI: 10.1213/ANE.0b013e31824590a5

Table 1. Description of Individual In-Hospital Surgical Morbidities Included in the Composite

Outcome	Description	ICD-9
In-Hospital mortality		
Neurological	Nervous system complications, anoxic brain damage, cerebral hypoxia, postoperative stroke	997.0
Cardiac	Cardiac arrest, cardiac insufficiency, cardiorespiratory failure, or heart failure during or resulting from a procedure; acute pulmonary edema or pulmonary edema, postoperative	997.1 518.4
Pulmonary and respiratory	Respiratory complications; adult respiratory distress syndrome, acute respiratory insufficiency, shock lung; tracheostomy complications; pulmonary embolism/infarction; transfusion-related acute lung injury	997.3 518.5 519.0 415.11 518.7
Infectious	Ventilator associated pneumonia, Mendelson's syndrome, or pneumonia/aspiration resulting from a procedure; postoperative infection; sepsis, septicemia, or other postoperative infections; postoperative shock	997.31 997.39 998.5 999.3 998.0
Urinary	Complications of urinary tract stoma or internal anastomosis and bypass of urinary tract; oliguria/anuria due to procedure; acute renal failure/insufficiency, or acute tubular necrosis due to procedure	997.5
Hemorrhagic		
Wound disruption	Hemorrhage, hematoma, or seroma complicating a procedure	998.1
	Dehiscence of operation wound, disruption of suture materials or other closure method, rupture of operation wound	998.3
Peripheral vascular	Phlebitis or thrombophlebitis during or resulting from a procedure	997.2

ICD-9 = International Classification of Diseases, 9th revision.

There are thus well-established biochemical reasons to be concerned about the toxic effects of N_2O, but evidence that routine use of N_2O causes clinically important toxicity remains elusive. We therefore evaluated the relationship between intraoperative usage of N_2O and all-cause 30-day mortality as well as an endpoint consisting of 8 major inpatient complications and all-cause in-hospital mortality in adults having noncardiac surgery with general anesthesia. Specifically, we tested the hypothesis that N_2O use increases the odds of both 30-day mortality and a set of major inpatient complications.

METHODS

With IRB approval, written informed consent was waived for this retrospective cohort analysis of 49,016 adults who had noncardiac surgery at the Cleveland Clinic Main Campus between 2005 and 2009. Exposure to N_2O and outcome variables were obtained from the Cleveland Clinic Perioperative Health Documentation System. The Cleveland Clinic Perioperative Health Documentation System contains nearly all patients who had noncardiac surgery since May of 2005 at Cleveland Clinic's main campus. It integrates preoperative variables (demographics, conditions, etc), intraoperative variables (via the Anesthesia Record Keeping system), and postoperative outcomes (by linking to the larger Cleveland Clinic billing data systems). Patients were excluded from our analysis if they did not have general anesthesia, required emergent surgery, or had ASA physical statusscores >4.

Our primary outcomes were all-cause 30-day mortality and a set of major in-hospital complications, including all-cause mortality, neurological, cardiac, pulmonary/respiratory, infectious, urinary and hemorrhagic complications, wound disruption, and peripheral vascular complications (as defined in Table 1). As described below in more detail, we did not analyze the set of outcomes as a collapsed composite of "any-versus-none." Rather, a multivariate (i.e., multiple outcomes per patient) analysis was used to simultaneously capture the complete information on each component for a patient and the correlations among components. (Throughout this article, we use *multivariate* to refer to a model with multiple [and likely correlated] outcome variables, and *multivariable* to refer to a model with multiple independent variables.)

Propensity Score Matching

Each patient who received N_2O intraoperatively ("nitrous patient") was matched to a patient who did not ("nonnitrous patient") using propensity score matching.[21] Specifically, we first estimated the probability of receiving N_2O (i.e., the propensity score) for each patient using logistic regression with N_2O (versus air) as the outcome and adjusting for all baseline potential confounding variables listed in Table 2. Medical history conditions were carefully defined to be preexisting (i.e., not hospital acquired) by using ICD-9 codes corresponding to chronic conditions. For example, (baseline) pulmonary disease includes COPD and asthma; dementia includes chronic organic psychotic brain syndromes, senile dementia, vascular dementia, and brain syndrome with brain disease; digestive disease includes esophageal disorders, gastro duodenal ulcer, and liver diseases; CVD includes essential hypertension, coronary atherosclerosis, cardiac dysrhythmias, and congestive heart failure.

We then 1:1 matched nitrous and nonnitrous patients using a greedy distance matching algorithm (SAS macro: gmatch[a]), restricting successful matches to those with the same type of surgery (as characterized into 1 of 244 mutually exclusive, clinically appropriate categories

[a] Bergstralh E, Kosanke J. Gmatch SAS program. In: Mayo Clinic Division of Biomedical Statistics and Informatics. Rochester: Mayo Clinic (HSR CodeXchange), 2003. Computerized matching of cases to controls using the greedy matching algorithm with a fixed number of controls per case. Controls may be matched to cases using one or more factors (Xs). Available at: http://mayoresearch.mayo.edu/mayo/research/biostat/sasmacros.cfm. Accessed December 1, 2010.

Table 2. Summary of Demographics and Baseline Characteristics Before and After the Propensity Matching

Variable	Before matching: Nitrous (*N* = 16,961)	Before matching: Nonnitrous (*N* = 20,648)	*P*	D*	After matching: Nitrous (*N* = 10,746)	After matching: Nonnitrous (*N* = 10,746)	*P*	D*
Gender (male), %	7807 (46)	9619 (47)	0.28	−0.01	4990 (46)	4877 (45)	0.12	0.02
Age, years	55 ± 16	56 ± 16	<.001	−0.09	56 ± 16	56 ± 16	0.95	−0.00
Body mass index, kg/m^2	28 [24, 32]	28 [24, 33]	<0.001	−0.04	28 [24, 32]	28 [24, 33]	0.81	0.00
Race, %			<0.001	0.05			0.70	0.01
Caucasian	13735 (81)	17121 (83)			8864 (82)	8878 (83)		
African American	2074 (12)	2258 (11)			1186 (11)	1201 (11)		
ASA physical status, %			<0.001	0.24			<0.001	0.11
I	1080 (6)	956 (5)			466 (4)	686 (6)		
II	8299 (49)	8448 (41)			4906 (46)	5053 (47)		
III	7115 (42)	9909 (48)			4999 (47)	4569 (43)		
IV	467 (3)	1335 (6)			375 (3)	438 (4)		
Charlson comorbidity score, %			<0.001	0.18			<0.001	0.08
0	9285 (55)	9552 (46)			5267 (49)	5581 (52)		
1	2620 (15)	3536 (17)			1672 (16)	1692 (16)		
2	2799 (17)	3931 (19)			2026 (19)	1965 (18)		
3	862 (5)	1319 (6)			690 (6)	544 (5)		
4	1395 (8)	2310 (11)			1091 (10)	964 (9)		
Admitted for complication, yes, %	1010 (6)	954 (5)	<0.001	0.06	499 (5)	581 (5)	0.01	−0.04
Medical history								
Cancer, yes, %	5286 (31)	6811 (33)	<0.001	−0.04	3740 (35)	3560 (33)	0.01	0.04
CVD, yes, %	7933 (47)	10352 (50)	<0.001	−0.07	5198 (48)	5109 (48)	0.22	0.02
Dementia, yes, %	83 (<1)	124 (1)	0.15	−0.01	54 (1)	52 (<1)	0.85	0.00
Diabetes, yes, %	2185 (13)	3086 (15)	<0.001	−0.06	1444 (13)	1390 (13)	0.28	0.01
Digestive disease, yes, %	4754 (28)	6792 (33)	<0.001	−0.11	3361 (31)	2946 (27)	<0.001	0.09
Pulmonary disease, yes, %	1702 (10)	2455 (12)	<0.001	−0.06	1199 (11)	1096 (10)	0.02	0.03
Chronic renal failure, yes, %	582 (3)	826 (4)	0.004	−0.03	439 (4)	376 (4)	0.03	0.03
Malabsorption, yes, %	42 (<1)	74 (<1)	0.05	−0.02	35 (<1)	38 (<1)	0.73	−0.00
Bone marrow failure, yes, %	22 (<1)	84 (<1)	<0.001	−0.05	15 (<1)	30 (<1)	0.03	−0.03
Year of surgery, %			<0.001	0.48			<0.001	0.10
2005	3278 (19)	2312 (11)			1550 (14)	1473 (14)		
2006	6170 (36)	4808 (23)			3502 (33)	3051 (28)		
2007	3865 (23)	5336 (26)			2680 (25)	2884 (27)		
2008	2908 (17)	6177 (30)			2367 (22)	2658 (25)		
2009	740 (4)	2015 (10)			647 (6)	680 (6)		
Anesthesiologist,† %			<.001	0.58			<0.001	−0.17
A	726 (4)	498 (2)			362 (3)	393 (4)		
B	504 (3)	579 (3)			340 (3)	303 (3)		
C	338 (2)	705 (3)			282 (3)	265 (2)		
D	121 (1)	790 (4)			111 (1)	115 (1)		
E	422 (2)	436 (2)			263 (2)	303 (3)		

Summary statistics were presented as percentage of patients, mean ± SD, or median [Q1, Q3]; Student *t* test, Wilcoxon rank-sum test, or Pearson's chi-squared test, as appropriate. ASA = American Society for Anesthesiologists; CVD = cardiovascular disease; D = standardized differences; RSI = risk stratification index.

*D = standardized differences (nitrous minus nonnitrous: difference in means or proportions divided by pooled standard deviation; >0.1 in absolute value indicates imbalance.

†The 5 most frequent anesthesiologists are listed.

using the Agency for Healthcare Research and Quality's Clinical Classifications [AHRQ-CCS] categories) and with a difference in estimated logit of the propensity score (i.e., log ($\hat{p}/(1-\hat{p})$), $\hat{p}$: estimated propensity score) within 0.2 standard deviation of the propensity score logit across all patients, i.e., within 0.2 * 0.681 = 0.1362).[22]

Assessment of balance on the covariables used for the propensity score matching was performed using standardized differences (i.e., difference in means or proportions divided by the pooled SD). Imbalance was defined as a standardized difference >0.1 in absolute value (as suggested by Austin and others)[23,24]; any such covariables would be considered in the models comparing nitrous and nonnitrous patients on outcomes (see Primary Analyses) to reduce potential confounding. All of the analyses used this subset of matched patients.

Primary Analyses

Propensity score-matched nitrous and nonnitrous patients were compared on the 30-day mortality outcome using a multivariable logistic regression adjusting for any residual imbalanced covariables. We then assessed the "common effect" or "global" odds ratio (OR) of N_2O across the individual in-hospital major complications/mortality using a multivariate (i.e., multiple outcomes) generalized estimating equation (GEE) model with unstructured covariance matrix.[25] We thus did not compare groups on the collapsed composite of "any-versus-none." Instead, we used a GEE model to estimate a single odds ratio for the association between N_2O and the set of complications; the model contained one record for each possible complication per patient (i.e., 9 rows per patient) and adjusted for the within-subject correlation across the outcomes. To account for multiple testing while maintaining a type I error of 0.05, we used a significance criterion of $P < 0.025$ for each of the 2 primary outcomes (Bonferroni adjustment).

We assessed the heterogeneity of the N_2O effect across the components of the in-hospital outcomes in a separate "distinct-effects" GEE model in which the individual component

odds ratios were compared.[26] Significant heterogeneity, especially in opposite directions, would suggest that the individual odds ratios be given more importance than the global odds ratio.[26,27] Since heterogeneity was found, we reported and tested the individual odds ratios (total of 9) from the distinct effects GEE model along with the overall common effect odds ratio. A Bonferroni correction for multiple comparisons was used to control the type I error at 0.025, so that $P < 0.003$ was considered significant (i.e., 0.025/9 = 0.003).

Secondary Analyses

We also assessed the interaction between N_2O and age, gender, and year of surgery on each of the primary outcomes using logistic regression or multivariate GEE model, as appropriate. In the presence of a significant interaction ($P < 0.10$), the association between N_2O and the outcome was estimated within levels of the interacting factor.

Finally, we descriptively compared the propensity score-matched nitrous and nonnitrous patients on intraoperative hemodynamic characteristics, including vasopressor (ephedrine, phenylephrine, and epinephrine), antihypertensive, opioid (morphine equivalent, mg), and bronchodilator usage, using standardized difference and by standard statistical tests. Intraoperative hemodynamic monitoring data, inhalation anesthetics, and oxygen were acquired from our electronic anesthesia record-keeping system, which continuously records minute-by-minute data from the physiologic monitors throughout the intraoperative period. Arterial blood pressure in patients with invasive arterial catheters was recorded each minute, and in patients without an arterial line it was recorded at 1- to 5-minute intervals.

SAS software version 9.2 for UNIX (SAS Institute, Cary, NC) (for propensity score matching and outcomes assessment) and R software version 2.8.1 for Windows (The R Foundation for Statistical Computing, Vienna, Austria) (for figure and tables) were used for all statistical analyses. All the reported confidence intervals (CIs) were appropriately adjusted by Bonferroni correction. All tests were 2-tailed.

RESULTS

Thirty-seven thousand six hundred nine patients (16,961 [45%] N_2O and 20,648 [55%] nonnitrous) met our inclusion criteria. We successfully matched 10,746 N_2O patients (75% of the total) with 10,746 nonnitrous for a total of 21,492 patients. Our propensity score-matched subset retained 136 (77% of 177 categories before matching) AHRQ-CCS software categories (Supplemental Data File 1, see Supplemental Digital Content 1, http://links.lww.com/AA/A350). The 41 (23%) unmatched AHRQ-CCS categories represented only 0.4% of our study population.

As seen on the left side of Table 2, nitrous patients were generally healthier (lower Charlson comorbidity score and lower ASA status), and less likely to have digestive disease (standardized differences >0.1 in. absolute value). As expected, all of the factors in Table 2 were much better balanced in the 21,492 patients who were matched by propensity scores (Table 2, right panel). Only ASA status year of surgery and the anesthesiologist were slightly imbalanced between the matched nitrous and nonnitrous patients, with absolute standardized differences of 0.11, 0.10, and 0.17, respectively. We thus adjusted for ASA status and year of surgery in the multivariable model comparing the propensity-matched nitrous and nonnitrous patients on outcomes. We did not readjust for anesthesiologist because balance was excellent and the standardized difference for a variable with 75 categories can be overly sensitive. The summary of baseline factors between matched and unmatched patients is also provided in Supplemental Data File 2 (see Supplemental Digital Content 2, http://links.lww.com/AA/A351). Table 3 summarizes intraoperative factors between the propensity score-matched nitrous and nonnitrous patients. Nitrous patients, on average, were given less desflurane and sevoflurane (standardized differences >0.3 in absolute value). Intraoperative inspired oxygen concentration was slightly less in nitrous patients (median, 46%) than in those who were not (median 55%, standardized difference −1.0). No clinically important differences (i.e., standardized difference >0.1 in absolute value) were observed on any other intraoperative factors between nitrous and nonnitrous patients, although some of them were statistically different due to large sample size ($P < 0.05$).

Using the propensity score-matched groups, receiving N_2O was associated with decreased odds of in-hospital major complications/mortality ($P < 0.001$); the corresponding common effect odds ratio of N_2O administration across the individual in-hospital complications/mortality was estimated as 0.83 (97.5% CI: 0.74–0.92) (Table 4 and Fig. 1). Furthermore, receiving N_2O was associated with decreased odds of 30-day mortality ($P = 0.02$; OR: 0.67 [97.5% CI: 0.46–0.97], Table 4 and Fig. 1).

The association between intraoperative administration of N_2O and outcome was not consistent across the individual in-hospital surgical morbidities (N_2O × Morbidity interaction $P < 0.001$). We therefore also evaluated the association between N_2O and each specific major complication included in the set of in-hospital outcomes (Table 4 and Fig. 1). Intraoperative administration of N_2O was significantly associated only with decreased odds of pulmonary/respiratory morbidity (OR, 95% Bonferroni-adjusted CI: 0.59, 0.44–0.78; $P < 0.001$). The average amount of N_2O received intraoperatively was descriptively similar between patients with history of pulmonary disease (53% ± 11%) and patients without (54% ± 10%, standardized difference of –0.13). Besides pulmonary/respiratory morbidity, all other odds ratios (except for neurological and peripheral vascular, both slightly above 1.0) were in the direction of N_2O administration being protective, which helps explain why the overall common effect odds ratio was significantly less than 1.0.

We also found that the association between intraoperative administration of N_2O and the 30-day mortality depended on age (N_2O × Age interaction $P = <0.007$). However, intraoperative administration of N_2O was not significantly associated with 30-day mortality within any of the 4 quartiles of age. Furthermore, there was no N_2O × Age interaction effect on the set of major in-hospital complications/mortality ($P = 0.82$). Finally, intraoperative administration of N_2O did not depend on either gender or year of surgery for either of the primary outcomes (all $P > 0.10$).

DISCUSSION

Intraoperative use of N_2O was associated with decreased 30-day mortality in this nonrandomized propensity-matched study. This result is contrary to the ENIGMA trial

Table 3. Summary of Intraoperative Characteristics (Induction to End of Case) Among the Propensity Score Matched Patients

Variable	Nitrous (*N* = 10,746)	Nonnitrous (*N* = 10,746)	*P*[a]	D[†]
Duration of surgery, hours	3.6 [2.4, 5.0]	3.6 [2.4, 4.9]	0.30	0.01
Estimated blood loss‖, cc	150 [50, 350]	150 [50, 300]	<0.001	0.07
Urine¶, cc	350 [195, 640]	350 [200, 650]	0.37	−0.02
Red blood cell, cc	0 [0, 0]	0 [0, 0]	0.78	0.00
Crystalloid, L	3.1 [1.8, 4.5]	3.1 [1.9, 4.15]	0.57	0.01
Colloid, L	0 [0, 1]	0 [0, 1]	0.31	0.01
Heart rate,* beats/minute				
Minimum	56 ± 10	57 ± 10	<.001[b]	−0.07
Maximum	102 ± 17	103 ± 17	0.01[b]	−0.04
Standard deviation	9 ± 3	9 ± 3	0.01[b]	0.04
Mean arterial pressure,* mm Hg				
Minimum	58 ± 11	58 ± 11	<.001[b]	0.05
Maximum	127 [113, 147]	127 [113, 148]	0.17	−0.02
Standard deviation	13 [11, 16]	14 [11, 17]	<.01	−0.06
Systolic blood pressure,* mm Hg				
Minimum	79 ± 17	78 ± 17	0.02[b]	0.03
Maximum	173 ± 30	173 ± 31	0.04[b]	−0.03
Standard deviation	18 ± 6	19 ± 6	0.001[b]	−0.04
Diastolic blood pressure,* mm Hg				
Minimum	46 ± 9	46 ± 9	<.001[b]	0.05
Maximum	97 [87, 112]	98 [87, 113]	0.32	−0.01
Standard deviation	10 [8, 13]	10 [8, 13]	<.001	−0.06
Average desflurane,** %	2.6 ± 1.6	3.3 ± 1.6	<.001[b]	−0.46
Average isoflurane,** %	0.5 ± 0.3	0.5 ± 0.3	0.41[b]	−0.02
Average sevoflurane,** %	0.8 ± 0.5	1.0 ± 0.6	<.001[b]	−0.30
Antihypertensive (number of boluses within case)	0 [0, 0]	0 [0, 0]	0.34	−0.01
Beta blocker, number of boluses within case	0 [0, 0]	0 [0, 0]	0.29	−0.01
Bronchodilator, number of boluses within case	0 [0, 0]	0 [0, 0]	0.16	0.02
Opioid consumption (morphine equivalent), mg	25 [15, 35]	25 [15, 35]	0.002	−0.04
Vasopressor, number of boluses within case	1 [0, 3]	1 [0, 3]	0.57	0.01
Average F_{IO_2},† %	46 [38, 53]	55 [50, 59]	<.001	−1.00

Summary statistics was presented as mean ± SD or median [Q1, Q3], as appropriate.
‖13% and ¶36% patients had missing values.
*Summarized within patient, including all minute-by-minute measurements from induction time to end of case.
**Within patient average of minute-by-minute end-tidal of inhaled anesthetic from induction time to end of case.
†Average F_{IO_2} was summarized within patients and included all minute-by-minute measurements from 10 minutes after incision time to 10 minutes before emergence time.
[a]Wilcoxon rank-sum test, unless noted. [b]Student *t* test.
‡Standardized differences (nitrous minus nonnitrous): the difference in means or proportions divided by the pooled standard deviation; >0.1 indicates slight imbalance.
D = standardized difference; F_{IO_2} = the fraction of inspired oxygen in a gas mixture.

and also to the 3.5-year follow-up[28] of patients randomized to N_2O or oxygen in the ENIGMA trial.[13] The odds of experiencing in-hospital mortality or a nonfatal major in-hospital complication were an estimated 17% lower (OR, 97.5% CI: 0.83, 0.74–0.92) in those patients given N_2O. The reduced odds of major outcomes were driven by significantly lower odds (−40%) of pulmonary/respiratory complications. In contrast, the odds of in-hospital mortality and infectious complications were similar in patients who were and were not given N_2O.

Table 4. Incidences of 30-Day and Individual In-hospital-Morbidity/Mortality Among Propensity-Matched Patients

Outcome	Nitrous (*n* = 10,746), *N* (%)	Nonnitrous (*n* = 10,746), *N* (%)
30-day mortality	60 (0.6)	89 (0.8)
In-hospital morbidity/mortality		
Cardiac	212 (2.0)	240 (2.2)
Hemorrhagic	231 (2.2)	237 (2.2)
In-hospital mortality	23 (0.2)	46 (0.4)
Infectious	190 (1.8)	218 (2.0)
Neurological	64 (0.6)	57 (0.5)
Peripheral vascular	25 (0.2)	24 (0.2)
Pulmonary/respiratory	191 (1.8)	310 (2.9)
Urinary/renal	128 (1.2)	127 (1.2)
Wound disruption	37 (0.3)	44 (0.4)
Any of the above	909 (8.5)	996 (9.3)

Cardiac complications, intraoperative arterial blood pressure, heart rate, and consumption of vasoactive drugs were all comparable in patients who were or were not given N_2O. This observation contrasts to a nonsignificant trend towards more cardiac complications in the ENIGMA trial.[13] We note, though, that ENIGMA patients were expected to remain hospitalized for at least 3 days, whereas our population included outpatients and patients undergoing minor procedures.[13] ENIGMA patients were also apparently given more N_2O than our patients (≈70% versus ≈55%). More important, complication tracking was far more intense in the ENIGMA trial that was randomized than in our registry analysis that depended on complications being coded for billing purposes. A long-term follow-up study of

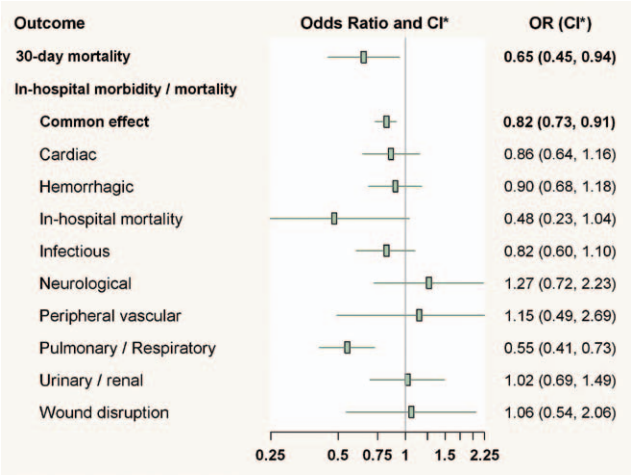

Figure 1. Odds ratios of 30-day mortality and each individual in-hospital morbidity/mortality, and the generalized estimating equation "common effect" odds ratio (OR) across the individual in-hospital outcomes, occurring in the nitrous and nonnitrous patients. Analyses used the propensity score-matched patients (n = 21,492), adjusting for ASA status and year of surgery. *Confidence intervals (CIs) were Bonferroni adjusted. Confidence intervals for the 2 primary outcomes: 30-day mortality and "overall" in-hospital morbidity/mortality were 97.5% (i.e., 0.05/2 = 0.025); for the 9 in-hospital outcomes were 99.7% (i.e., 0.025/9 = 0.003).

the ENIGMA trial[23] patients also demonstrated a marginal increase in risk of myocardial infarction in patients receiving N_2O, although the trial was somewhat compromised by patients lost to follow-up and low study power. Fortunately, a large randomized trial is in progress to specifically test the hypothesis that N_2O worsens cardiac morbidity (ENIGMA-2, ClinTrials NCT00430989). Adequately powered randomized data specific to the potential cardiac effects of N_2O will thus soon be available. But in the meantime, our results do not suggest that N_2O should be avoided for fear of cardiovascular complications, especially since interventions to reduce plasma homocysteine concentrations do not reduce cardiovascular events in nonsurgical settings.[29–31]

Surprisingly, N_2O use was associated with a substantial and statistically significant 41% reduction in odds of having pulmonary/respiratory complications. This may be the result of a selection bias, in that N_2O may have been avoided in patients with pulmonary disease, at least in those who required a high inspired oxygen fraction. As in other institutions,[32] patients who were not given N_2O appear to have been given roughly comparable amounts of medical air, which of course contains 21% oxygen. Consequently, the inspired oxygen fraction was about 10% greater than in patients not given N_2O. A 10% difference seems unlikely to provoke complications, but high inspired oxygen fractions can lead to oxygen absorption, alveolar collapse, and postoperative complications.[18,19]

A direct effect of N_2O on the lung may also have contributed to reduced pulmonary complications. It is well established that N_2O is an *N*-methyl-D-aspartate (NMDA) receptor antagonist. NMDA receptors are present in the lungs[33] and are key intermediates in the pathogenesis of hyperoxia-induced lung injury via reactive oxygen species.[34] As might thus be expected, several studies show that hyperoxia-induced pulmonary damage is attenuated by NMDA receptor antagonists.[34,35] Surfactant synthesis by alveolar epithelial type II cells is down-regulated by NMDA receptors.[36] To the extent that N_2O reduces activation of NMDA receptors, surfactant synthesis may be enhanced and lung injury reduced.[36]

It is reasonably well established that N_2O reduces the required concentration of volatile anesthetics by 20%–15%.[37] In the ENIGMA trial,[13] for example, volatile anesthetic use was reduced 23% in patients given N_2O. Our results were similar, with volatile anesthetic use being reduced 17%–26% in patients given N_2O. In contrast, opioid use was comparable, probably because individual opioid requirements are nonobvious, leaving clinicians to give opioids largely by protocol.

An advantage of our registry is that the sample size is large and presumably fairly generalizable. Furthermore, inclusion criteria were uniform and reliability was enhanced by consistent data collection. There are nonetheless distinct limitations to retrospective analysis of registries. For example, inspired concentrations of N_2O were not recorded. Consequently, our analysis is based on the dichotomous use of N_2O, rather than administered dose. This limitation prevented us from assessing a dose-response relationship between nitrous oxide and outcome, a key component of establishing causal inference. But most important, our analysis is retrospective, which eliminates the protections against confounding due to selection bias that is normally provided by randomization. Our use of appropriate statistical techniques, especially propensity matching, nonetheless provides some protection against selection bias and confounding due to measured baseline factors. But to the extent that there are additional unmeasured (and thus not unadjusted) confounding factors, our results might be biased. A limitation of propensity score matching is that some patients are not matched and therefore not included in the analysis, thus reducing precision of the estimated treatment effect and also limiting the generalizability of conclusions to patients similar to those studied. As a sensitivity analysis (data not presented) we also assessed the association between nitrous oxide use and outcome adjusting for confounding using a multivariable model instead of propensity score matching; this analysis using all patients gave nearly identical results as our propensity score matching.

An additional limitation is that our outcomes, aside from 30-day mortality, are based on in-hospital ICD-9 billing codes rather than being specifically and prospectively evaluated. It is thus likely that some clinically important in-hospital events, such as silent myocardial infarctions, were not recorded. Furthermore, postdischarge complications were not included in our analysis. To the extent that outcomes occurred postoperatively or were missed through incomplete coding, reported frequencies will underestimate the true incidence. But unless outcome identification in our registry is biased (i.e., nonrandomly erroneous in patients given or not given N_2O), reported odds ratios will remain accurate.

In summary, our analysis of a large registry indicates that intraoperative N_2O administration was associated with lower odds of both 30-day mortality and of the odds of a set of serious in-hospital complication events. N_2O is the longest-serving anesthetic; aside from its specific and well-known contraindications, the results of this study do not support eliminating N_2O from anesthetic practice.

DISCLOSURES

Name: Alparslan Turan, MD.
Contribution: This author helped design the study, conduct the study, and write the manuscript.
Attestation: Alparslan Turan has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Edward Mascha, PhD.
Contribution: This author helped design the study, analyze the data, and write the manuscript.
Attestation: Edward Mascha has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Jing You, MS.
Contribution: This author helped analyze the data and write the manuscript.
Attestation: Jing You has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Andrea Kurz, MD.
Contribution: This author helped design the study, conduct the study, and write the manuscript.
Attestation: Andrea Kurz has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Ayako Shiba, MD.
Contribution: This author helped design the study, conduct the study, and write the manuscript.
Attestation: Ayako Shiba has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Leif Saager, MD.
Contribution: This author helped design the study, analyze the data, and write the manuscript.
Attestation: Leif Saager has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Daniel I. Sessler, MD.
Contribution: This author helped design the study and write the manuscript.
Attestation: Daniel I. Sessler reviewed the analysis of the data and approved the final manuscript.
This manuscript was handled by: Sorin J. Brull, MD.

REFERENCES

1. Lassen HC, Henriksen E, Neukirch F, Kristensen HS. Treatment of tetanus: severe bone-marrow depression after prolonged nitrous-oxide anaesthesia. Lancet 1956;270:527–30
2. Boivin JF. Risk of spontaneous abortion in women occupationally exposed to anaesthetic gases: a meta-analysis. Occup Environ Med 1997;54:541–8
3. Ciaccio M, Bellia C. Hyperhomocysteinemia and cardiovascular risk: effect of vitamin supplementation in risk reduction. Curr Clin Pharmacol 2010;5:30–6
4. Myles PS, Chan MT, Leslie K, Peyton P, Paech M, Forbes A. Effect of nitrous oxide on plasma homocysteine and folate in patients undergoing major surgery. Br J Anaesth 2008;100:780–6
5. Schneemilch CE, Hachenberg T, Ansorge S, Ittenson A, Bank U. Effects of different anaesthetic agents on immune cell function in vitro. Eur J Anaesthesiol 2005;22:616–23
6. Nunn JF. Clinical aspects of the interaction between nitrous oxide and vitamin B12. Br J Anaesth 1987;59:3–13
7. Andres E, Loukili NH, Noel E, Kaltenbach G, Abdelgheni MB, Perrin AE, Noblet-Dick M, Maloisel F, Schlienger JL, Blicklé JF. Vitamin B12 (cobalamin) deficiency in elderly patients. CMAJ 2004;171:251–9
8. Tyagi SC, Smiley LM, Mujumdar VS. Homocyst(e)ine impairs endocardial endothelial function. Can J Physiol Pharmacol 1999;77:950–7
9. Tawakol A, Forgione MA, Stuehlinger M, Alpert NM, Cooke JP, Loscalzo J, Fischman AJ, Creager MA, Gewirtz H. Homocysteine impairs coronary microvascular dilator function in humans. J Am Coll Cardiol 2002;40:1051–8
10. Myles PS, Chan MT, Kaye DM, McIlroy DR, Lau CW, Symons JA, Chen S. Effect of nitrous oxide anesthesia on plasma homocysteine and endothelial function. Anesthesiology 2008;109:657–63
11. Hohner P, Backman C, Diamond G, Friedman A, Haggmark S, Johansson G, Karp K, Reiz S. Anaesthesia for abdominal aortic surgery in patients with coronary artery disease: part II. Effects of nitrous oxide on systemic and coronary haemodynamics, regional ventricular function and incidence of myocardial ischaemia. Acta Anaesthesiol Scand 1994;38:793–804
12. Badner NH, Beattie WS, Freeman D, Spence JD. Nitrous oxide–induced increased homocysteine concentrations are associated with increased postoperative myocardial ischemia in patients undergoing carotid endarterectomy. Anesth Analg 2000;91:1073–9
13. Myles PS, Leslie K, Chan MT, Forbes A, Paech MJ, Peyton P, Silbert BS, Pascoe E, ENIGMA Trial Group. Avoidance of nitrous oxide for patients undergoing major surgery: a randomized controlled trial. Anesthesiology 2007;107:221–31
14. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, Zernak C, Danner K, Jokela R, Pocock SJ, Trenkler S, Kredel M, Biedler A, Sessler DI, Roewer N, IMPACT Investigators. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med 2004;350:2441–51
15. Greif R, AKça O, Horn E-P, Kurz A, Sessler DI, Outcomes Research™ Group. Supplemental perioperative oxygen to reduce the incidence of surgical wound infection. N Engl J Med 2000;342:161–7
16. Belda FJ, Aguilera L, Garcia de la Asuncion J, Alberti J, Vicente R, Ferrandiz L, Rodríguez R, Company R, Sessler DI, Aguilar G, Botello SG, Ortí R, Spanish Reduccion de la Tasa de Infeccionq Uirurgica Group. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. JAMA 2005;294:2035–42
17. Meyhoff CS, Wetterslev J, Jorgensen LN, Henneberg SW, Simonsen I, Pulawska T, Walker LR, Skovgaard N, Heltø K, Gocht-Jensen P, Carlsson PS, Rask H, Karim S, Carlsen CG, Jensen FS, Rasmussen LS, PROXI Trial Group. Perioperative oxygen fraction—effect on surgical site infection and pulmonary complications after abdominal surgery: a randomized clinical trial. Rationale and design of the PROXI-Trial. Trials 2008;9:58
18. Martinez G, Cruz P. [Atelectasis in general anesthesia and alveolar recruitment strategies]. Rev Esp Anestesiol Reanim 2008;55:493–503
19. Rothen HU. Oxygen: avoid too much of a good thing! Eur J Anaesthesiol 2010;27:493–4
20. Zoremba M, Dette F, Hunecke T, Braunecker S, Wulf H. The influence of perioperative oxygen concentration on postoperative lung function in moderately obese adults. Eur J Anaesthesiol 2010;27:501–7
21. Rosenbaum PR, Rubin DB. The central rose of the propensity score in observational studies for casual effects. Biometrika 1983;70:41–55
22. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28:3083–107
23. Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. Stat Med 2007;26:734–53

24. Imai K, King G, Stuart E. Misunderstandings between experimentalists and observationalists about causal inference. J R Stat Soc Ser A Stat Soc 2008;171:481–502
25. Legler JLM, Ryan L. Efficiency and power of tests for multiple binary outcomes. J Am Stat Assoc 1995;90:680–93
26. Mascha EJ, Imrey PB. Factors affecting power of tests for multiple binary outcomes. Stat Med 2010;29:2890–904
27. Mascha EJ, Sessler DI. Statistical grand rounds: design and analysis of studies with binary-event composite endpoints: guidelines for anesthesia research. Anesth Analg 2011;112:1461–71
28. Leslie K, Myles PS, Chan MT, Forbes A, Paech MJ, Peyton P, Silbert BS, Williamson E. Nitrous oxide and long-term morbidity and mortality in the ENIGMA Trial. Anesth Analg 2011;112:387–93
29. Bazzano LA. Folic acid supplementation and cardiovascular disease: the state of the art. Am J Med Sci 2009;338:48–9
30. Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M, McQueen MJ, Probstfield J, Fodor G, Held C, Genest J Jr, Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med 2006;354:1567–77
31. Bonaa KH, Njolstad I, Ueland PM, Schirmer H, Tverdal A, Steigen T, Wang H, Nordrehaug JE, Arnesen E, Rasmussen K; NORVIT Trial Investigators. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med 2006;354: 1578–88
32. Baum JA. The carrier gas in anaesthesia: nitrous oxide/oxygen, medical air/oxygen and pure oxygen. Curr Opin Anaesthesiol 2004;17:513–6
33. Said SI, Berisha HI, Pakbaz H. Excitotoxicity in the lung: N-methyl-D-aspartate-induced, nitric oxide-dependent, pulmonary edema is attenuated by vasoactive intestinal peptide and by inhibitors of poly(ADP-ribose) polymerase. Proc Natl Acad Sci USA 1996;93:4688–92
34. Said SI, Pakbaz H, Berisha HI, Raza S. NMDA receptor activation: critical role in oxidant tissue injury. Free Radic Biol Med 2000;28:1300–2
35. Tang F, Yue S, Luo Z, Feng D, Wang M, Qian C, Zhen X, Duan Y. Role of *N*-methyl-D-aspartate receptor in hyperoxia-induced lung injury. Pediatr Pulmonol 2005;40:437–44
36. Shen L, Li L, She H, Yue S, Li C, Luo Z. Inhibition of pulmonary surfactants synthesis during *N*-methyl-D-aspartate-induced lung injury. Basic Clin Pharmacol Toxicol 2010;107:751–7
37. Eger EI 2nd, Lampe GH, Wauk LZ, Whitendale P, Cahalan MK, Donegan JH. Clinical pharmacology of nitrous oxide: an argument for its continued use. Anesth Analg 1990;71:575–85