Published in final edited form as:
Anesthesiology. 2009 March ; 110(3): 563–573. doi:10.1097/ALN.0b013e318197ff81.

Effect of Nitrous Oxide Use on Long-term Neurologic and Neuropsychological Outcome in Patients Who Received Temporary Proximal Artery Occlusion during Cerebral Aneurysm Clipping Surgery

Jeffrey J. Pasternak, M.D.[*], **Diana G. McGregor, M.B.B.S.**[**], **William L. Lanier, M.D.**[***], **Darrell R. Schroeder, M.S.**[#], **Deborah A. Rusy, M.D.**[##], **Bradley Hindman, M.D.**[###], **William Clarke, Ph.D.**[$], **James Torner, Ph.D.**[$$], and **Michael M. Todd, M.D. [on behalf of On behalf of the IHAST Investigators]**[$$$]

[*]Assistant Professor, Department of Anesthesiology, Mayo Clinic College of Medicine, Rochester, Minnesota

[**]Clinical Associate Professor, Department of Anesthesiology, Stanford University School of Medicine, Stanford, California

[***]Professor, Department of Anesthesiology, Mayo Clinic College of Medicine, Rochester, Minnesota

[#]Assistant Professor, Department of Biostatistics, Mayo Clinic College of Medicine, Rochester, Minnesota

[##]Associate Professor, Department of Anesthesiology, University of Wisconsin College of Medicine, Madison, Wisconsin

[###]Professor, Department of Anesthesiology, University of Iowa Carver College of Medicine, Iowa City, Iowa

[$]Professor, Department of Biostatistics, University of Iowa College of Public Health, Iowa City, Iowa, and Director of the University of Iowa Data Management Center

[$$]Professor and Head – Department of Epidemiology, University of Iowa College of Public Health, Iowa City, Iowa

[$$$]Professor and Head, Department of Anesthesiology, University of Iowa Carver College of Medicine, Iowa City, Iowa, Principal Investigator of IHAST Investigation

Abstract

Background—We explored the relationship between nitrous oxide use and neurological and neuropsychological outcome in a population of patients likely to experience intraoperative cerebral ischemia: *i.e.,* those who had temporary cerebral arterial occlusion during aneurysm clipping surgery.

Methods—A *post hoc* analysis of a subset of the data from the Intraoperative Hypothermia for Aneurysm Surgery Trial was conducted. Only subjects who had temporary arterial occlusion during

Address Correspondence to: Jeffrey J. Pasternak, M.D., Department of Anesthesiology, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, Phone: 507-255-4235, Fax: 507-255-6463, e-mail: pasternak.jeffrey@mayo.edu.
On behalf of the Department of Anesthesiology, Mayo Clinic College of Medicine, Rochester, Minnesota.

Brief Summary Statement: Nitrous oxide use during cerebral aneurysm clipping surgery – in those patients requiring temporary vessel occlusion of an artery supplying the aneurysm – was associated with increased short-term (< 14d), but not long-term (3 mo), neurologic deficits.

surgery were included in the analysis. Metrics of short-term and long-term (*i.e.*, 3 months post-surgery) outcome were evaluated via both univariate and multivariate logistic regression analysis. An odds ratio (OR) of greater than 1.0 denotes a worse outcome in patients receiving nitrous oxide.

Results—We evaluated 441 patients, of which 199 received nitrous oxide. Patients receiving nitrous oxide had a greater risk of delayed ischemic neurologic deficits (*i.e.*, the clinical manifestation of vasospasm) (OR=1.78, 95% confidence interval [CI]=1.08–2.95, p=0.025). However, at 3 months after surgery, there was no difference in any metric of gross neurologic outcome: Glasgow Outcome Score (OR=0.67, CI=0.44–1.03, p=0.065), Rankin Score (OR=0.74, CI=0.47–1.16, p=0.192), National Institutes of Health Stroke Scale (OR=1.02, CI=0.66–1.56, p=0.937), or Barthel's Index (OR=0.69, CI=0.38–1.25, p=0.22). The risk of impairment on at least one test of neuropsychological function was reduced in those who received nitrous oxide (OR=0.56, CI=0.36–0.89, p=0.013).

Conclusion—In our patient population, use of nitrous oxide was associated with an increased risk for the development of delayed ischemic neurologic deficits; however, there was no evidence of detriment to long-term gross neurologic or neuropsychological outcome.

Introduction

From February 2000 to April 2003, investigators from 31 medical centers around the world prospectively collected data on 1001 patients having cerebral aneurysm surgery within 14 days after aneurysmal subarachnoid hemorrhage.[1] The primary focus of the research, *i.e.*, the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST), was to determine whether induced mild systemic hypothermia (33°C) would protect patients from perioperative brain injury. Although the principle outcome of the IHAST trial was negative (*i.e.*, induced hypothermia had no effect on neurologic or neuropsychological function 3 months after surgery), the IHAST database was designed to collect information on many other factors of potential importance to the care and outcome of cerebral aneurysm surgery patients. Consistent with this plan, recent publications from our research group have reported on the associations of intraoperative blood glucose concentrations and nitrous oxide use (or non-use) with long-term patient outcomes. [2,3]

The latter of these reports attempted to resolve controversies regarding the effect of nitrous oxide on outcome following cerebral ischemia. Despite contradictory results from animal models –*i.e.*, some studies report benefit[4,5] while others report detriment[6–10]—we found no consistent effect of nitrous oxide on outcome when the data from all IHAST patients were examined in aggregate.[2] Specifically, using multivariate regression analysis to examine the outcome of 373 patients who received nitrous oxide (at the discretion of the attending anesthesiologist) versus 627 patients who did not, there were no differences in long-term gross neurological and neuropsychological outcome. Groups differed only in the finding that, despite a greater fraction of patient in the nitrous oxide group having an intensive care unit stay of greater than 5 days, a greater fraction of nitrous oxide patients were discharged to home versus other long-term care facilities. Based on these results, we concluded that "there is no scientific evidence for categorically avoiding nitrous oxide in the patient at risk for ischemic brain injury."

Prior to our study of nitrous oxide use in the 1001 IHAST patients, some had warned that nitrous oxide should not be used in patients suffering from, or at high risk for, ischemic brain injury. [11–13] Even though there are no data in humans trials to support such a view (either before or after our IHAST subgroup analysis), we elected to once again probe the IHAST database to determine if there were subsets of patients at very high risk for intraoperative ischemic brain injury in whom we might identify a nitrous oxide effect. In our earlier manuscript in which we evaluated blood glucose concentrations and outcome,[3] we theorized that cerebral aneurysm surgery patients should have had three periods of high risk for ischemic

brain injury: 1) immediately after aneurysm rupture, 2) at the time of surgical clipping of the aneurysm, and 3) as the result of any cerebral vasospasm. Inasmuch as the IHAST patient population included only those who remained functionally normal or near normal immediately after aneurysm rupture (*i.e.*, period 1), and patients did not receive nitrous oxide until this phase had passed, we would expect that the second two periods would be more likely responsive to a nitrous oxide effect, should one exist. Furthermore, at period 2, a subset of patients had intentional intraoperative occlusion of the cerebral artery feeding the aneurysm (*i.e.*, to facilitate surgical clipping). Patients undergoing temporary vessel occlusion (*i.e.*, "temporary clipping") would be expected to have an increased risk for intraoperative ischemic injury compared to those in whom there was no temporary vessel occlusion. By focusing only on the patients with intraoperative arterial occlusion, we hypothesized that it would be possible to identify an effect of nitrous oxide that was not apparent in the overall IHAST patient population. In other words, if nitrous oxide had a direct effect on ischemic neurons, or it had an indirect effect on the brain as a result of increasing the rate of vasospasm (*e.g.*, as a result of nitrous oxide's effect on serum homocysteine concentrations),[14] we might be able to identify that effect in this subset of highest risk patients.

Based on these considerations, the present research examined the association of nitrous oxide use and delayed ischemic neurologic deficits (DIND; *i.e.*, the clinical manifestation of vasospasm), hospital course, disposition upon hospital discharge, and neurologic and neuropsychological function 3 months after surgery in the 441 IHAST patients who had temporary occlusion of a proximal artery during cerebral aneurysm surgery.

Materials and Methods

Our study was based exclusively on a *post hoc* analysis of the IHAST database. IHAST was a large (1001 patient), international, multi-center, randomized and partially-blinded, prospective, clinical trial. Details regarding trial design are described elsewhere.[1] In brief, non-pregnant adults with a preoperative World Federation of Neurological Surgeons Score of I, II, or III, who had aneurysmal subarachnoid hemorrhage no more than 14 days prior to surgery, were eligible for enrollment. Specific exclusion criteria included a body mass index of $\geq 35 kg/m^2$, any cold-related disorder (*e.g.*, Raynaud's disease), and tracheal intubation at the time of enrollment. Extensive information regarding the patients' pre-subarachnoid hemorrhage health status and events occurring between the time of hospital admission and surgery were collected. The study was approved by each center's local Human Studies Committee and informed consent was obtained from each patient or their legal representative. All study personnel, except the anesthesiologist involved in each patient's intraoperative care, were blinded to treatment assignment.

Anesthesia was limited to either intravenous thiopental or etomidate for induction of anesthesia, and inhaled isoflurane or desflurane for maintenance, supplemented by either intravenous fentanyl or remifentanil. Inhaled nitrous oxide use was at the discretion of the anesthesiologists, and no limitations were imposed by the study protocol on the concentration of nitrous oxide administered.

Following the induction of anesthesia, an esophageal temperature probe was inserted, and the patient was positioned for surgery. In patients randomized to hypothermia, esophageal temperature was reduced as quickly as possible, with the goal of achieving a temperature between 32.5°C and 33.5° by the time a clip was applied to the first aneurysm. Temperature in patients randomized to normothermia was kept between 36°C and 37°C. Rewarming of hypothermic patients began after the last aneurysm had been secured, and was continued until normothermia was achieved. Utilization of proximal temporary artery occlusion to facilitate clipping of the aneurysm, or administration of a supplemental cerebral metabolism suppressant

anesthetic (etomidate or thiopental) intraoperatively, was at the discretion of the individual surgeons and anesthesiologists.

No attempt was made to control post-operative care, but all adverse events, procedures, and other aspects of treatment were monitored for either 14 days, or until hospital discharge (if this occurred before 14 days). Of particular note, a clinical diagnosis of DIND was made if there was: a) a decrease in the Glasgow Coma Score with alteration in level of consciousness, or b) the development of a new or worsening focal neurological deficit after the exclusion of other causes (*e.g.*, drug effect, hydrocephalus, aneurysmal rebleeding, intracranial hematoma, cerebral edema, or metabolic disturbances such as hypoxia, hyponatremia, or aberrant glucose homeostasis).

A final follow-up examination was conducted approximately 3 months after surgery. Outcome measures included: a) the modified Glasgow Outcome Score (GOS; this was the primary outcome measure for the trial),[15] b) Rankin Disability Score,[16] c) Barthel's Activities of Daily Living Index, [17] d) National Institutes of Health Stroke Scale (NIHSS),[18] e) site to which the patient was discharged from the hospital where surgery was performed (*e.g.*, to home, an acute care hospital, or a chronic care/rehabilitation facility), and f) a 5-test neuropsychological battery that included the Benton Visual Retention Test,[19] Controlled Oral Word Association, [20] Rey-Osterrieth Complex Figure Test,[21] Grooved Pegboard, and Trail Making Tests.[22] Details regarding neuropsychological testing and scoring can be found elsewhere.[23] T-scores for individual tests (after adjustment for age and education) were averaged to obtain a single composite score if at least three neuropsychological tests were completed; a composite score of 30 or less (two standard deviations below the population norm of 50) was considered evidence of neuropsychological impairment. We also determined the number of subjects who were impaired (T-score <30) on at least one test in the battery, regardless of the composite score.

For living patients who were unable to complete the neuropsychological tests due to their overall gross neurologic status, imputed impairment was determined in a manner described elsewhere for the entire IHAST population. [23] Briefly, a computerized imputation process was developed which determined the likelihood of neuropsychological impairment based on scores obtained from four tests of gross neurologic function (*i.e.*, GOS, Rankin Score, NIHSS Score, and Barthel's Index of Daily Living) derived from data obtained from 873 patient in the original IHAST trial who were able to complete neuropsychological testing.[1] The imputation process was based on relationships between performance on tests of gross function and neuropsychological function in other patients enrolled in the IHAST trial. This process was only used to impute the likelihood of impairment on the composite score in living patients if the composite score was not directly computed using the patient's actual scores. The category of "impairment of 1 or more neuropsychological tests" was imputed only if no neuropsychological test was completed and there was imputed impairment of the composite score. All evaluations were performed by trained examiners who were certified by the University of Iowa Steering Committee.

All data analysis was conducted by the Data Management Center at the University of Iowa using SAS version 9.1.3 (SAS Institute, Inc., Cary, NC). Univariate comparisons of various measures in patients who did or did not receive nitrous oxide were performed using Student's t-test, Pearson's Chi-square Test, or Fisher's Exact Test depending on the characteristics and distribution of the data. It was not possible to structure the analysis according to nitrous oxide dose as nitrous oxide use was reported in the IHAST database as either *used* or *not used*.

All neurological and neuropsychological outcomes were analyzed using both univariate and multivariate logistic regression. For binary outcomes, standard logistic regression analyses

were performed and, for ordered categorical outcomes with more than 2 categories, cumulative logistic (proportional odds) models were used. Since the use of nitrous oxide was not based on random assignment, multivariate analyses were performed to assess the effect of nitrous oxide on outcomes after adjusting for a standard set of covariates, determined by IHAST Coordinating Center to be important covariates to include in all post-hoc analyses of neurological and neuropsychological outcomes of the IHAST trial. The covariates for the multivariable analysis include: race (white vs. nonwhite), age, gender, baseline World Federations of Neurological Surgeons Score, baseline NIHSS score, Fisher grade, history of hypertension, time from subarachnoid hemorrhage to surgery, largest aneurysm size (1–11, 12–24, ≥25 mm in greatest dimension), aneurysm location (posterior *vs.* anterior), and IHAST treatment assignment (normothermic *vs.* hypothermic). For analysis purposes, length of stay in the intensive care unit, total duration of hospitalization, and destination upon discharge from the treating institution were stratified as binary responses (<5d *vs.* ≥ 5d, <15d *vs.* ≥15 d, and home *vs.* other facility or death, respectively). GOS was treated as an ordered categorical variable using all possible responses (1=minor or no disability, 2=moderate disability, 3=severe disability, 4=vegetative state, 5=death) and also using a binary response (1 *vs.* others). DIND was treated as a binary response (yes vs. no), NIHSS was analyzed using 5 ordered categories (0=no deficit, 1–7=mild deficit, 8–14=moderate deficit, 15–42=severe deficit, death), Rankin score was treated as a binary variable (0–1= minimal or no deficit, >1=significant deficit), and Barthel's Activities of Daily Living Index scores was treated as a binary variable (95–100=minimal to no impairment, <95=impairment).[1] Specific details related to the scoring of neuropsychological tests can be found elsewhere.[23] Briefly, the results of each test were compared to normative data (adjusted for age, gender, and years of education) with a binary outcome (presence or absence of impairment) determined for each test. For the present report, two binary neuropsychological outcomes are included: impairment for the composite score and impairment on any individual test.

Since the IHAST study was a randomized trial evaluating whether intraoperative hypothermia would improve neurologic outcomes, initial analyses were performed to evaluate whether the effect of the randomized treatment (normothermic vs hypothermic) differed for patients that received nitrous oxide versus not. These analyses were performed using models that included nitrous oxide use (no *vs.* yes), IHAST treatment assignment (normothermic *vs.* hypothermic), and the nitrous oxide-by-treatment assignment interaction effect. After confirming that there were no significant interaction effects, subsequent logistic regression models that included nitrous oxide use as the only explanatory variable were used to assess the univariate association of nitrous oxide use on outcomes. Since the explanatory variable of interest for this investigation was nitrous oxide use, the findings from the multiple logistic regression models are summarized by presenting the odds ratio and corresponding 95% confidence interval for nitrous oxide use. For all logistic regression analyses, the models are parameterized so that an odds ratio significantly greater than 1.0 would indicate an increased likelihood of a worse outcome in patients receiving nitrous oxide. In all cases, two-sided tests were performed with p-values ≤ 0.05 used to denote statistical significance.

Results

Details regarding the primary IHAST trial results can be found elsewhere.[1,23] Briefly, induced hypothermia had no effect on any gross neurological or neuropsychological variable studied.

In the subset of 441 IHAST patients who underwent intraoperative cerebral artery occlusion to facilitate aneurysm clipping, demographics and data pertaining to preoperative neurologic status, stratified based on intra-operative nitrous oxide use, can be found in table 1. Groups did not differ with regard to sex, pre-operative medical history, and time from initial subarachnoid hemorrhage to induction of anesthesia. There were statistically significant, but probably

clinically inconsequential, differences between groups with respect to age (50±11y *vs.* 52±12y for nitrous oxide and no nitrous oxide groups, respectively; p=0.041) and fraction of patients who were white, not of Hispanic origin (76% *vs.* 85% for nitrous oxide and no nitrous oxide groups, respectively; p=0.019). Preoperative World Federation of Neurological Surgeons Score data were equivalent. There was a significant difference between groups with respect to both initial National Institutes of Health Stroke Scale (p=0.035) and Fisher Grade (p=0.01).

Aneurysm characteristics and intra-operative data were largely equivalent between the two groups and are summarized in table 2. There was no difference in the fraction of patients in each group that received either isoflurane or desflurane during maintenance of general anesthesia. It should be noted that the fraction of patients that received isoflurane and desflurane in each group is greater than the total number of patients in that group reflecting that in a few patients, the volatile agent was changed during the course of the same general anesthetic.

Patients in the nitrous oxide group had a significantly greater mean arterial blood pressure (83 ±14mmHg *vs.* 77±14mmHg for no nitrous oxide; p<0.001) and blood glucose (141±35mg/dl *vs.* 126±35mg/dl for no nitrous oxide; p<0.001) at the time of first permanent clip placement as well as a greater time interval between induction of anesthesia and placement of the first permanent clip (240±80min *vs.* 211±75min for no nitrous oxide; p<0.001) and the time between placement of the last permanent clip and arrival in the recovery area (116±32min *vs.* 94±34min for no nitrous oxide; p<0.001) A greater fraction of patients in the nitrous oxide group also received a supplemental metabolic depressant (*i.e.*, protective) anesthetic agent prior to vessel occlusion and aneurysm clipping (46% *vs.* 35% for no nitrous oxide; p=0.024). Although there was no difference in the fraction of patients that had a temporary clip placed for > 20 min duration, the mean duration of iatrogenic temporary arterial occlusion was greater in the nitrous oxide group (11.9±13.1min *vs.* 9.3±7.7min for no nitrous oxide; p=0.012). Statistically significant but probably clinically inconsequential differences existed between groups in core temperature both upon arrival in the operating suite and 2h following surgery, but not at the time of first permanent clip placement. Although a lower fraction of nitrous oxide-treated patients had an aneurysm that was judged difficult or very difficult to expose (39% *vs.* 51% for no nitrous oxide; p=0.008), there was no difference between groups in the fraction of patients judged to have moderate or severe brain swelling upon dural opening. Other intraoperative factors were equivalent.

Postoperative data are summarized in table 3. Following both univariate and multivariate analysis (which corrected for factors thought to influence outcome), a significantly greater fraction of patients in the nitrous oxide group had an intensive care unit length of stay of ≥ 5d compared to the group that did not receive nitrous oxide (69% and 46% for nitrous oxide and no nitrous oxide groups, respectively; univariate and multivariate p<0.001 for both). There was no difference between groups in the fraction of patients with an overall hospital length of stay of ≥15 d (59% *vs.* 55% for nitrous oxide and no nitrous oxide groups, respectively; p=0.424 and p=0.209 for univariate and multivariate analysis, respectively). Further, a greater fraction of patients in the group that did not receive nitrous oxide were not discharged to home (48% *vs.* 33% for the nitrous oxide group; p=0.001 and p=0.006 for univariate and multivariate analysis, respectively).

Both early (*i.e.*, DIND) and late (*i.e.*, 3-month postoperative assessments of neurologic and neuropsychological) outcome results are summarized in table 4. In those who received nitrous oxide, there was a greater fraction who displayed postoperative neurologic changes consistent with DIND (28% *vs.* 21% in the no nitrous oxide group) based on multivariate (adjusted OR=1.78, CI=1.08–2.95, p=0.025), but not univariate (p=0.108) analysis.

There was no significant association between nitrous oxide use and outcome at 3 mo following subarachnoid hemorrhage as measured by GOS stratified as a binary variable (univariate p=0.059; adjusted OR=0.70, CI=0.45–1.10, multivariate p=0.123). When stratified as an ordered categorical variable, use of nitrous oxide was associated with improved GOS score on univariate (unadjusted OR=0.67, CI=0.46–0.99, p=0.043), but not multivariate logistic regression analysis (adjusted OR=0.67, CI=0.44–1.03, p=0.065). There was no association between nitrous oxide use and outcome based on the Rankin Disability Score (univariate p=0.078; adjusted OR=0.74, CI=0.47–1.16, multivariate p=0.192), NIHSS (univariate p=0.741; adjusted OR=1.02, CI=0.66–1.56, multivariate p=0.937), or Barthel's Index of Daily Living (univariate p=0.076; adjusted OR=0.69, CI=0.38–1.25, multivariate p=0.220).

Regarding the evaluation of neuropsychological outcome 3 months following subarachnoid hemorrhage, impairment of the composite score was imputed for 10 (5.0%) and 11 (4.5%) patients in the nitrous oxide and no nitrous oxide groups, respectively (p=0.81). Impairment in > 1 neuropsychological test was imputed for 8 (4.0%) and 8 (3.3%) of patients in the nitrous oxide and no nitrous oxide groups, respectively (p=0.69). There was no difference in the fraction of patients who exhibited impairment of the neuropsychological composite score (20% for nitrous oxide group and 20% in the group that did not receive nitrous oxide; univariate p=0.918; adjusted OR=0.81, CI=0.44–1.49, multivariate p=0.493). However, a lesser fraction of patient in the group that received nitrous oxide (54%) exhibited impairment on at least one test of neuropsychological function compared to the group that did not receive nitrous oxide (67%) (univariate p=0.008; adjusted OR=0.56, CI=0.36-0.89, multivariate p=0.013).

Discussion

In this *post hoc* investigation of 441 patients having cerebral aneurysm surgery, in whom temporary occlusion of a cerebral artery was employed, intraoperative use of nitrous oxide had no detrimental effect on either neurological status, functional status, or neuropsychological function 3 months following surgery. Nitrous oxide use was associated with both an increased odds for the development of DIND and fewer patients being discharged from the intensive care unit within 5 days. However, despite no difference between groups in the fraction of patients requiring an overall hospital stay of ≥ 15 days, a greater fraction of those who received nitrous oxide were discharged from their treating hospital to home versus other acute care hospitals or chronic / rehabilitative facilities.

Some prior investigations have reported that nitrous oxide adversely effects the brain because of its effect on cerebral metabolism or intracranial pressure.[24–28] Other investigations employing animal models have reported that nitrous oxide can augment injury in the ischemic brain.[6,7,29] Nevertheless, these effects have not been validated in humans. Additional research employing animal models of ischemia have reported that exposure to nitrous oxide, a known N-methyl-D-aspartate receptor antagonist,[30,31] can reduce infarct size probably by limiting injury due to glutamate excitotoxicity.[5,30]

A prior investigation by our group that studied all 1001 patients in the IHAST database determined that the use of nitrous oxide during cerebral aneurysm clipping had no effect on the development of DIND (a manifestation of cerebral vasospasm) or both long term (*i.e.*, 3 months post-surgery) gross neurological and neuropsychological function.[2] However, a limitation of our prior investigation was that many of the 1001 patients may not have experienced a meaningful (*i.e.*, outcome-determining) cerebral ischemic insult at the same time that nitrous oxide was being administered. For example, not all patients who suffer a subarachnoid hemorrhage and undergo surgical clipping have alterations of cerebral hemodynamics sufficient to produce clinically important focal or global cerebral ischemic insults.[1,32] Further, intraoperative nitrous oxide should have little or no impact on ischemic

episodes that occurred prior to surgery (*i.e.*, at the time of initial hemorrhage) due to the temporal relationship. In our current investigation, we analyzed data exclusively from patients in whom temporary occlusion of a major cerebral artery was employed to facilitate placement of a permanent clip on the aneurysm. In this subgroup analysis, ischemic events to the brain were not only more likely than in the 1001 IHAST patients as a whole, but more importantly, any intraoperative ischemic events would have occurred *during* exposure to nitrous oxide in many patients.

Use of temporary proximal vascular occlusion to facilitate placement of a permanent aneursym clip is a relatively common practice. In the IHAST investigation, 44% of 1001 patients had intraoperative proximal vascular occlusion.[1] This technique has been reported to reduce the risk of aneurysm rupture and helps facilitate surgical dissection, potentially improving the rate of successful placement of a permanent clip.[33] However, utilization of temporary proximal vessel occlusion has adverse consequences as well. In patients having aneurysm clipping with somatosensory evoked potential monitoring, Mizoi discovered a loss of signals in 43% of patients at the time of temporary proximal vessel occlusion.[34] In a similar investigation, Schick *et al* reported that in patients in whom proximal vessel occlusion was utilized, complete loss of somatosensory evoked potential signals occurred in 38%.[35] Further, given the time course of signal loss, the authors concluded that there was no safe permissible time for temporary arterial occlusion, a finding supported by other investigations.[36,37] Additional studies have reported that a longer duration of temporary occlusion is associated with an increased risk of infarction.[38,39] Given that all patients included in our analysis underwent selective arterial occlusion, important intraoperative ischemic events were likely in a large fraction of these 411 patients. Of note, there was no difference between groups in the fraction of patients that underwent occlusion of specific vessels (untabulated data).

Our investigation evaluated one metric of short-term neurological function: DIND, the clinical manifestation of cerebral vasospasm. There are mechanistic reasons to expect that nitrous oxide could influence this event. In *in vivo* studies, methylation of homocysteine, a reaction catalyzed by the enzyme methionine synthase, results in the production of methionine. Nitrous oxide is a known inhibitor of methionine synthase and exposure to nitrous oxide has been reported to acutely increase serum homocysteine concentrations.[14] Among its many effects, homocysteine is known to increase platelet production of thromboxane A_2, a potent vasoconstrictor.[40] In our prior investigation which included data from all 1001 IHAST subjects, nitrous oxide use was *not* associated with the development of DIND (OR=1.29, C.I.=0.91–1.83; P=0.157).[2] However, when only patients in whom temporary arterial occlusion was utilized were included in the analysis, use of nitrous oxide increased the odds of developing DIND post-operatively (OR=1.78; CI=1.08–2.95; P=0.025). It is currently unknown if use of temporary vessel occlusion served as an independent risk factor to increase the risk for developing DIND. This issue is currently being evaluated by another *post hoc* probe of the IHAST database.

Multiple possible explanations may account for increased DIND in nitrous oxidetreated patients. First, it is possible that the use of a temporary arterial clip resulted in irritation of the vascular smooth muscle, and, upon exposure to elevated serum homocysteine concentrations, increased the risk for vasospasm. Another possible explanation is that nitrous oxide augmented the ischemic insult to neurons and glia during temporary arterial occlusion and this, in turn, accounted for the increased number of patients experiencing short-term neurologic deficits. This finding may, in part, account for the greater fraction of patients in the nitrous oxide group who were discharged from the intensive care unit in ≥ 5 days.

The development of vasospasm following subarachnoid hemorrhage, independent of nitrous oxide use, is reported to reduce the chance of a good recovery by a factor of 3.[41] However, the increased rate of DIND in the nitrous oxide group in our research did not influence overall

hospital length of stay, discharge destination, or any metric of longterm gross neurologic or neuropsychological function. It is possible that, although nitrous oxide increased the incidence of symptomatic DIND, the severity of DIND associated with nitrous oxide use was not sufficient to modulate long-term outcome.

The long term outcomes in this "higher risk" group of 441 patients is generally consistent with our prior analysis of all 1001 IHAST patients;[2] specifically, use of nitrous oxide intraoperatively had no detrimental effect on long term gross neurologic or neuropsychological function. Our analysis showed a significantly reduced risk of a poor outcome at 3 mo based on the categorized GOS following univariate analysis, however, that effect was found to be insignificant after multivariate logistic regression analysis. Given that nitrous oxide use was not the randomized variable in this investigation, based on our data, we conclude that use of nitrous oxide had no significant effect on GOS 3 mo after surgery. However, unlike our earlier analysis, this current investigation, which included only patients who had temporary occlusion of a major cerebral artery, revealed a significantly reduced risk of impairment on one or more neuropsychological tests at three months in those who received nitrous oxide intraoperatively. We use caution when interpreting this finding. This apparent "protective" effect by nitrous oxide may be due to many factors. For example, the baseline neuropsychological function of patients included in this analysis is unknown. It is possible that there were differences in baseline cognitive function between groups. Also, differences in various intra-operative factors, such as a greater use of neuroprotective agents intra-operatively, a 6mmHg greater mean arterial blood pressure at the time of clip placement, and less difficulty with aneurysm exposure in those who received nitrous oxide may have confounded our results (see table 2). Variations in postoperative care, factors not recorded as part of the IHAST trial, also may have affected our results. Finally, this positive finding in favor of nitrous oxide use could have been the result of a type I statistical error.

There are several limitations of our study that deserve comment. First, because use of nitrous oxide was not a randomized variable, statistical correction with factors thought to influence outcome was necessary. In order to minimize bias, in the multivariate logistic regression analysis, we corrected for the standard set of variables, determined by the IHAST coordinating center, that are being applied to all *post hoc* investigations using the IHAST database. This standard set of covariates was chosen either because, using the data from the parent investigation, an individual item was a prerandomization variable found to be univariately associated with outcome or because the extensive subarachnoid hemorrhage literature suggests its link with outcome.

Another shortcoming of this current investigation is the potential for type 1 statistical error. For every comparison performed using the same data, the chance of a false positive result increases with each comparison. Given that this manuscript describes a post hoc analysis of a dataset, one must consider that our significant findings in this investigation may describe false positives. However, given the few positive comparisons reported in our analysis, the risk for a family-wise error remains small.

There also is the potential for type II statistical error given that effective sample sizes were not determined as part of the study design. The sample size for the original IHAST analysis (target N=1000, with approximately 500 per treatment group) was selected to permit detection of a 10 percentage point difference (*e.g.*, 60% *vs.* 70%) in GOS between groups with statistical power of 91% using a two-sided, alpha=0.05 level test.1 For the present study, the effective sample-size (N=441; 199 with nitrous oxide, 242 without nitrous oxide) provides statistical power of 82% to detect a 13 percentage point difference (*e.g.*, 60% *vs.* 73%) between groups, but only provides statistical power of 60% to detect a 10-percentage point difference between groups. However, given the numerous instances in which the data tended to show an

improvement – not harm – associated with nitrous oxide use, it seems reasonable to conclude that at least no profound harmful long-term effect was inflicted on patients with the use of nitrous oxide in conjunction with temporary arterial occlusion during aneurysm surgery.

Finally, another limitation of this investigation was the lack of measurement of cerebral blood flow or monitoring for evidence of cerebral ischemia during cerebral arterial occlusion. Use of such monitoring modalities was not required by the original IHAST investigation and, if performed, these data were not recorded in the IHAST database. Without these data, it is unknown if differences existed between groups with respect to both the number of patients who experienced ischemic episodes and the extent of ischemia. We attempted to estimate the severity of any ischemic insults by assessing other variables within the IHAST database (*e.g.*, duration of temporary occlusion, mean arterial blood pressure, and use of neuroprotective agents).

In summary, use of nitrous oxide in a group of patients at high risk for cerebral ischemia had no detrimental effect on long-term gross neurological or neuropsychological function. Nitrous oxide use was associated with an increased risk of developing DIND, but this did not correlate with long-term outcome. Given the findings of this investigation, we confirm our previous impression from the study of nitrous oxide in the entire IHAST population: There is no evidence to support the unconditional avoidance of nitrous oxide in patients at risk for cerebral ischemia.

Acknowledgements

The authors would like to acknowledge both Ming Yang, B.S. (Graduate Research Assistant, Department of Biostatistics, University of Iowa School of Public Health, Iowa City, Iowa) and Emine Baym, B.S. (Graduate Research Assistant, Department of Biostatistics, University of Iowa School of Public Health, Iowa City, Iowa) for their assistance with data compilation and statistical calculations. We would also like to acknowledge Julie Weeks, M.P.T (Program Associate, Department of Anesthesiology, University of Iowa Carver College of Medicine, Iowa City, Iowa) for her help facilitating data organization.

The Intraoperative Hypothermia for Aneurysm Surgery Trial, on which this investigation is based, was supported by a grant from the National Institute of Neurological Disease and Stroke (RO1 NS38554) in Bethesda, Maryland.

References

1. Todd MM, Hindman BJ, Clarke WR, Torner JC. Mild intraoperative hypothermia during surgery for intracranial aneurysm. N Engl J Med 2005;352:135–145. [PubMed: 15647576]
2. McGregor DG, Lanier WL, Pasternak JJ, Rusy DA, Hogan K, Samra S, Hindman B, Todd MM, Schroeder DR, Bayman EO, Clarke W, Torner J, Weeks J. Effect of nitrous oxide on neurologic and neuropsychological function after intracranial aneurysm surgery. Anesthesiology 2008;108:568–579. [PubMed: 18362587]
3. Pasternak JJ, McGregor DG, Schroeder DR, Lanier WL, Shi Q, Hindman BJ, Clarke WR, Torner JC, Weeks JB, Todd MM. Hyperglycemia in patients undergoing cerebral aneurysm surgery: its association with long-term gross neurologic and neuropsychological function. Mayo Clin Proc 2008;83:406–419. [PubMed: 18380986]
4. Abraini JH, David HN, Nicole O, MacKenzie ET, Buisson A, Lemaire M. Neuroprotection by nitrous oxide and xenon and its relation to minimum alveolar concentration. Anesthesiology 2004;101:260–261. [PubMed: 15220810]
5. David HN, Leveille F, Chazalviel L, MacKenzie ET, Buisson A, Lemaire M, Abraini JH. Reduction of ischemic brain damage by nitrous oxide and xenon. J Cereb Blood Flow Metab 2003;23:1168–1173. [PubMed: 14526227]
6. Baughman VL, Hoffman WE, Miletich DJ, Albrecht RF, Thomas C. Neurologic outcome in rats following incomplete cerebral ischemia during halothane, isoflurane, or N2O. Anesthesiology 1988;69:192–198. [PubMed: 3407968]

7. Baughman VL, Hoffman WE, Thomas C, Albrecht RF, Miletich DJ. The interaction of nitrous oxide and isoflurane with incomplete cerebral ischemia in the rat. Anesthesiology 1989;70:767–774. [PubMed: 2719309]
8. Matta BF, Lam AM. Nitrous oxide increases cerebral blood flow velocity during pharmacologically induced EEG silence in humans. J Neurosurg Anesthesiol 1995;7:89–93. [PubMed: 7772973]
9. Pelligrino DA, Miletich DJ, Hoffman WE, Albrecht RF. Nitrous oxide markedly increases cerebral cortical metabolic rate and blood flow in the goat. Anesthesiology 1984;60:405–412. [PubMed: 6424512]
10. Sakabe T, Kuramoto T, Inoue S, Takeshita H. Cerebral effects of nitrous oxide in the dog. Anesthesiology 1978;48:195–200. [PubMed: 626426]
11. Baughman VL. N2O: of questionable value. J Neurosurg Anesthesiol 1995;7:79–81. [PubMed: 7772971]
12. Reinstrup P, Messeter K. Cerebrovascular response to nitrous oxide. Acta Anaesthesiol Scand 1994;38:761–762. [PubMed: 7887091]
13. Cottrell, J. Brain protection in neurosurgery: the good, the bad and the maybe; 54th Annual Refresher Course Lectures and Basic Science Reviews, Lecture 113; Park Ridge, IL: American Society of Anesthesiologists; 2003. p. 1-7.
14. Badner NH, Drader K, Freeman D, Spence JD. The use of intraoperative nitrous oxide leads to postoperative increases in plasma homocysteine. Anesth Analg 1998;87:711–713. [PubMed: 9728858]
15. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975;1:480–484. [PubMed: 46957]
16. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med J 1957;2:200–215.
17. Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. Md State Med J 1965;14:61–65. [PubMed: 14258950]
18. Wityk RJ, Pessin MS, Kaplan RF, Caplan LR. Serial assessment of acute stroke using the NIH Stroke Scale. Stroke 1994;25:362–365. [PubMed: 8303746]
19. Sivan, A. The Benton Visual Retention Test. Vol. 5th Edition. San Antonio, TX: The Psychological Corporation; 1992.
20. Benton, A.; Hamsher, K. The Multilingual Aphasia Examination. Iowa City, IA: AJA Associates; 1994.
21. Lezak, M. Neuropsychological Assessment. Vol. 3rd Edition. New York, NY: Oxford University Press; 1995. p. 475-480.
22. Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education. Arch Clin Neuropsychol 2004;19:203–214. [PubMed: 15010086]
23. Anderson SW, Todd MM, Hindman BJ, Clarke WR, Torner JC, Tranel D, Yoo B, Weeks J, Manzel KW, Samra S. Effects of intraoperative hypothermia on neuropsychological outcomes after intracranial aneurysm surgery. Ann Neurol 2006;60:518–527. [PubMed: 17120252]
24. Carlsson C, Hagerdal M, Siesjo BK. The effect of nitrous oxide on oxygen consumption and blood flow in the cerebral cortex of the rat. Acta Anaesthesiol Scand 1976;20:91–95. [PubMed: 1266561]
25. Laitinen LV, Johansson GG, Tarkkanen L. The effect of nitrous oxide on pulsatile cerebral impedance and cerebral blood flow. Br J Anaesth 1967;39:781–785. [PubMed: 4864239]
26. Moss E, McDowall DG. I.C.P. increases with 50% nitrous oxide in oxygen in severe head injuries during controlled ventilation. Br J Anaesth 1979;51:757–761. [PubMed: 387054]
27. Sakabe T, Kuramoto T, Kumagae S, Takeshita H. Cerebral responses to the addition of nitrous oxide to halothane in man. Br J Anaesth 1976;48:957–962. [PubMed: 791308]
28. Theye RA, Michenfelder JD. The effect of nitrous oxide on canine cerebral metabolism. Anesthesiology 1968;29:1119–1124. [PubMed: 5726748]
29. Hoffman WE, Baughman VL, Albrecht RF. Interaction of catecholamines and nitrous oxide ventilation during incomplete brain ischemia in rats. Anesth Analg 1993;77:908–912. [PubMed: 8105726]

30. Jevtovic-Todorovic V, Todorovic SM, Mennerick S, Powell S, Dikranian K, Benshoff N, Zorumski CF, Olney JW. Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nature Medicine 1998;4:460–463.

31. Yamakura T, Harris RA. Effects of gaseous anesthetics nitrous oxide and xenon on ligand-gated ion channels. Comparison with isoflurane and ethanol. Anesthesiology 2000;93:1095–1101. [PubMed: 11020766]

32. Kassell NF, Torner JC, Haley EC, Jane JA, Adams HP, Kongable GL. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results. J Neurosurg 1990;73:18–36. [PubMed: 2191090]

33. Taylor CL, Selman WR. Temporary vascular occlusion during cerebral aneurysm surgery. Neurosurg Clin N Am 1998;9:673–679. [PubMed: 9738099]

34. Mizoi K, Yoshimoto T. Permissible temporary occlusion time in aneurysm surgery as evaluated by evoked potential monitoring. Neurosurgery 1993;33:434–440. [PubMed: 8413875]

35. Schick U, Dohnert J, Meyer JJ, Vitzthum HE. Effects of temporary clips on somatosensory evoked potentials in aneurysm surgery. Neurocrit Care 2005;2:141–149. [PubMed: 16159056]

36. Thome C, Vajkoczy P, Horn P, Bauhuf C, Hubner U, Schmiedek P. Continuous monitoring of regional cerebral blood flow during temporary arterial occlusion in aneurysm surgery. J Neurosurg 2001;95:402–411. [PubMed: 11565860]

37. Momma F, Wang AD, Symon L. Effects of temporary arterial occlusion on somatosensory evoked responses in aneurysm surgery. Surg Neurol 1987;27:343–352. [PubMed: 3824140]

38. Ogilvy CS, Carter BS, Kaplan S, Rich C, Crowell RM. Temporary vessel occlusion for aneurysm surgery: risk factors for stroke in patients protected by induced hypothermia and hypertension and intravenous mannitol administration. J Neurosurg 1996;84:785–791. [PubMed: 8622152]

39. Kett-White R, Hutchinson PJ, Al-Rawi PG, Czosnyka M, Gupta AK, Pickard JD, Kirkpatrick PJ. Cerebral oxygen and microdialysis monitoring during aneurysm surgery: effects of blood pressure, cerebrospinal fluid drainage, and temporary clipping on infarction. J Neurosurg 2002;96:1013–1019. [PubMed: 12066900]

40. Guthikonda S, Haynes WG. Homocysteine: role and implications in atherosclerosis. Curr Atheroscler Rep 2006;8:100–106. [PubMed: 16510043]

41. Dorsch NW. Cerebral arterial spasm--a clinical review. Br J Neurosurg 1995;9:403–412. [PubMed: 7546361]

Appendix

Appendix

The members of IHAST were as follows:

University of Iowa — Steering Committee: M. Todd, B. Hindman, W. Clarke, K. Chaloner, J. Torner, P. Davis, M. Howard, D. Tranel, S. Anderson; **Clinical Coordinating Center:** M. Todd, B. Hindman, J. Weeks, L. Moss, J. Winn; **Data Management Center:** W. Clarke, K. Chaloner, M. Wichman, R. Peters, M. Hansen, D. Anderson, J. Lang, B. Yoo; **Physician Safety Monitor:** H. Adams; **Project Advisory Committee** — G. Clifton (University of Texas, Houston), A. Gelb (University of California, San Francisco), C. Loftus (Temple University, Philadelphia), A. Schubert (Cleveland Clinic, Cleveland); **Physician Protocol Monitor** — D. Warner (Duke University, Durham, N.C.); **Data and Safety Monitoring Board** — W. Young, chair (University of California, San Francisco), R. Frankowski (University of Texas Health Science Center at Houston School of Public Health, Houston), K. Kieburtz (University of Rochester School of Medicine and Dentistry, Rochester, N.Y.), D. Prough, University of Texas Medical Branch, Galveston), L. Sternau (Mt. Sinai Medical Center, Miami); **NIH, National Institute of Neurological Disease and Stroke, Bethesda, Md.** — J. Marler, C. Moy, B. Radziszewska

Participating Centers (the number of randomized patients at each center is listed in parentheses) —

Addenbrooke's Hospital, Cambridge, United Kingdom (93): B. Matta, P. Kirkpatrick, D. Chatfield, C. Skilbeck, R. Kirollos, F. Rasulo, K. English, C. Duffy, K. Pedersen, N. Scurrah, R. Burnstein, A. Prabhu, C. Salmond, A. Blackwell, J. Birrell, S. Jackson

University of Virginia Health System, Charlottesville, Virginia, United States of America (86): N. Kassell, T. Pajewski, H. Fraley, A. Morris, T. Alden, M. Shaffrey, D. Bogdonoff, M. Durieux, Z. Zuo, K. Littlewood, E. Nemergut, R. Bedford, D. Stone, P. Balestrieri, J. Mason, G. Henry, P. Ting, J. Shafer, T. Blount, L. Kim, A. James, E. Farace, L. Clark, M. Irons, T. Sasaki, K. Webb

Auckland City Hospital, Auckland, New Zealand (69): T. Short, E. Mee, J. Ormrod, J. Jane, T. Alden, P. Heppner, S. Olson, D. Ellegala, C. Lind, J. Sheehan, M. Woodfield, A. Law, M. Harrison, P. Davies, D. Campbell, N. Robertson, R. Fry, D. Sage, S. Laurent, C. Bradfield, K. Pedersen, K. Smith, Y. Young, C. Chambers, B. Hodkinson, J. Biddulph, L. Jensen, J. Ogden, Z. Thayer, F. Lee, S. Crump, J. Quaedackers, A. Wray, V. Roelfsema

Sozialmedizinisches Zentrum Ost–Donauspital, Vienna, Switzerland (58): R. Greif, G. Kleinpeter, C. Lothaller, E. Knosp, W. Pfisterer, R. Schatzer, C. Salem, W. Kutalek, E. Tuerkkan, L. Koller, T. Weber, A. Buchmann, C. Merhaut, M. Graf, B. Rapf

Harborview Medical Center, Seattle, Washington, United States of America (58): A. Lam, D. Newell, P. Tanzi, L. Lee, K. Domino, M. Vavilala, J. Bramhall, M. Souter, G. Britz, H. Winn, H. Bybee

St. Vincent's Public Hospital, Melbourne, Australia (57): T. Costello, M. Murphy, K. Harris, C. Thien, D. Nye, T. Han, P. McNeill, B. O'Brien, J. Cormack, A. Wyss, R. Grauer, R. Popovic, S. Jones, R. Deam, G. Heard, R. Watson, L. Evered, F. Bardenhagen, C. Meade, J. Haartsen, J. Kruger, M. Wilson

University of Iowa Health Care, Iowa City, Iowa, United States of America (56): M. Maktabi, V. Traynelis, A. McAllister, P. Leonard, B. Hindman, J. Brian, F. Mensink, R. From, D. Papworth, P. Schmid, D. Dehring, M. Howard, P. Hitchon, J. VanGilder, J. Weeks, L. Moss, K. Manzel, S. Anderson, R. Tack, D. Taggard, P. Lennarson, M. Menhusen

University of Western Ontario, London, Ontario, Canada (53): A. Gelb, S. Lownie, R. Craen, T. Novick, G. Ferguson, N. Duggal, J. Findlay, W. Ng, D. Cowie, N. Badner, I. Herrick, H. Smith, G. Heard, R. Peterson, J. Howell, L. Lindsey, L. Carriere, M. von Lewinski, B. Schaefer, D. Bisnaire, P. Doyle-Pettypiece, M. McTaggart

Keck School of Medicine at University of Southern California, Los Angeles, California, United States of America (51): S. Giannotta, V. Zelman, E. Thomson, E. Babayan, C. McCleary, D. Fishback

University of Michigan Medical Center, Ann Arbor, Michigan, United States of America (41): S. Samra, B. Thompson, W. Chandler, J. Mcgillicuddy, K. Tremper, C. Turner, P. Smythe, E. Dy, S. Pai, V. Portman, J. Palmisano, D. Auer, M. Quigley, B. Giordani, A. Freymuth, P. Scott, R. Silbergleit, S. Hickenbottom

University of California San Francisco, San Francisco, California, United States of America (39): L. Litt, M. Lawton, L. Hannegan, D. Gupta, P. Bickler, B. Dodson, P. Talke, I. Rampil, B. Chen, P. Wright, J. Mitchell, S. Ryan, J. Walker, N. Quinnine, C. Applebury

Alfred Hospital, Melbourne, Australia (35): P. Myles, J. Rosenfeld, J. Hunt, S. Wallace, P. D'Urso, C. Thien, J. McMahon, S. Wadanamby, K. Siu, G. Malham, J. Laidlaw, S. Salerno, S. Alatakis, H. Madder, S. Cairo, A. Konstantatos, J. Smart, D. Lindholm, D. Bain, H. Machlin, J. Moloney, M. Buckland, A. Silvers, G. Downey, A. Molnar, M. Langley, D. McIlroy, D. Daly, P. Bennett, L. Forlano, R. Testa, W. Burnett, F. Johnson, M. Angliss, H. Fletcher

Toronto Western Hospital, University Health Network, Toronto, Canada (32): P. Manninen, M. Wallace, K. Lukitto, M. Tymianski, P. Porter, F. Gentili, H. El-Beheiry, M. Mosa, P. Mak, M. Balki, S. Shaikh, R. Sawyer, K. Quader, R. Chelliah, P. Berklayd, N. Merah, G. Ghazali, M. McAndrews, J. Ridgley, O. Odukoya, S. Yantha

Wake Forest University Baptist Medical Center, Winston-Salem, North Carolina, United States of America (31): J. Wilson, P. Petrozza, C. Miller, K. O'Brien, C. Tong, M. Olympio, J. Reynolds, D. Colonna, S. Glazier, S. Nobles, D. Hill, H. Hulbert, W. Jenkins

Mayo Clinic College of Medicine, Rochester, Minnesota, United States of America (28): W. Lanier, D. Piepgras, R. Wilson, F. Meyer, J. Atkinson, M. Link, M. Weglinski, K. Berge, D. McGregor, M. Trenerry, G. Smith, J. Walkes, M. Felmlee-Devine

West fälische Wilhelms-Universitat Muenster, Muenster, Germany (27): H. Van Aken, C. Greiner, H. Freise, H. Brors, K. Hahnenkamp, N. Monteiro de Oliveira, C. Schul, D. Moskopp, J. Woelfer, C. Hoenemann, H. Gramke, H. Bone, I. Gibmeier, S. Wirtz, H. Lohmann, J. Freyhoff, B. Bauer

University of Wisconsin Clinical Science Center, Madison, Wisconsin, United States of America (26): K. Hogan, R. Dempsey, D. Rusy, B. Badie, B. Iskandar, D. Resnick, P. Deshmukh, J. Fitzpatrick, F. Sasse, T. Broderick, K. Willmann, L. Connery, J. Kish, C. Weasler, N. Page, B. Hermann, J. Jones, D. Dulli, H. Stanko, M. Geraghty, R. Elbe

Montreal Neurological Hospital, Montreal, Canada (24): F. Salevsky, R. Leblanc, N. Lapointe, H. MacGregor, D. Sinclair, D. Sirhan, M. Maleki, M. Abou-Madi, D. Chartrand, M. Angle, D. Milovan, Y. Painchaud

Johns Hopkins Medical Institutions, Baltimore, Maryland, United States of America (23): M. Mirski, R. Tamargo, S. Rice, A. Olivi, D. Kim, D. Rigamonti, N. Naff, M. Hemstreet, L. Berkow, P. Chery, J. Ulatowski, L. Moore, T. Cunningham, N. McBee, T. Hartman, J. Heidler, A. Hillis, E. Tuffiash, C. Chase, A. Kane, D. Greene-Chandos, M. Torbey, W. Ziai, K. Lane, A. Bhardwaj, N. Subhas

Cleveland Clinic Foundation, Cleveland, Ohio, United States of America (20): A. Schubert, M. Mayberg, M. Beven, P. Rasmussen, H. Woo, S. Bhatia, Z. Ebrahim, M. Lotto, F. Vasarhelyi, J. Munis, K. Graves, J. Woletz, G. Chelune, S. Samples, J. Evans, D. Blair, A. Abou-Chebl, F. Shutway, D. Manke, C. Beven

New York Presbyterian Hospital–Weill Medical College of Cornell University, New York, New York, United States of America (15): P. Fogarty-Mack, P. Stieg, R. Eliazo, P. Li, H. Riina, C. Lien, L. Ravdin, J. Wang, Y. Kuo

Stanford University Medical Center, Palo Alto, California, United States of America (15): R. Jaffe, G. Steinberg, D. Luu, S. Chang, R. Giffard, H. Lemmens, R. Morgan, A. Mathur, M. Angst, A. Meyer, H. Yi, P. Karzmark, T. Bell-Stephens, M. Marcellus

Plymouth Hospitals National Health Service Trust, Plymouth, United Kingdom (14): J. Sneyd, L. Pobereskin, S. Salsbury, P. Whitfield, R. Sawyer, A. Dashfield, R. Struthers, P. Davies, A. Rushton, V. Petty, S. Harding, E. Richardson

University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, United States of America (11): H. Yonas, F. Gyulai, L. Kirby, A. Kassam, N. Bircher, L. Meng, J. Krugh, G. Seever, R. Hendrickson, J. Gebel

Austin Health, Melbourne, Australia (10): D. Cowie, G. Fabinyi, S. Poustie, G. Davis, A. Drnda, D. Chandrasekara, J. Sturm, T. Phan, A. Shelton, M. Clausen, S. Micallef; Methodist University Hospital, Memphis, Tennessee, United States of America (8): A. Sills, F. Steinman, P. Sutton, J. Sanders, D. Van Alstine, D. Leggett, E. Cunningham, W. Hamm, B. Frankel, J. Sorenson, L. Atkins, A. Redmond, S. Dalrymple

University of Alabama at Birmingham, Birmingham, Alabama, United States of America (7): S. Black, W. Fisher, C. Hall, D. Wilhite, T. Moore II, P. Blanton, Z. Sha

University of Texas Houston Health Science Center, Houston, Texas, United States of America (7): P. Szmuk, D. Kim, A. Ashtari, C. Hagberg, M. Matuszczak, A. Shahen, O. Moise, D. Novy, R. Govindaraj

University of Colorado Health Science Center, Denver, Colorado, United States of America (4): L. Jameson, R. Breeze, I. Awad, R. Mattison, T. Anderson, L. Salvia, M. Mosier

University of Oklahoma Health Science Center, Oklahoma City, Oklahoma, United States of America (3): C. Loftus, J. Smith, W. Lilley, B. White, M. Lenaerts.

Table 1

Baseline Characteristics

	Nitrous Oxide Use		
	Yes	**No**	**p-value**
N	199	242	
Demographics			
Age (y) (mean ± SD)	50 ± 11	52 ± 12	0.041[a]
Sex (% Female)	126 (63)	154 (64)	1[b]
Race (% white not of hispanic origin)	152 (76)	206 (85)	0.019[b]
Preoperative Medical History			
History of diabetes mellitus (% with diabetes mellitus)	7(4)	5 (2)	0.351[b]
History of hypertension (% with hypertension)	82 (41)	82 (34)	0.113[b]
History of smoking (% current smokers)	105 (53)	142 (59)	0.213[b]
Pre-operative Neurologic Status			
Pre-operative WFNS Score:			0.679[b]
GCS=15 and no motor deficit or aphasia	138 (69)	158 (65)	
GCS=13–14 and no motor deficit or aphasia	52 (26)	71 (29)	
GCS=13–14 with motor deficit or aphasia	9 (5)	13 (5)	
NIHSS Score at Baseline:			0.035[c]
NIHSS=0	117 (59)	120 (50)	
NIHSS=1–7	61 (31)	101 (42)	
NIHSS=8–14	8 (4)	5 (2)	
NIHSS=15–42	0 (0)	1 (0)	
NIHSS missing	13 (7)	15 (6)	
Pre-operative Fisher Grade:			0.01[b]
Fisher grade=1	15 (8)	12 (5)	
Fisher grade=2	59 (30)	77 (32)	
Fisher grade=3	105 (53)	111 (46)	
Fisher grade=4	20 (10)	42 (17)	
Interval between subarachnoid hemorrhage and induction of anesthesia (d)			0.063[a]
Mean ± SD	3.0 ± 3.0	3.5 ± 3.1	
Median (Range)	2 (0–14)	2 (0–14)	

Catagorical data expressed as n (% within group)

[a]Based on Student's t-test

[b]Based on Pearson chi-square test

[c]Based on Fisher exact test

GCS=Glasgow Coma Score

NIHSS=National Institutes of Health Stroke Scale

SD=Standard Deviation

WFNS=World Federation of Neurological Surgeons

Table 2

Aneurysm and Intraoperative Characteristics

	Nitrous Oxide Use		
	Yes	**No**	**p-value**
N	199	242	
Aneurysm Characteristics			
Largest aneurysm diameter (mm)	8.2 ± 5.5	9.0 ± 5.6	0.117[a]
Aneurysm location (number in anterior circulation of first aneurysm clipped)[d]	184 (92)	229 (95)	0.354[b]
Number of aneurysms treated (number with 1 aneurysm treated)	175 (88)	218 (90)	0.471[b]
Intraoperative Factors			
Isoflurane used[e]	164 (82)	193 (80)	0.480[b]
Desflurane used[e]	47 (24)	59 (24)	0.862[b]
Mean Arterial Pressure at first permanent clip placement (mmHg)	83 ± 14	77 ± 14	<0.001[a]
Blood Glucose at first permanent clip placement (mg/dl)	141 ± 35	126 ± 35	<0.001[a]
Time from induction of anesthesia to placement of first clip (min)	240 ± 80	211 ± 75	<0.001[a]
Time from placement of last clip to arrival in recovery area (min)	116 ± 32	94 ± 34	<0.001[a]
Protective Drugs Used for clipping	91 (46)	85 (35)	0.024[b]
Etomidate used	12 (6)	7 (3)	0.106[b]
Thiopental used	79 (40)	78 (32)	0.103[b]
Temporary Clip Applied for ≥ 20 min	30 (15)	28 (12)	0.279[b]
Total duration of temporary clipping (min)	11.9 ± 13.1	9.3 ± 7.7	0.012[a]
Temperature (°C):			
On arrival in the operating room	36.7 ± 0.7	36.8 ± 0.6	0.023[a]
At placement of first clip	35.1 ± 1.9	35.1 ± 1.8	0.905[a]
2 hours after surgery	37.1 ± 0.8	36.7±1.0	<0.001[b]
Moderate or severe brain swelling at dural opening	87 (44)	95 (39)	0.343[b]
Aneurysm exposure judged difficult or very difficult	77 (39)	124 (51)	0.008[b]
Intraoperative controlled hypotension was used	6 (3)	14 (6)	0.164[b]
Unintended hypotension occurred up to 2 hours postoperatively	2 (1)	11 (5)	0.044[c]
Vasopressor use	34 (17)	43 (18)	0.841[b]
Intraoperative leak or rupture of aneurysm	88 (44)	115 (48)	0.462[b]
Estimated intraoperative blood loss (ml)	481 ± 468	468 ± 367	0.745[a]
Intraoperative blood loss ≥ 1000 ml	18 (9)	19 (8)	0.655[b]
Intraoperative crystalloid administration (ml)	3513 ± 1474	3397 ± 1543	0.420[a]
Intraoperative red blood-cell transfusion	32 (16)	32 (13)	0.396[b]
Intraoperative urinary output (ml)	1748 ± 1028	1941 ± 1224	0.073[a]
New cardiac arrhythmia intraoperatively	5 (3)	9 (4)	0.589[c]

Continuous data expressed as mean ± standard deviation, catagorical data expressed as n (% within group)

[a] Based on Student's t-test

[b] Based on chi-square test

[c] Based on Fisher exact test

[d] Anterior aneurysms include those involving the carotid, ophthalmic, anterior choroidal, middle cerebral, anterior communicating, posterior communicating, and anterior cerebral arteries. Posterior aneurysms include those involving the vertebrobasilar and posterior-inferior cerebellar arteries.

[e] Use of isoflurane and desflurane exceeds 100% in both groups reflecting that, in a few patients in each group, agent use was changed during the course of the same general anesthetic.

Table 3

Postoperative Data - Nitrous Oxide Versus No Nitrous Oxide

Metric	Nitrous Oxide Group	No Nitrous Oxide Group	Univariate Analysis p-value	Multivariate Analysis Odds Ratio	95% CI	p-value
Length of Intensive Care Unit Stay						
N	199	242				
≥ 5 days (%)	137 (69)	112 (46)	<0.001	3.04	1.93–4.79	<0.001
Hospital Duration (total days)						
N	199	240				
≥ 15 days hospital duration (%)	117 (59)	132 (55)	0.424	1.32	0.86–2.04	0.209
Discharge Destination						
N	199	240				
NOT discharged to home (%)	66 (33)	116 (48)	0.001	0.516	0.32–0.82	0.006

CI=Confidence Interval

Values in "No Nitrous Oxide Group" and "Nitrous Oxide Group" columns represent numbers of patients (% within group).

Discharge destination refers to the facility to which patients were sent upon discharge from the center where surgery was performed and included locations such as the patient's home, another acute care hospital, or chronic/rehabilitation facility.

Both unadjusted (univariate) and adjusted (multivariate) analyses were performed using standard logistic regression for binary outcomes and cumulative logistic regression for ordered categorical outcomes. For the multivariate analysis, the findings are summarized by presenting the odds ratio corresponding to the increased (or decreased) likelihood of the given outcome for patients receiving nitrous oxide compared to patients not receiving nitrous oxide. In all cases, the models are parameterized so that an odds ratio significantly greater than 1.0 would indicate an increased likelihood of a worse outcome in patients receiving nitrous oxide. The odds ratios are adjusted for treatment assignment (normothermia, hypothermia), age, gender, race (white versus other), baseline World Federation of Neurological Surgeons score, Fisher grade, baseline National Institutes of Health Stroke Scale (0, 1–7, 8–14, 15–42), aneurysm location (anterior, posterior), aneurysm size, history of hypertension, and time from subarachnoid hemorrhage to surgery.

Table 4

Gross Neurologic and Neuropsychometric Outcome Results - Nitrous Oxide Versus No Nitrous Oxide

			Univariate Analysis	Multivariate Analysis		
Metric	**Nitrous Oxide Group**	**No Nitrous Oxide Group**	**p-value**	**Odds Ratio**	**95% CI**	**p-value**
DIND (yes or no)						
N	199	242	0.108	1.78	1.08–2.95	0.025
DIND=yes	55 (28)	51 (21)				
GOS at 3-months (1 vs. >1)						
N	199	242	0.059	0.70	0.45–1.10	0.123
1 (Minor or no disability)	135 (68)	143 (59)				
GOS at 3-months (1,2,3,4,5)						
N	199	242	0.043	0.67	0.44–1.03	0.065
1 (Minor or no disability)	135 (68)	143 (59)				
2 (Moderate disability)	40 (20)	55 (23)				
3 (Severe disability)	12 (6)	23 (10)				
4 (Vegetative state)	0 (0)	0 (0)				
5 (Death)	12 (6)	21 (9)				
Rankin Score at 3-months (0 or 1 vs. >1)						
N	199	242	0.078	0.74	0.47–1.16	0.192
Score 0 or 1 (Mild or no neurologic disability)	137 (69)	147 (61)				
NIHSS at 3-months (0,1–7,8–14,>14, death)						
N	194	240	0.741	1.02	0.66–1.56	0.937
0 (No deficit)	120 (62)	149 (62)				
1–7 (Mild deficit)	57 (29)	58 (24)				
8–14 (Moderate deficit)	3 (2)	8 (3)				
15–42 (Severe Deficit)	2 (1)	4 (2)				

			Univariate Analysis	Multivariate Analysis		
Metric	**Nitrous Oxide Group**	**No Nitrous Oxide Group**	**p-value**	**Odds Ratio**	**95% CI**	**p-value**
Death	12 (6)	21 (9)				
Barthel's Index at 3-months (95–100,<95)						
N	198	242	0.076	0.69	0.38–1.25	0.22
95–100	170 (86)	192 (79)				
<95	16 (8)	29 (12)				
Death	12 (6)	21 (9)				
Impairment on neuropsychological composite score (yes or no)						
N	187	221	0.918	0.81	0.44–1.49	0.493
Impairment=yes	38 (20)	44 (20)				
Impairment on at least 1 neuropsychological tests (yes or no)						
N	187	221	0.008	0.56	0.36–0.89	0.013
Impairment=yes	101 (54)	148 (67)				

Values in "No Nitrous Oxide Group" and "Nitrous Oxide Group" columns represent numbers of patients (% within group)

CI=Confidence Interval

DIND=Delayed Ischemic Neurologic Deficit

GOS=Glasgow Outcome Score

NIHSS=National Institutes of Health Stroke Scale

Statistical analysis of data for impairment on both the neuropsychological composite score and at least 1 neuropsychologic test include only surviving patients; patients who had died were not included in the denominator.

Both unadjusted (univariate) and adjusted (multivariate) analyses were performed using standard logistic regression for binary outcomes and cumulative logistic regression for ordered categorical outcomes. For the multivariate analysis, the findings are summarized by presenting the odds ratio corresponding to the increased (or decreased) likelihood of the given outcome for patients receiving nitrous oxide compared to patients not receiving nitrous oxide. In all cases, the models are parameterized so that an odds ratio significantly greater than 1.0 would indicate an increased likelihood of a worse outcome in patients receiving nitrous oxide. The odds ratios are adjusted for treatment assignment (normothermia, hypothermia), age, gender, race (white versus other), baseline World Federation of Neurological Surgeons score, Fisher grade, baseline National Institutes of Health Stroke Scale (0, 1–7, 8–14, 15–42), aneurysm location (anterior, posterior), aneurysm size, history of hypertension, and time from subarachnoid hemorrhage to surgery.