Anesthesiology 2009; 110:563–73

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

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Background: **The authors explored the relationship between nitrous oxide use and neurologic and neuropsychological outcome in a population of patients likely to experience intraoperative cerebral ischemia: 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 surgery were included in the analysis. Metrics of short-term and long-term (*i.e.*, 3 months after surgery) outcome were evaluated *via* both univariate and multivariate logistic regression analysis. An odds ratio (OR) greater than 1.0 denotes a worse outcome in patients receiving nitrous oxide.**

Results: **The authors 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 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 this 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.**

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Received from the Department of Anesthesiology, Mayo Clinic College of Medicine, Rochester, Minnesota. Submitted for publication June 5, 2008. Accepted for publication November 6, 2008. The Intraoperative Hypothermia for Aneurysm Surgery Trial, on which this investigation is based, was supported by grant No. R01 NS38554 from the National Institute of Neurological Disease and Stroke, Bethesda, Maryland.

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FROM February 2000 through April 2003, investigators from 31 medical centers around the world prospectively collected data on 1,001 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 principal 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 nitrous oxide use (or nonuse) and intraoperative blood glucose concentrations with long-term patient outcomes.[2,3]

The former of these reports attempted to resolve controversies regarding the effect of nitrous oxide on outcome after cerebral ischemia. Despite contradictory results from animal models—*i.e.*, some studies report benefit,[4,5] whereas 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 neurologic 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 patients at risk for ischemic brain injury.

Before our study of nitrous oxide use in the 1,001 IHAST patients, some had warned that nitrous oxide should not be used in patients with, or at high risk for, ischemic brain injury.[11–13] Although there are no data in human 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 whether 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 previous article 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 with 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. That is, 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 current research examined the association of nitrous oxide use and delayed ischemic neurologic deficits (DINDs; *i.e.*, the clinical manifestation of vasospasm), hospital course, disposition on 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 (1,001-patient), international, multicenter, randomized, partially blinded, prospective, clinical trial. Details regarding trial design are described elsewhere.[1] In brief, nonpregnant adults with a preoperative World Federation of Neurological Surgeons Score of I, II, or III and who had aneurysmal subarachnoid hemorrhage no more than 14 days before surgery were eligible for enrollment. Specific exclusion criteria included a body mass index 35 kg/m^2 or greater, any cold-related disorder (*e.g.*, Raynaud 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.

After the induction of anesthesia, an esophageal temperature probe was inserted, and the patient was positioned for surgery. In patients randomly assigned to hypothermia, esophageal temperature was reduced as quickly as possible, with the goal of achieving a temperature between 32.5° and 33.5°C by the time a clip was applied to the first aneurysm. Temperature in patients randomly assigned to normothermia was kept between 36° and 37°C. Rewarming of hypothermic patients began after the last aneurysm had been secured and was continued until normothermia was achieved. Use 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 postoperative 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 (1) a decrease in the Glasgow Coma Score with alteration in level of consciousness or (2) development of a new or worsening focal neurologic 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 (1) the modified Glasgow Outcome Score (GOS; this was the primary outcome measure for the trial)[15]; (2) the Rankin Disability Score[16]; (3) the Barthel Activities of Daily Living Index[17]; (4) the National Institutes of Health Stroke Scale (NIHSS)[18]; (5) the 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 (6) a neuro-

psychological 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 (2 SDs 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 because of 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 Index of Daily Living) derived from data obtained from 873 patients in the original IHAST trial who were able to complete neuropsychological testing.[1] The imputation process was based on relations 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 "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, Iowa City, Iowa.

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 a Student *t* test, Pearson chi-square test, or Fisher exact test depending on the characteristics and distribution of the data. It was not possible to structure the analysis according to nitrous oxide dose because nitrous oxide use was reported in the IHAST database as either used or not used.

All neurologic 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 two categories, cumulative logistic (proportional odds) models were used. Because 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 neurologic and neuropsychological outcomes of the IHAST trial. The covariates for the multivariable analysis included race (white *vs.* nonwhite), age, sex, 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, $\geq$ 25 mm in greatest dimension), aneurysm location (posterior *vs.* anterior), and IHAST treatment assignment (normothermic *vs.* hypothermic). For analysis purposes, duration of stay in the intensive care unit, total duration of hospitalization, and destination after discharge from the treating institution were stratified as binary responses ($<$ 5 days *vs.* $>$ 5 days, $<$ 15 days *vs.* $>$ 15 days, 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 five 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 Activities of Daily Living Index score 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 with normative data (adjusted for age, sex, and years of education), with a binary outcome (presence or absence of impairment) determined for each test. For the current report, two binary neuropsychological outcomes are included: impairment for the composite score and impairment on any individual test.

Because 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 who received nitrous oxide *versus* those who did 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. Because the explanatory variable of interest for this investigation was

Table 1. Baseline Characteristics

	Nitrous Oxide Use		
	Yes	No	*P* Value
n	199	242	
Demographics			
Age, mean ± SD, yr	50 ± 11	52 ± 12	0.041*
Sex, % female	126 (63)	154 (64)	1†
Race, % white, not of Hispanic origin	152 (76)	206 (85)	0.019†
Preoperative medical history			
History of diabetes mellitus (% with diabetes mellitus)	7 (4)	5 (2)	0.351†
History of hypertension (% with hypertension)	82 (41)	82 (34)	0.113†
History of smoking (% current smokers)	105 (53)	142 (59)	0.213†
Preoperative neurologic status			
Preoperative WFNS score			0.679†
GCS = 15 with no motor deficit or aphasia	138 (69)	158 (65)	
GCS = 13–14 with 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‡
0	117 (59)	120 (50)	
1–7	61 (31)	101 (42)	
8–14	8 (4)	5 (2)	
15–42	0 (0)	1 (0)	
Missing	13 (7)	15 (6)	
Preoperative Fisher grade			0.01†
1	15 (8)	12 (5)	
2	59 (30)	77 (32)	
3	105 (53)	111 (46)	
4	20 (10)	42 (17)	
Interval between subarachnoid hemorrhage and induction of anesthesia, days			0.063*
Mean ± SD	3.0 ± 3.0	3.5 ± 3.1	
Median (range)	2 (0–14)	2 (0–14)	

Categorical data are expressed as n (% within group).

* Based on Student *t* test. † Based on Pearson chi-square test. ‡ Based on Fisher exact test.

GCS = Glasgow Coma Score; NIHSS = National Institutes of Health Stroke Scale; WFNS = World Federation of Neurological Surgeons.

nitrous oxide use, the findings from the multiple logistic regression models are summarized by presenting the odds ratio (OR) and corresponding 95% confidence interval (CI) for nitrous oxide use. For all logistic regression analyses, the models are parameterized so that an OR 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 $P \leq 0.05$ 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 neurologic 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 intraoperative nitrous oxide use, can be found in table 1. Groups did not differ with regard to sex, preoperative medical history, or 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 ± 11 *vs.* 52 ± 12 yr 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 NIHSS score ($P = 0.035$) and Fisher grade ($P = 0.01$).

Aneurysm characteristics and intraoperative 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 who received either isoflurane or desflurane during maintenance of general anesthesia. It should be noted that the fraction of patients who received isoflurane and desflurane in each group was 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.

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*
Aneurysm location (number in anterior circulation of first aneurysm clipped)§	184 (92)	229 (95)	0.354†
Number of aneurysms treated (number with one aneurysm treated)	175 (88)	218 (90)	0.471†
Intraoperative factors			
Isoflurane used‖	164 (82)	193 (80)	0.480†
Desflurane used‖	47 (24)	59 (24)	0.862†
Mean arterial pressure at first permanent clip placement, mmHg	83 ± 14	77 ± 14	< 0.001*
Blood glucose at first permanent clip placement, mg/dl	141 ± 35	126 ± 35	< 0.001*
Time from induction of anesthesia to placement of first clip, min	240 ± 80	211 ± 75	< 0.001*
Time from placement of last clip to arrival in recovery area, min	116 ± 32	94 ± 34	< 0.001*
Protective drugs for used clipping	91 (46)	85 (35)	0.024†
Etomidate used	12 (6)	7 (3)	0.106†
Thiopental used	79 (40)	78 (32)	0.103†
Temporary clip applied for ≥ 20 min	30 (15)	28 (12)	0.279†
Total duration of temporary clipping, min	11.9 ± 13.1	9.3 ± 7.7	0.012*
Temperature, °C			
On arrival in the operating room	36.7 ± 0.7	36.8 ± 0.6	0.023*
At placement of first clip	35.1 ± 1.9	35.1 ± 1.8	0.905*
2 h after surgery	37.1 ± 0.8	36.7 ± 1.0	< 0.001*
Moderate or severe brain swelling at dural opening	87 (44)	95 (39)	0.343†
Aneurysm exposure judged difficult or very difficult	77 (39)	124 (51)	0.008†
Intraoperative controlled hypotension used	6 (3)	14 (6)	0.164†
Unintended hypotension occurred up to 2 h postoperatively	2 (1)	11 (5)	0.044‡
Vasopressor use	34 (17)	43 (18)	0.841†
Intraoperative leak or rupture of aneurysm	88 (44)	115 (48)	0.462†
Estimated intraoperative blood loss, ml	481 ± 468	468 ± 367	0.745*
Intraoperative blood loss ≥ 1,000 ml	18 (9)	19 (8)	0.655†
Intraoperative crystalloid administration, ml	3,513 ± 1,474	3,397 ± 1,543	0.420*
Intraoperative erythrocyte transfusion	32 (16)	32 (13)	0.396†
Intraoperative urinary output, ml	1,748 ± 1,028	1,941 ± 1,224	0.073*
New cardiac arrhythmia intraoperatively	5 (3)	9 (4)	0.589‡

Continuous data are expressed as mean ± SD. Categorical data are expressed as n (% within group).

* Based on Student *t* test. † Based on chi-square test. ‡ Based on Fisher exact test. § 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. ‖ 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.

Patients in the nitrous oxide group had a significantly greater mean arterial blood pressure (83 ± 14 *vs.* 77 ± 14 mmHg for no nitrous oxide; $P < 0.001$) and blood glucose (141 ± 35 *vs.* 126 ± 35 mg/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 ± 80 *vs.* 211 ± 75 min for no nitrous oxide; $P < 0.001$) and the time between placement of the last permanent clip and arrival in the recovery area (116 ± 32 *vs.* 94 ± 34 min 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 before 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 who had a temporary clip placed for longer than 20 min, the mean duration of iatrogenic temporary arterial occlusion was greater in the nitrous oxide group (11.9 ± 13.1 *vs.* 9.3 ± 7.7 min for no nitrous oxide; $P = 0.012$). Statistically significant but probably clinically inconsequential differences existed between groups in core temperature both at the time of arrival in the operating suite and 2 h after 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 on dural opening. Other intraoperative factors were equivalent.

Postoperative data are summarized in table 3. After 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 duration of stay of 5 or more days compared with the group that did not receive

Table 3. Postoperative Data: 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
Duration 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 (%)	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

Values in No Nitrous Oxide Group and Nitrous Oxide Group columns are number of patients (% within group). Discharge destination refers to the facility to which patients were sent after discharge from the center where surgery was performed and included locations such as the patient's home, another acute care hospital, or a 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. Odds ratios are adjusted for treatment assignment (normothermia, hypothermia), age, sex, race (white *vs.* other), baseline World Federation of Neurological Surgeons score, Fisher grade, baseline National Institutes of Health Stroke Scale score (0, 1–7, 8–14, 15–42), aneurysm location (anterior, posterior), aneurysm size, history of hypertension, and time from subarachnoid hemorrhage to surgery.

CI = confidence interval.

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 duration of stay of 15 or more days (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 analyses, 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 months after 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 score (univariate $P = 0.741$; adjusted OR, 1.02; CI, 0.66–1.56; multivariate $P = 0.937$), or Barthel 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 after subarachnoid hemorrhage, impairment of the composite score was imputed for 10 patients (5.0%) in the nitrous oxide group and 11 patients (4.5%) in the no nitrous oxide group ($P = 0.81$). Impairment on more than one neuropsychological test was imputed for 8 patients (4.0%) in the nitrous oxide group and 8 patients (3.3%) in the no nitrous oxide group ($P = 0.69$). 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 no nitrous oxide group; univariate $P = 0.918$; adjusted OR, 0.81; CI, 0.44–1.49; multivariate $P = 0.493$). However, a lesser fraction of patients in the group that received nitrous oxide (54%) exhibited impairment on at least one test of neuropsychological function compared with 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 used, intraoperative use of nitrous oxide had no detrimental effect on neurologic status, functional status, or neuropsychological function 3 months after 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

Table 4. Gross Neurologic and Neuropsychometric Outcome Results: Nitrous Oxide *versus* No Nitrous Oxide

Metric	Univariate Analysis			Multivariate Analysis		
	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
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)				
Death	12 (6)	21 (9)				
Barthel 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 are number of patients (% within group). Statistical analysis of data for impairment on both the neuropsychological composite score and at least one neuropsychologic test include only surviving patients; patients who 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 with 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. Odds ratios are adjusted for treatment assignment (normothermia, hypothermia), age, sex, race (white *vs.* other), baseline World Federation of Neurological Surgeons score, Fisher grade, baseline National Institutes of Health Stroke Scale score (0, 1–7, 8–14, 15–42), aneurysm location (anterior, posterior), aneurysm size, history of hypertension, and time from subarachnoid hemorrhage to surgery.

CI = confidence interval; DIND = delayed ischemic neurologic deficit; GOS = Glasgow Outcome Score; NIHSS = National Institutes of Health Stroke Scale.

difference between groups in the fraction of patients requiring an overall hospital stay of 15 or more 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 previous investigations have reported that nitrous oxide adversely effects the brain because of its effect on cerebral metabolism or intracranial pressure.[24–28] Other investigations using 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 using 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 previous investigation by our group that studied all 1,001 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 after surgery) gross neurologic and neuropsychological function.[2] However, a limitation of our pre-

vious investigation was that many of the 1,001 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 have 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 before surgery (*i.e.*, at the time of initial hemorrhage) due to the temporal relation. In our current investigation, we analyzed data exclusively from patients in whom temporary occlusion of a major cerebral artery was used 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 1,001 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 aneurysm clip is a relatively common practice. In the IHAST investigation, 44% of 1,001 patients had intraoperative proximal vascular occlusion.[1] This technique has been reported to reduce the risk of aneurysm rupture and helps to facilitate surgical dissection, potentially improving the rate of successful placement of a permanent clip.[33] However, use of temporary proximal vessel occlusion has adverse consequences as well. In patients having aneurysm clipping with somatosensory evoked potential monitoring, Mizoi and Yoshimoto[34] discovered a loss of signals in 43% of patients at the time of temporary proximal vessel occlusion. In a similar investigation, Schick *et al.*[35] reported that in patients in whom proximal vessel occlusion was used, complete loss of somatosensory evoked potential signals occurred in 38%. 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 who underwent occlusion of specific vessels (untabulated data).

Our investigation evaluated one metric of short-term neurologic 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 previous investigation that included data from all 1,001 IHAST subjects, nitrous oxide use was not associated with the development of DIND (OR, 1.29; CI, 0.91–1.83; $P = 0.157$).[2] However, when only patients in whom temporary arterial occlusion was used were included in the analysis, use of nitrous oxide increased the odds of developing DIND postoperatively (OR, 1.78; CI, 1.08-2.95; $P = 0.025$). It is currently unknown whether use of temporary vessel occlusion served as an independent risk factor to increase the risk for development of 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 oxide–treated patients. First, it is possible that the use of a temporary arterial clip resulted in irritation of the vascular smooth muscle, and, after exposure to increased 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 or more days.

The development of vasospasm after 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 duration of stay, discharge destination, or any metric of long-term 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 previous analysis of all 1,001 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 months based on the categorized GOS after 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 months after surgery. However, unlike our previous analysis, this current in-

vestigation, 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 3 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 intraoperative factors, such as a greater use of neuroprotective agents intraoperatively, a 6-mmHg 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 (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. 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 I statistical error. For every comparison performed using the same data, the chance of a false-positive result increases with each comparison. Given that this article describes a *post hoc* analysis of a data set, 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 = 1,000, 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 current 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 whether 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, 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 neurologic 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.

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

References

1. Todd MM, Hindman BJ, Clarke WR, Torner JC: Mild intraoperative hypothermia during surgery for intracranial aneurysm. N Engl J Med 2005; 352:135–45

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; 108:568–79

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; 83:406–19

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; 101:260–1

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; 23:1168–73

6. Baughman VL, Hoffman WE, Miletich DJ, Albrecht RF, Thomas C: Neurologic outcome in rats following incomplete cerebral ischemia during halothane, isoflurane, or N_2O. ANESTHESIOLOGY 1988; 69:192–8

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; 70:767–74

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
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; 60:405–12
10. Sakabe T, Kuramoto T, Inoue S, Takeshita H: Cerebral effects of nitrous oxide in the dog. ANESTHESIOLOGY 1978; 48:195–200
11. Baughman VL: N2O: Of questionable value. J Neurosurg Anesthesiol 1995; 7:79–81
12. Reinstrup P, Messeter K: Cerebrovascular response to nitrous oxide. Acta Anaesthesiol Scand 1994; 38:761–2
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, Illinois, American Society of Anesthesiologists, 2003, pp 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; 87:711–3
15. Jennett B, Bond M: Assessment of outcome after severe brain damage. Lancet 1975; 1:480–4
16. Rankin J: Cerebral vascular accidents in patients over the age of 60, II: Prognosis. Scott Med J 1957; 2:200–15
17. Mahoney FI, Barthel DW: Functional evaluation: The Barthel Index. Md State Med J 1965; 14:61–5
18. Wityk RJ, Pessin MS, Kaplan RF, Caplan LR: Serial assessment of acute stroke using the NIH Stroke Scale. Stroke 1994; 25:362–5
19. Sivan A: The Benton Visual Retention Test, 5th edition. San Antonio, The Psychological Corporation, 1992
20. Benton A, Hamsher K: The Multilingual Aphasia Examination. Iowa City, AJA Associates, 1994
21. Lezak M: Neuropsychological Assessment, 3rd edition. New York, Oxford University Press, 1995, pp 475–80
22. Tombaugh TN: Trail Making Test A and B: Normative data stratified by age and education. Arch Clin Neuropsychol 2004; 19:203–14
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; 60:518–27
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; 20:91–5
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: 781–5
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: 757–61
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; 48:957–62
28. Theye RA, Michenfelder JD: The effect of nitrous oxide on canine cerebral metabolism. ANESTHESIOLOGY 1968; 29:1119–24
29. Hoffman WE, Baughman VL, Albrecht RF: Interaction of catecholamines and nitrous oxide ventilation during incomplete brain ischemia in rats. Anesth Analg 1993; 77:908–12
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. Nat Med 1998; 4:460–3
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; 93:1095–101
32. Kassell NF, Torner JC, Haley EC, Jane JA, Adams HP, Kongable GL: The International Cooperative Study on the Timing of Aneurysm Surgery, part I: Overall management results. J Neurosurg 1990; 73:18–36
33. Taylor CL, Selman WR: Temporary vascular occlusion during cerebral aneurysm surgery. Neurosurg Clin North Am 1998; 9:673–9
34. Mizoi K, Yoshimoto T: Permissible temporary occlusion time in aneurysm surgery as evaluated by evoked potential monitoring. Neurosurgery 1993; 33: 434–40
35. Schick U, Dohnert J, Meyer JJ, Vitzthum HE: Effects of temporary clips on somatosensory evoked potentials in aneurysm surgery. Neurocrit Care 2005; 2:141–9
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; 95:402–11
37. Momma F, Wang AD, Symon L: Effects of temporary arterial occlusion on somatosensory evoked responses in aneurysm surgery. Surg Neurol 1987; 27: 343–52
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; 84:785–91
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; 96:1013–9
40. Guthikonda S, Haynes WG: Homocysteine: Role and implications in atherosclerosis. Curr Atheroscler Rep 2006; 8:100–6
41. Dorsch NW: Cerebral arterial spasm: A clinical review. Br J Neurosurg 1995; 9:403–12

Appendix

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