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Acute postoperative neurological deterioration associated with surgery for ruptured intracranial aneurysm: incidence, predictors, and outcomes

Clinical article

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Object. Subarachnoid hemorrhage (SAH) results in significant morbidity and mortality, even among patients who reach medical attention in good neurological condition. Many patients have neurological decline in the perioperative period, which contributes to long-term outcomes. The focus of this study is to characterize the incidence of, characteristics predictive of, and outcomes associated with acute postoperative neurological deterioration in patients undergoing surgery for ruptured intracranial aneurysm.

Methods. The Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) was a multicenter randomized clinical trial that enrolled 1001 patients and assesssed the efficacy of hypothermia as neuroprotection during surgery to secure a ruptured intracranial aneurysm. All patients had a radiographically confirmed SAH, were classified as World Federation of Neurosurgical Societies (WFNS) Grade I–III immediately prior to surgery, and underwent surgery to secure the ruptured aneurysm within 14 days of SAH. Neurological assessment with the National Institutes of Health Stroke Scale (NIHSS) was performed preoperatively, at 24 and 72 hours postoperatively, and at time of discharge. The primary outcome variable was a dichotomized scoring based on an IHAST version of the Glasgow Outcome Scale (GOS) in which a score of 1 represents a good outcome and a score > 1 a poor outcome, as assessed at 90-days' follow-up. Data from IHAST were analyzed for occurrence of a postoperative neurological deterioration. Preoperative and intraoperative variables were assessed for associations with occurrence of postoperative neurological deterioration. Differences in baseline, intraoperative, and postoperative variables and in outcomes between patients with and without postoperative neurological deterioration were compared with Fisher exact tests. The Wilcoxon rank-sum test was used to compare variables reported as means. Multiple logistic regression was used to adjust for covariates associated with occurrence of postoperative deficit.

Results. Acute postoperative neurological deterioration was observed in 42.6% of the patients. New focal motor deficit accounted for 65% of postoperative neurological deterioration, while 60% was accounted for using the NIHSS total score change and 51% by Glasgow Coma Scale score change. Factors significantly associated with occurrence of postoperative neurological deterioration included: age, Fisher grade on admission, occurrence of a procedure prior to aneurysm surgery (ventriculostomy), timing of surgery, systolic blood pressure during surgery, ST segment depression during surgery, history of abnormality in cardiac valve function, use of intentional hypotension during surgery, duration of anterior cerebral artery occlusion, intraoperative blood loss, and difficulty of aneurysm exposure. Of the 426 patients with postoperative neurological deterioration at 24 hours after surgery, only 46.2% had a good outcome (GOS score of 1) at 3 months, while 77.7% of those without postoperative neurological deterioration at 24 hours had a good outcome ($p < 0.05$)

Conclusions. Neurological injury incurred perioperatively or in the acute postoperative period accounts for a large percentage of poor outcomes in patients with good admission WFNS grades undergoing surgery for aneurysmal SAH. Avoiding surgical factors associated with postoperative neurological deterioration and directing investigative efforts at developing improved neuroprotection for use in aneurysm surgery may significantly improve long-term neurological outcomes in patients with SAH.
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Key Words • **postoperative deficit** • **subarachnoid hemorrhage** • **surgery** • **aneurysm** • **vascular disorders**

Abbreviations used in this paper: BP = blood pressure; DIND = delayed ischemic neurological deficit; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; IHAST = Intraoperative Hypothermia for Aneurysm Surgery Trial; ISAT = International Subarachnoid Aneurysm Trial; NIHSS = National Institutes of Health Stroke Scale; OR = odds ratio; SAH = subarachnoid hemorrhage; WFNS = World Federation of Neurosurgical Societies.

Aneurysmal SAH is associated with significant morbidity and mortality. Only approximately two-thirds of patients with good admission WFNS grades have a good recovery. Several events in the clinical course of patients with SAH may contribute to outcome. These may include focal and global cerebral ischemia associated with the initial hemorrhage, rebleed-

ing of the aneurysm, spasm of cerebral vessels producing ischemia, hydrocephalus, and surgical and medical complications of treatment.

In spite of the increased use of endovascular coil embolization, surgical clipping during the acute phase of SAH is sometimes the preferred method to prevent rebleeding of the aneurysm, particularly in younger patients or those with certain kinds of aneurysmal anatomy.[2] For example, many neurosurgeons prefer surgical clipping for middle cerebral artery aneurysms, as evidenced by the hesitancy of clinicians to randomize patients with middle cerebral artery aneurysms to a trial of surgical clipping versus endovascular coil embolization (the ISAT).[11] Surgical clipping is often performed within a few days after the initial hemorrhage, at a time when cerebrovascular physiology is still substantially altered.[3] The combination of this underlying brain and vascular pathophysiology and the surgical intervention is known to carry a risk of acute postoperative neurological deterioration. However, the incidence of acute postoperative neurological deterioration and its relationship to long-term outcome is not well defined.

The IHAST was designed to evaluate the effectiveness of mild systemic intraoperative hypothermia (33°C) in improving neurological outcome for patients undergoing surgical treatment of acutely ruptured intracranial aneurysms. The central hypothesis was that hypothermia would decrease intraoperative injury due to ischemic phenomena associated with SAH. The study measured the neurological status of patients prior to randomization, at the start of surgery, and serially during a 3-month postoperative follow-up period. The data gathered in this study provided an opportunity to examine the incidence of acute postoperative neurological deterioration and determine whether there is an association with long-term outcomes. The specific questions posed in this analysis are: 1) What is the incidence and what are the characteristics of acute neurological deterioration seen in the postoperative period? 2) What pre- and intraoperative factors are associated with acute postoperative neurological deterioration? 3) What is the relationship between these deficits and the long-term neurological outcome?

Methods

The IHAST was an international, multicenter, randomized, and partially blinded prospective clinical trial enrolling 1001 patients. Details of trial design and primary outcomes are described elsewhere.[20] The study was approved by each participating center's local institutional review board, and informed consent was obtained from either the patients or their legal representatives. The IHAST included nonpregnant adults with a WFNS grade[4] of I, II, or III who had suffered an angiographically confirmed aneurysmal SAH no more than 14 days prior to surgery. Exclusion criteria included a body mass index greater than 35 kg/m^2, any cold-related disorders (for example, Raynaud syndrome), and the presence of an endotracheal tube at the time of enrollment. A permuted-block randomization scheme was used, stratified by center and interval between SAH and surgery (0–7 days, 8–14 days). Two hours (or less) prior to the planned start of surgery, the patient's neurological status was reevaluated and if the WFNS grade remained I–III, the patient was enrolled via a telephone-accessed computer system. This directed the anesthesiologist to select a numbered opaque envelope containing the patient's randomized treatment assignment. The envelope was opened only after the induction of anesthesia—this constituted randomization. If, prior to induction, eligibility criteria were no longer met (for example, if the patient's neurological condition deteriorated), the envelope was not opened and the patient was not considered to have been randomized. Patients were randomized into one of 2 groups: intraoperative hypothermia (target temperature at the time of aneurysm clipping, 33°C) or normothermia (36.5°C). All study personnel, except the anesthesiologists involved in each patient's intraoperative care, were blinded to treatment assignment. All but 1 patient received nimodipine as part of their routine perioperative care.

Information regarding patients' pre-SAH health status and events occurring between the time of hospital admission and surgery was collected. Detailed events occurring intraoperatively and in the immediate perioperative period (0–2 hours postoperatively) were also recorded. Other relevant postoperative information that was collected daily included GCS scores, whether the patient was still intubated and/or was still in an intensive care unit, and the presence of DINDs. A more detailed neurological evaluation, using the NIHSS, was performed at 24 and 72 hours postoperatively and again at the time of discharge.[22] Patient discharge destination (for example, home, another acute care hospital, a rehabilitation center) was also noted.

A final follow-up examination was conducted approximately 3 months after surgery. Follow-up data were available for 1000 of 1001 randomized patients. Outcome measures included 1) the dichotomized GOS score (this was the primary outcome measure for the trial, reported as used by the TOAST [Trial of ORG 10172 in Acute Stroke Treatment] investigators[16] and based on the description in the 1981 article by Jennet et al.,[6] 2) the Rankin Disability Scale score,[17] 3) the Barthel Activities of Daily Living Index,[10] and 4) the NIHSS score.[22] All evaluations were performed by trained examiners who were unaware of the patients' temperature group assignments, and who were certified by the University of Iowa Steering Committee.

Consistent with prior IHAST publications, acute neurological deterioration at 24 hours after surgery was defined by the presence of any one or more of the following conditions at that time: 1) a decrease of 2 or more points on the GCS as compared with the preoperative value; 2) an increase of 4 or more points on the NIHSS as compared with the preoperative value; 3) an increase of 1 or more points on the motor component of any limb on the NIHSS as compared with the preoperative value; 4) tracheal intubation; 5) death; 6) report by the anesthesiologist of a new focal neurological deficit within the first 2 hours of surgery; and 7) the diagnosis of DIND.[5]

Statistical Analysis

Univariate comparisons of various measures in patients with and without new acute postoperative neurological deterioration were performed using the Pearson

chi-square test, Fisher exact test, or Wilcoxon rank-sum test, depending on the data distribution. Similarly, univariate assessments of neurological, neuropsychological, or functional outcomes in the 2 groups were performed using either the Pearson chi-square test, Fisher exact test, or Cochran-Mantel-Haenszel test of general association.

Preoperative and intraoperative variables that differed between the neurological deterioration and no neurological deterioration groups with a univariate p value < 0.10 were evaluated using a stepwise logistic regression. Variables that remained in the final model were those associated with outcome at $p < 0.05$, independent of other variables. All results are 2-sided, and the univariate p values are not adjusted for multiple comparisons. Statistical analyses were performed using SAS software version 9.2.

Results

Demographic Characteristics

The 1000 patients in the trial with 3-month follow-up data averaged 52 years of age at time of enrollment; 66% were female. The preoperative neurological grade using the WFNS scale was Grade I in 66%, Grade II in 29%, and Grade III in 5%. The distribution of SAH determined by the Fisher grade showed that 34% of the cases were Grade II and 47% were Grade III, based upon the baseline CT scans. The median interval from SAH to surgery was 2 days; 90% of patients underwent surgery within the 0- to 7-day interval. Surgeons used temporary clipping in 45% of the operations.

Time Course of Neurological Injury

The timing of occurrence of neurological injury in the study is elucidated by serial NIHSS score measurements. Assessment of the NIHSS score at baseline, 24 and 72 hours postoperatively, at discharge, and 3 months postoperatively demonstrates the acute magnitude of neurological deterioration in the perioperative and immediate postoperative period, with a trend toward improving neurological status over time (Fig. 1).

Occurrence of Postoperative Neurological Deterioration

New acute postoperative neurological deterioration at 24 hours after surgery, based on the presence of one or more criteria was observed in 426 (42.6%) of the patients. Of the 660 patients whose condition was classified at baseline as WFNS Grade I, 37.7% showed one or more signs of neurological deterioration 24 hours after surgery. In general, as the baseline NIHSS score increased, a 4-point worsening in NIHSS score 24 hours postoperatively was observed more frequently (Fig. 2). However, even in the group of patients with baseline NIHSS score of 0 (completely normal results on neurological examination), a 4-point worsening in NIHSS at 24 hours after surgery was observed in 19% of patients (and a 2-point worsening occurred in 34% of this same patient group).

Neurological Deficit Components

Complete NIHSS scores were unavailable at 24 hours in 9.5% of patients (largely due to continued postoperative endotracheal intubation). Of the new neurological deficits, 65% were accounted for by the NIHSS motor response alone (indicating new focal motor deficit), 60% using the NIHSS total score change, and 51% by GCS score change (Fig. 3). This indicates that the acute neurological deterioration was clinically evident from the change in motor function in the majority of cases.

Patient and Operative Factors Associated With New Postoperative Deficits

Univariate Analysis. Factors such as demographic characteristics, patient history, preoperative status, and intraoperative events and procedures were analyzed to determine which variables were associated with the occurrence of new postoperative deficits. Baseline characteristics including pre-SAH status and condition on presentation with SAH are detailed in Table 1. A linear relationship between age and occurrence of new postoperative deficit was observed. In patients under age 50 the rate of postoperative neurological deterioration was 34%, while for those age 75 or older the rate was 63%. There did not appear to be a threshold of age associated with occurrence of a new postoperative deficit. The pre-SAH Rankin Scale score was found to be associated with occurrence of postoperative neurological deterioration: 84.5% of patients who developed postoperative neurological deterioration were asymptomatic prior to SAH, while 90.6% of patients without any postoperative neurological deterioration were asymptomatic prior to SAH ($p = 0.006$). Worse scores on both eye opening and verbal components of the GCS (on presentation) were associated with more frequent occurrence of postoperative neurological deterioration. Seventy-seven percent of patients without postoperative neurological deterioration demonstrated spontaneous eye opening, whereas only 69% of patients with postoperative neurological deterioration opened their eyes spontaneously ($p = 0.006$). Eighty-nine percent of patients without postoperative neurological deterioration were oriented on presentation, while only 74.4% of patients who showed postoperative neurological deterioration were oriented on presentation ($p < 0.001$). Aneurysm location was also noted to be associated with occurrence of postoperative neurological deterioration. Patients with postoperative neurological deterioration more frequently had a ruptured aneurysm of the anterior communicating artery (37.1% vs 34.1%), middle cerebral artery (21.8% vs 19.7%), or vertebrobasilar artery (7.7% vs 4.4%), whereas patients without postoperative neurological deterioration more frequently had a ruptured aneurysm of the posterior communicating artery (25.1% vs 21.8%) or other artery (16.7% vs 11.6%) ($p = 0.029$).

Preoperative and intraoperative events and procedures were also analyzed to assess for association with occurrence of postoperative neurological deterioration and are detailed in Tables 2–4.

Multivariate Analysis. Those pre- and intraoperative factors that differed between the no postoperative neurological deterioration and postoperative neurological deterioration groups with a p value < 0.10 were then evaluated using a stepwise logistic regression. Variables

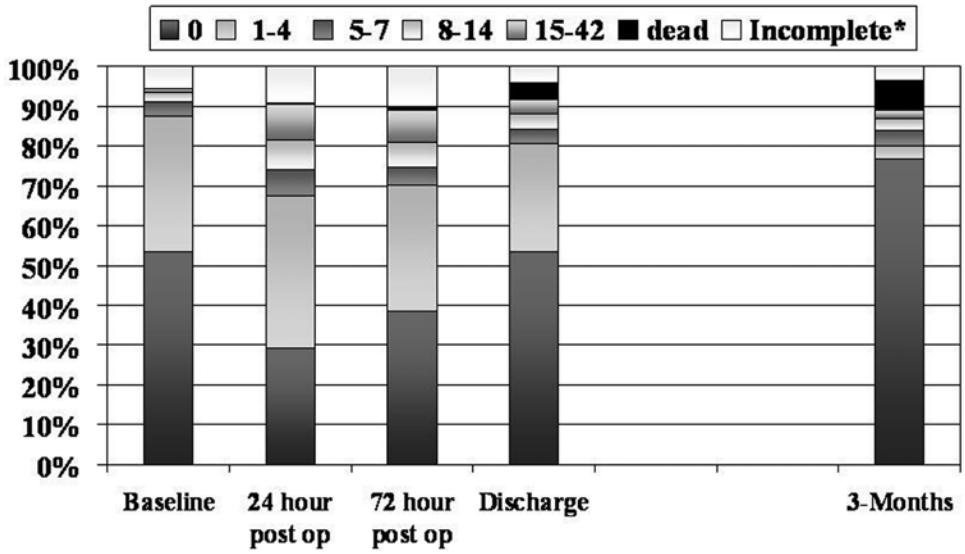

Fig. 1. Time course of neurological injury. Graph showing distribution of NIHSS scores at baseline, 24 hours postoperatively, 72 hours postoperatively, at discharge, and at 3 months' follow-up demonstrates acute neurological deterioration in the immediate postoperative period with a trend toward improving neurological status over time. *Incomplete NIHSS scores related to prolonged postoperative intubation.

that remained in the final model were those associated with postoperative neurological deterioration at $p < 0.05$, independent of other variables. These included patient age, preexisting abnormality in cardiac valve function, Fisher grade on first head CT, occurrence of any procedure before aneurysm surgery (almost exclusively the placement of ventriculostomies), systolic BP at the beginning of surgery (increased systolic BP at induction associated with increased rate of postoperative neurological decline), the use of intentional intraoperative hypotension (mean arterial pressure < 60 mm Hg for 15 consecutive minutes or more), intraoperative blood loss, duration of temporary clip application of at least 20 minutes, difficulty of aneurysm exposure, and interval (days) between SAH and surgery (Table 5). Specifically, surgery on Day 4, 5, or 6 following SAH (Day 0 refers to the day of SAH) was associated with significantly higher rates of postoperative deficit. We also observed a variation in rates of postoperative deficits between treating medical centers (ranging from 25% to 100%).

Neurological Deterioration and Outcome

To determine whether postoperative neurological deterioration was associated with outcome, we examined the 3-month GOS scores. Among all patients who had a good outcome (3-month GOS score 1), 30.6% had neurological deterioration at 24 hours postoperatively. In contrast, 64.1% of the patients with a poor outcome (3-month GOS score 2–5) had neurological deterioration at 24 hours after surgery ($p < 0.001$) (Fig. 4). Of the 426 patients with neurological deterioration at 24 hours after surgery, only 46.2% had a good outcome at 3 months,

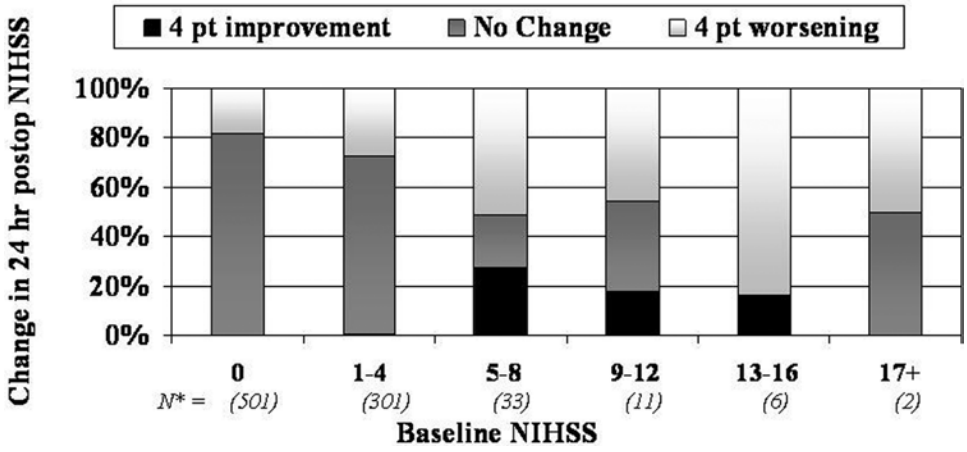

Fig. 2. Change in NIHSS scores from baseline to 24 hours postoperatively. Graph showing the distribution of 4-point change in NIHSS scores is shown as distributed by baseline NIHSS. *Baseline NIHSS scores were unavailable in 56 cases, 24-hour postoperative scores were unavailable (related to prolonged endotracheal intubation) in 95 cases, including 5 of those in which baseline scores were unavailable. Pt = point.

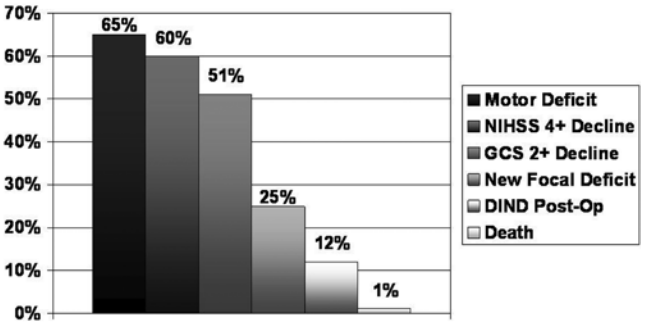

Fig. 3. Components of neurological deterioration. Graph showing the percentage of cases with new postoperative neurological deterioration at 24 hours after surgery (y-axis) stratified by condition: an increase of 1 or more points on the motor component on the NIHSS, an increase of 4 or more points on the NIHSS, a decrease of 2 or more points on the GCS score, a report of a new focal neurological deficit within the first 2 hours of surgery, diagnosis of DIND, tracheal intubation, and death. Note that cases may be counted in more than one category.

while 77.7% of those without postoperative neurological deterioration at 24 hours after surgery had a good outcome ($p < 0.05$) (Fig. 5). A similar pattern was seen for all other outcome measures (Rankin Scale score, 3-month NIHSS, occurrence of DIND, and discharge home) (Fig. 5). Vegetative survival or death occurred in 12.9% of cases in which patients exhibited postoperative neurological deterioration, compared with 1.2% in those in which they did not ($p < 0.05$).

Eighty-nine percent of all deaths in the study (55 of 62) occurred in patients who had postoperative neurological deterioration. Twenty-one percent of these deaths (13 of 62) occurred within 7 days of SAH, 44% (27 of 62) within 21 days, and 35% (22 of 62) after 21 days. The primary causes of death in patients with postoperative neurological deterioration were cerebral infarction or cerebral edema (69%), pneumonia or acute respiratory failure (9%), sepsis or septic shock (9%), and pulmonary embolism (7%). There was 1 death attributed primarily to SAH, 1 attributed to anoxic brain injury, 1 to brain compression (herniation), and 1 to ventricular fibrillation.

Similar patterns were observed even in patients presenting in the best clinical condition (WFNS Grade I on admission): there was a 54.6% incidence of good recovery (GOS score 1) in patients with postoperative neurological deterioration versus 82% in those without postoperative neurological deterioration in this subgroup. The vegetative survival and death rates were 9.2% and 0.5%, respectively, among patients with a baseline WFNS grade of I. Other outcome measures showed consistent results among patients with a preoperative WFNS grade of I: 3-month NIHSS scores of 8 or more were present in 14.4% of the postoperative neurological deterioration group versus 1.9% in the no neurological deterioration group ($p < 0.001$). Three-month Rankin Scale scores of 2 or more were observed in 45.8% of the postoperative neurological deterioration group versus 16.3% of the no neurological deterioration group ($p < 0.001$). DIND was observed in 28.1% of the postoperative neurological deterioration group versus 12.9% of the no neurological deterioration group ($p < 0.001$), and 42.2% of patients with postoperative neurological deterioration were discharged home while 82.0% of patients without postoperative neurological deterioration were discharged home ($p < 0.001$).

To demonstrate the magnitude of the effect of postoperative neurological deterioration on outcome, with and without the presence of DIND, a flowchart shows the influence on 3-month GOS score (Fig. 6). In patients with no postoperative neurological deterioration and no occurrence of DIND, poor outcomes (GOS > 1) were observed in 21%, compared with 31% among patients with DIND and no postoperative neurological deterioration, 50% among patients with postoperative neurological deterioration and no DIND, and 63% among patients with both postoperative neurological deterioration and DIND (Fig. 6).

Discussion

The IHAST was designed to test the effectiveness of hypothermia as a neuroprotective intervention aimed at preventing neurological deterioration in patients with SAH who presented in good clinical grade. Hypothermia proved unsuccessful in preventing long-term (3-month GOS) poor outcomes.[20] Additionally, in a subset of 441 patients who underwent temporary clipping during aneurysm surgery in IHAST, neither hypothermia nor use of supplemental neuroprotective drugs (thiopental and etomidate) was effective in preventing poor outcomes, either in the short term (24-hour neurological examination) or long term (3-month GOS).[5] Thus we sought to explore the nature of the poor neurological outcomes encountered in IHAST and better understand what factors contributed to neurological deterioration in these patients.

Principal Findings

Among SAH patients presenting for surgery in good clinical condition (WFNS Grade I–III), a substantial portion of the neurological decline contributing to 3-month neurological outcome was observed in the immediate perioperative period, within 24 hours of surgery. Forty-six percent of patients with neurological deterioration 24 hours postoperatively went on to recover from this acute perioperative neurological injury. The most common manifestations of neurological deterioration at 24 hours after surgery were development of a new motor deficit or decline in GCS or NIHSS score. New nonmotor neurological deficits and DIND composed a smaller portion of the perioperative neurological deterioration.

The occurrence of postoperative neurological deterioration was found to be associated with many pre- and intraoperative factors. Several baseline characteristics, including age, preexisting abnormality in cardiac valve function, and Fisher grade on initial head CT, were associated with postoperative neurological deterioration. Several variables that likely indicate the overall severity of the patient's condition and comorbid cardiac dysfunction were also noted to be associated with occurrence of a postoperative neurological deterioration (difficulty of aneurysm exposure, systolic BP in the operating room, and occurrence of a procedure prior to aneurysm surgery). Finally, factors reflective of surgical and anesthetic management were also noted to predict occurrence of a

TABLE 1: Baseline characteristics by absence or presence of postoperative neurological deterioration at 24 hours*

Characteristic	No Neurol Deterioration (n = 574)	Neurol Deterioration (n = 426)	Total (n = 1000)	p Value†
mean age (yrs)	50 ± 12	54 ± 13	52 ± 13	<0.001
female sex	378 (66)	277 (65)	655 (66)	0.785
WFNS score				<0.001
I (GCS 15, no motor deficit)	411 (72)	249 (59)	660 (66)	
II (GCS 13 or 14, no motor deficit	148 (26)	141 (33)	289 (29)	
III (GCS 13 or 14, any motor deficit)	15 (3)	36 (9)	51 (5)	
baseline NIHSS score				<0.001
0	348 (61)	187 (44)	535 (54)	
1–7	180 (31)	195 (46)	375 (38)	
8–14	11 (2)	15 (4)	26 (3)	
15–42	1 (0.2)	7 (2)	8 (1)	
missing	34 (6)	22 (5)	56 (6)	
Fisher grade on 1st head CT‡				<0.001
1	39 (7)	15 (4)	54 (5)	
2	217 (38)	125 (29)	342 (34)	
3	265 (46)	209 (49)	474 (47)	
4	53 (9)	77 (18)	130 (13)	
hydrocephalus	201 (35)	194 (46)	395 (40)	0.001
medical history§				
abnormality in cardiac valvular function	2 (0.3)	7 (2)	9 (1)	0.032
abnormality in coronary circulation	22 (4)	31 (7)	53 (5)	0.022
hypertension	203 (35)	195 (46)	398 (40)	0.001
diabetes mellitus	17 (3)	24 (6)	41 (4)	0.037
presenting signs/symptoms				
loss of consciousness at time of SAH	152 (27)	140 (33)	292 (30)	0.029
speech disorder at initial presentation	40 (7)	51 (12)	91 (9)	0.008
focal or lateralized motor deficit	59 (10)	64 (15)	123 (12)	0.025
right LE motor deficit	21 (4)	33 (8)	54 (5)	0.007
right UE motor deficit	20 (4)	27 (6)	47 (5)	0.048

* Values represent numbers of patients (%) except where otherwise indicated. Means are presented ± SDs. Abbreviations: LE = lower extremity; Neurol = Neurological; UE = upper extremity.

† Fisher exact test, Wilcoxon rank-sum test.

‡ Grade 1: no subarachnoid blood. Grade 2: diffuse subarachnoid blood or thin layer with all vertical layers < 1 mm thick. Grade 3: localized subarachnoid clot and/or vertical layers ≥ 1 mm thick. Grade 4: diffuse (thin layer) or no subarachnoid blood, but with intraparenchymal or intraventricular clot.

§ Occlusive cerebrovascular disease, prior ischemic stroke, myocardial infarction, and lower extremity claudication were found more frequently in the histories of patients in the neurological deterioration than in the no neurological deterioration group (< 5%).

postoperative neurological deterioration, such as use of intentional hypotension, prolonged duration of temporary arterial occlusion, blood loss, and timing of surgery (interval between SAH and surgery). Notably, surgery on Days 4, 5, and 6 following SAH (Day 0 being the day of SAH) was associated with higher rates of neurological deterioration. While blood loss and prolonged temporary arterial occlusion may arguably be more indicative of the complexity of the aneurysm treated or of intraoperative rupture and less of surgical management or decision making, the strong association with postoperative neurological deterioration is notable.

An important and not unexpected finding of this study is the association between the occurrence of postoperative neurological deterioration and long-term outcome. Patients with postoperative neurological deterioration had much less favorable outcomes as indicated by GOS and all other outcome measures. This trend was observed even in the patients whose condition was classified as "best grade"—that is, those who presented with a WFNS grade of I. This strongly implicates the operative and perioperative period as a direct contributor to long-term neurological outcomes.

Significance of the Perioperative Period

While several studies have supported the relationship between baseline characteristics and intraoperative factors with long-term outcome, few have directed attention

TABLE 2: Preoperative status, events, and procedures*

Characteristic	No Neurol Deterioration (n = 574)	Neurol Deterioration (n = 426)	Total (n = 1000)	p Value†
time to surgery (days)				0.0623
0–1	219 (38)	149 (35)	368 (37)	
2	112 (20)	72 (17)	184 (18)	
3	77 (13)	50 (12)	127 (13)	
4	47 (8)	51 (12)	98 (10)	
5–6	44 (8)	51 (12)	95 (10)	
7–14	74 (13)	53 (12)	127 (13)	
WFNS score (at time of anesthesia induction)				<0.001
I (GCS 15, no motor deficit)	455 (80)	282 (66)	737 (74)	
II (GCS 13 or 14, no motor deficit)	109 (19)	119 (28)	228 (23)	
III (GCS 13 or 14, any motor deficit)	10 (2)	25 (6)	35 (4)	
preoperative events				
development of significant dysrhythmia	10 (2)	18 (4)	28 (3)	0.021
patient had fever >38.5°C	20 (4)	29 (7)	49 (5)	0.018
preoperative procedures				
endotracheal intubation	30 (5)	39 (9)	69 (7)	0.017
any other diagnostic procedure	75 (13)	99 (23)	174 (17)	<0.001
procedure associated w/ intercurrent event	37 (6)	73 (17)	110 (11)	<0.001
surgical procedure since hospitalization	24 (4)	41 (10)	65 (7)	0.001
any other intercurrent event since hospitalization	17 (3)	28 (7)	45 (5)	0.008

* Values represent numbers of patients (%) except where otherwise indicated.
† Chi-square test, Fisher exact test.

TABLE 3: Intraoperative events by absence or presence of postoperative neurological deterioration at 24 hours*

Characteristic	No Neurol Deterioration (n = 574)	Neurol Deterioration (n = 426)	Total (n = 1000)	p Value†
brain swelling at dural opening‡				0.031
none	218 (38)	144 (34)	362 (36)	
slight	157 (27)	112 (26)	269 (27)	
moderate	176 (31)	136 (32)	312 (31)	
severe	22 (4)	34 (8)	56 (6)	
information unavailable	1 (0.2)	0 (0)	1 (0.1)	
mean preinduction systolic BP (mm Hg)	145 ± 22	150 ± 24	147 ± 23	0.004
preinduction ST segment depression ≥1 mm	5 (1)	13 (3)	18 (2)	0.014
preinduction abnormal T wave inversion, any lead	35 (6)	47 (11)	82 (8)	0.007
parent vessel angiographic vasospasm	42 (7)	49 (12)	91 (9)	0.026
intraoperative aneurysm leak or rupture	161 (28)	156 (37)	317 (32)	0.005
mean estimated blood loss (ml)	359 ± 247	507 ± 515	422 ± 391	<0.001
blood loss ≥1000 ml	17 (3)	46 (11)	63 (6)	<0.001
mean urine output (ml)	1821 ± 1208	1924 ± 1133	1865 ± 1177	0.045
new signs of neurological injury§	0 (0)	106 (25)	106 (11)	<0.001
new major abnormality of Na, K, glucose levels§	10 (2)	3 (1)	13 (1)	0.050
anemia§	10 (2)	28 (7)	38 (4)	<0.001
recurrent SAH§	0 (0)	4 (1)	4 (0.4)	0.030

* Values represent numbers of patients (%) except where otherwise indicated. Means are presented ± SDs.
† Fisher exact test, Wilcoxon rank-sum test.
‡ Surgeons rated the degree of brain swelling at initial dural opening on a 4-point scale: 0 = no swelling, 1 = slight swelling, no treatment needed; 2 = moderate swelling, treatment needed but no delay in surgery encountered; 3 = severe swelling requiring treatment and delaying surgery for more than 10 minutes.
§ Occurred intraoperatively or within 2 hours of patient's leaving operating room.

TABLE 4: Intraoperative procedures and procedure-related characteristics by absence or presence of postoperative neurological deterioration at 24 hours*

Characteristic	No Neurol Deterioration (n = 574)	Neurol Deterioration (n = 426)	Total (n = 1000)	p Value†
supplemental O_2 on arrival in operating room	113 (20)	117 (28)	230 (23)	0.005
retrograde jugular venous catheter used	24 (4)	45 (11)	69 (7)	<0.001
ICP monitor in place	10 (2)	19 (5)	29 (3)	0.013
lumbar drain used during op	168 (30)	151 (35)	319 (32)	0.040
ease of aneurysm exposure				<0.001
easy	120 (21)	67 (16)	187 (19)	
moderate	284 (50)	174 (41)	458 (46)	
difficult	122 (21)	120 (28)	242 (24)	
very difficult	47 (8)	64 (15)	111 (11)	
information unavailable	1 (0.2)	1 (0.2)	2 (0.2)	
intracranial ICA occlusion				
no. of patients‡	50	39	89	
mean duration of occlusion (min)	8 ± 10	12 ± 10	10 ± 10	0.003
temporary clip use	246 (43)	199 (47)	445 (45)	0.222
mean duration of temporary clip application (min)§	10 ± 10	12 ± 11	10 ± 11	0.0244
duration of temporary clip application				0.0069
≤10 min	161 (66)	118 (60)	279 (63)	
11–19 min	62 (25)	42 (21)	104 (24)	
≥20 min	21 (9)	37 (19)	58 (13)	
ACA occlusion				
no. of patients‡	117	99	216	
mean duration (min)	9 ± 6	12 ± 9	11 ± 8	0.014
intentional use of hypotension	16 (3)	30 (7)	46 (5)	0.002
mean total crystalloid vol in ml	3398 ± 1474	3772 ± 1724	3557 ± 1595	0.001
fresh frozen plasma				0.020
no. of patients	4 (1)	5 (1)	9 (1)	
mean vol (ml)	315 ± 175	972 ± 455	680 ± 485	
intubated on arrival to postop area	202 (35)	217 (51)	419 (42)	<0.001
mean duration of op (min)	306 ± 92	340 ± 114	320 ± 101	<0.001
required reintubation¶	2 (0.3)	14 (3)	16 (2)	<0.001
underwent unplanned surgery¶	0 (0)	6 (1)	6 (1)	0.006
cerebral angiogram performed¶	15 (3)	77 (18)	92 (9)	<0.001
vasopressors used to support systemic circulation¶	28 (5)	54 (13)	82 (8)	<0.001
intubated or tracheostomy at 2 hrs postop	60 (11)	131 (31)	191 (19)	<0.001

* ACA = anterior cerebral artery; ICA = internal carotid artery; ICP = intracranial pressure.

† Fisher exact test, Wilcoxon rank-sum test, chi-square test.

‡ Number of patients in whom data were available. For both intracranial ICA and ACA occlusion, data were not available in 1 patient in the no neurological deterioration group. Data were available in all patients who underwent intracranial ICA and ACA occlusion in the neurological deterioration group.

§ Based on 445 patients (data were not available for 2 patients in each group).

¶ Occurred intraoperatively or within 2 hours of patient's leaving operating room.

to neurological deterioration occurring in the immediate perioperative period and implications of such deterioration on outcome. In the International Cooperative Study on the Timing of Aneurysm Surgery, causes of morbidity and mortality were collected and reported. Along with initial SAH, rebleeding, and vasospasm, surgical complication was noted to be a significant cause of death and disability in patients with ruptured cerebral aneurysms, especially in patients undergoing surgery on Days 7–10 post-SAH.[7] In a 1991 study, Öhman et al.[13] reported the causes of permanent deficits in a prospective series of 265 "good-grade" (Hunt and Hess Grades I–III) aneurysmal SAH patients. Following delayed cerebral ischemia and severity of the initial hemorrhage, permanent deficits attributable to surgery were reported in 3%. Ljunggren et al.[9] also recognized surgical trauma as a major cause of poor outcome and in a series of 160 good grade aneurysmal SAH patients found that 7% had poor outcomes

TABLE 5: Final logistic regression model—predictors of postoperative neurological deterioration at 24 hours

Characteristic	OR	95% CI	p Value
age	1.026	1.013–1.039	<0.0001
Hx of abnormality in cardiac valve function	7.743	1.072–55.921	0.0425
Fisher grade on 1st head CT			0.0039
1 (no SAH blood)	1	(reference)	
2 (diffuse blood)	1.728	0.811–3.679	
3 (localized clot or thick layer)	2.184	1.032–4.622	
4 (intraparenchymal or ventricular clot)	3.594	1.586–8.144	
procedure prior to aneurysm surgery	2.450	1.515–3.961	0.0003
center	—	—	<0.0001
interval from SAH to surgery (days)			0.0240
0–1	1	(reference)	
2	0.977	0.633–1.509	
3	0.807	0.482–1.349	
4	1.848	1.071–3.188	
5–6	1.919	1.103–3.340	
7–14	1.308	0.770–2.220	
intraop variables			
preinduction systolic BP	1.013	1.006–1.020	0.0003
intentional intraop hypotension	2.310	1.084–4.923	0.0301
blood loss	1.001	1.001–1.001	<0.0001
duration of temporary clip application ≥20 min	1.977	1.030–3.796	0.0405
difficulty of aneurysm exposure			0.0029
easy	1	(reference)	
moderate	1.032	0.687–1.551	
difficult	1.857	1.170–2.949	
very difficult	1.926	1.070–3.467	

attributable to surgery (in addition to 11% attributable to delayed ischemic deficit and 4% attributed to severity of initial hemorrhage). Post et al.[14] reported higher rates of surgical morbidity and mortality, with moderate postoperative neurological deficit or death in 35% of 86 surgically treated aneurysmal SAH patients (30% in good grade). However, mortality comprised a large component of these poor outcomes (8% overall, 6% in good grade). We found, in a more contemporary series with lower mortality rates, a much higher rate of poor outcomes resulting from neurological deterioration in the operative/perioperative period. It is important to recognize that this higher rate of postoperative neurological deterioration is likely related to the intensive prospective manner in which the data were collected, compared with retrospective series, and may reflect more accurately the patterns of morbidity in contemporary neurosurgical care.

Other studies have directed attention to operative factors relating to poor outcomes. In a 2008 study, Chong et al.[1] focused on intraoperative and perioperative factors contributing to poor clinical outcome and development of cerebral infarction, noting duration of temporary vessel occlusion, intraoperative hypotension, and intraoperative hypoxemia to be independently associated with cerebral infarction at 6 months in a multiple logistic regression analysis. Several studies have also addressed risks associ-

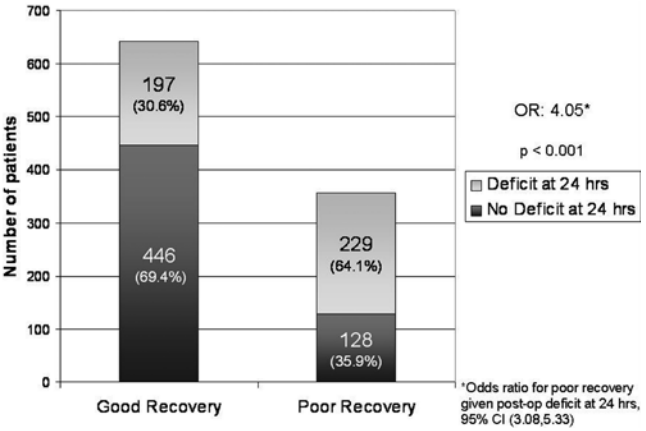

Fig. 4. Postoperative neurological deterioration and GOS. Graph showing the distribution of patients with postoperative neurological deterioration by outcome (GOS = 1 or GOS > 1) in patients with or without postoperative neurological deterioration at 24 hours). "Deficit at 24 hrs" is equivalent to new postoperative neurological deterioration and "no deficit at 24 hrs" is equivalent to no new postoperative neurological deterioration.

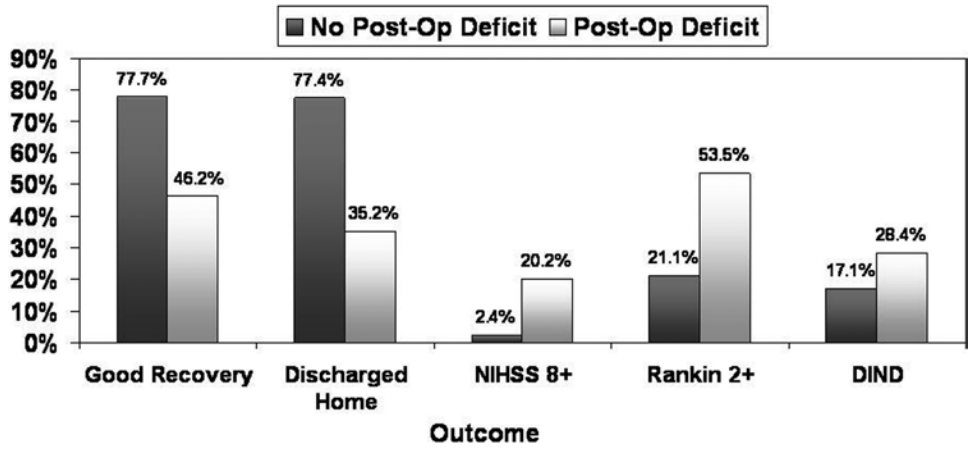

Fig. 5. Postoperative neurological deterioration and outcome. Graph showing the distribution of patients without and with postoperative neurological deterioration by various measures of outcome. Percentages correspond to the percentage of patients without (N = 574) and with (N = 426) neurological deterioration at 24 hours postoperatively with each outcome measure.

ated with use and prolonged duration of temporal vessel occlusion during aneurysm surgery.[5,19]

While these studies demonstrate the relationship between operative factors and outcome, they do not explore the timing of neurological decline and whether operative factors are associated with acute postoperative neurological deterioration. Very few studies have gone beyond assessment of operative factors and outcome to demonstrate a relationship between intraoperative factors and acute postoperative neurological decline. In 1995 Proust et al.[15] discussed postoperative thrombosis detected by catheter angiography as a major cause of postoperative deterioration in patients with ruptured cerebral aneurysms admitted in good clinical condition (Hunt and Hess Grades I–III). In this study, postoperative thrombosis was noted as a cause of postoperative deterioration more frequently than vasospasm or surgical trauma from prolonged retraction. Postoperative thrombosis was also reported, af-

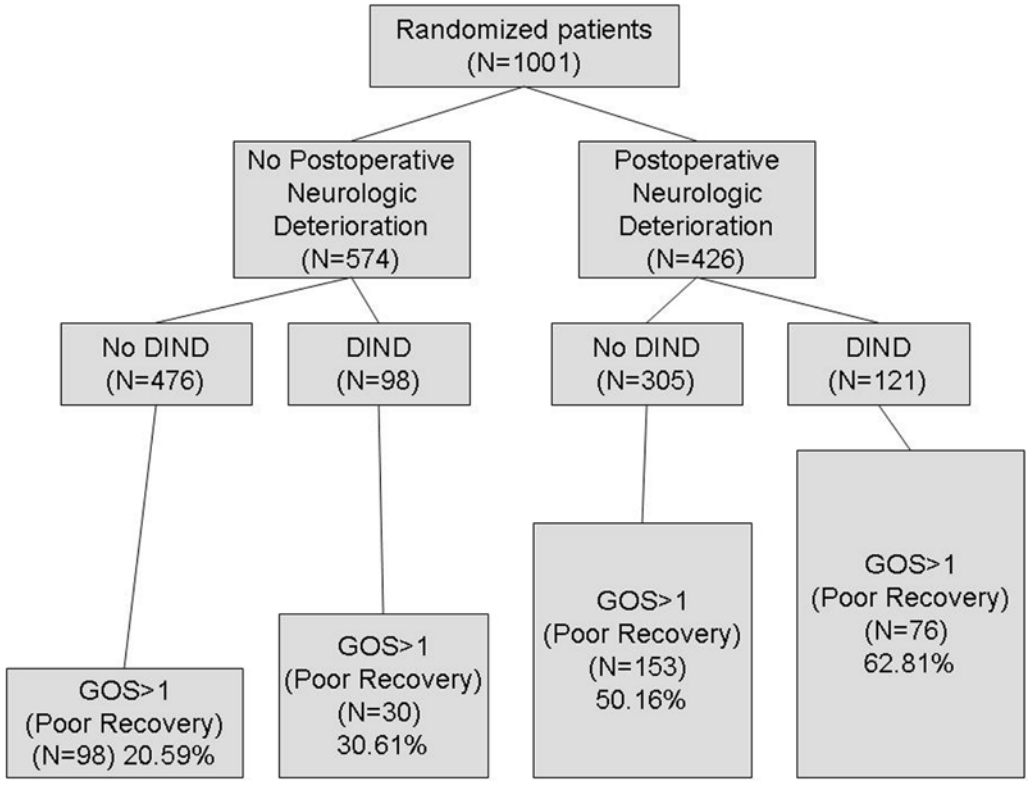

Fig. 6. Flowchart: enrollment to outcome. The flowchart demonstrates the proportion of patients with DIND and poor outcomes in the groups with and without postoperative neurological deterioration. Outcomes of 1000 patients with 3-month follow-up are shown: 1033 patients were enrolled, 1001 were randomized, and 1 was lost to follow-up at 3 months.

ter initial hemorrhage, as a more significant contributor to morbidity and mortality in patients with an SAH than vasospasm.

In exploring the etiology and outcome of postoperative neurological deterioration, this study demonstrates that 1) certain patients do not appear to tolerate anesthesia and surgery well (older patients and those with more significant hemorrhage or difficult aneurysm location) and 2) several operative factors may make an otherwise clinically good-grade patient more vulnerable to neurological insult at the time of surgery. Patients who tolerate surgery poorly (based on baseline characteristics) are older and have more significant initial hemorrhage (as evidenced by Fisher grade and difficulty of aneurysm exposure). These factors have been demonstrated previously to be strongly associated with outcome.[8,18] However, this study further demonstrates that the neurological deterioration in these patients may occur in association with surgery and may not reflect initial and preoperative clinical presentation, as all patients in IHAST were in good neurological condition preoperatively. This study also demonstrates that, independent of age or severity of hemorrhage, patients may be vulnerable to neurological deterioration if they undergo surgery during an intermediate time interval (4–6 days post-SAH) or in the presence of certain comorbidities. Patients who had underlying cardiac dysfunction (either preexisting, such as abnormality in valve function or potentially related to SAH, such as ST depression occurring intraoperatively), who were noted to have increased systolic BP at induction, or who were subjected to intentional hypotension intraoperatively did not tolerate surgery well—as evidenced by higher rates of new postoperative neurological deficit. Additionally, although in general, use of temporary arterial occlusion did not predispose to postoperative neurological deterioration, those patients exposed to prolonged (> 20 minutes) temporary arterial occlusion did have a higher risk of neurological deterioration. This is also not likely related to the presence of preoperative vasospasm, as very few patients were noted to have delayed ischemic deficit preoperatively, and all patients were in good clinical condition prior to surgery. However impaired autoregulation, which is known to occur following SAH,[3,21] may contribute to the vulnerability at surgery of those patients with an underlying cardiac dysfunction or those undergoing surgery 4–6 days post-SAH.

Implications for Management and Future Directions for Investigation

The findings of this study have implications not only for guiding surgical management of ruptured intracranial aneurysms but also for directing future investigations in SAH. This study emphasizes that aspects of care in the operating room are directly related to occurrence of neurological deterioration. For example, avoiding use of intentional hypotension and prolonged temporary vessel occlusion as well as minimizing blood loss may improve outcomes. Furthermore, the development of neuroprotective agents and management practices may reduce morbidity and mortality in patients with SAH by avoiding neurological injury that occurs in the perioperative period. The findings from this study contribute to our understanding of the perioperative period as a major contributor to neurological outcomes and validate efforts to advance neuroprotection in SAH.

Relevance of the Perioperative Period in the Endovascular Era

Understanding which patients are not likely to tolerate surgery well and the factors that contribute to poor surgical outcomes is of particular importance in an era in which endovascular treatment of cerebral aneurysms is becoming increasingly more common and more widely available. In 2002, the ISAT demonstrated decreased incidence of death and dependent survival at 2 months and 1 year in mostly good-grade SAH patients undergoing endovascular treatment of a ruptured intracranial aneurysm, compared with patients treated with neurosurgical clipping.[12] While there is clear evidence that, for patients similar to those included in ISAT, endovascular treatment is preferable to surgical treatment, this finding is not uniformly generalizable to all patients with aneurysmal SAH. There will continue to be a subset of patients for which endovascular treatment is either unavailable or does not represent the best treatment option. Perhaps especially for these patients, avoiding postoperative neurological deterioration and developing new strategies for neuroprotection will be critical to improving outcomes. Improving outcomes in SAH will be an evolution in tailoring the appropriate treatment modality on a patient-to-patient basis and minimizing the periprocedural risks of treatment, whether in the operating room or the endovascular suite.

In contrast to several retrospective studies addressing outcomes in patients with SAH and perioperative morbidity, this study benefits from the prospective and prespecified, protocol-driven data collection of a clinical trial, which enhances the completeness and validity of the data. Additionally, the strength of a study focusing on the perioperative time period is the potential to demonstrate critical clinical factors that may impact outcome. Many studies of SAH have focused on other factors affecting outcome, such as initial clinical and radiographic presentations and DIND. The IHAST has a unique advantage as a study that was designed with a focus on the perioperative period. Also, by limiting the trial to patients in good neurological condition on admission and preoperatively, IHAST was able to differentiate poor outcomes related to subsequent clinical and perioperative events from outcomes associated with severity of initial hemorrhage.

The study is limited by the fact that hemodynamic parameters that may affect neurological outcome, such as cerebral blood flow, were not measured in the study. As the study was a trial of hypothermia and did not randomize with respect to the factors which may be related to occurrence of postoperative deterioration, the presence of an unmeasured confounder cannot be excluded.

Conclusions

As evidenced by the time course of neurological deficit in IHAST, the major determinant of 3-month out-

comes in good-grade SAH patients undergoing surgery for aneurysmal SAH is neurological deterioration related to events occurring during surgery or immediately postoperatively. Avoiding surgical factors associated with occurrence of postoperative neurological deterioration and directing investigative efforts at developing improved neuroprotection for use in aneurysm surgery may significantly improve long-term neurological outcomes in SAH.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Mahaney, Todd, Torner. Acquisition of data: Todd, Torner. Analysis and interpretation of data: all authors. Drafting the article: Mahaney, Torner. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Mahaney. Statistical analysis: Bayman. Study supervision: Todd, Torner.

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