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Mild Hypothermia as a Protective Therapy during Intracranial Aneurysm Surgery: A Randomized Prospective Pilot Trial

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Abstract

OBJECTIVE: To conduct a pilot trial of mild intraoperative hypothermia during cerebral aneurysm surgery.

METHODS: One hundred fourteen patients undergoing cerebral aneurysm clipping with (n = 52) (World Federation of Neurological Surgeons score <=III) and without (n = 62) acute aneurysmal subarachnoid hemorrhage (SAH) were randomized to normothermic (target esophageal temperature at clip application of 36.5°C) and hypothermic (target temperature of 33.5°C) groups. Neurological status was prospectively evaluated before surgery, 24 and 72 hours

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postoperatively (National Institutes of Health Stroke Scale), and 3 to 6 months after surgery (Glasgow Outcome Scale). Secondary outcomes included postoperative critical care requirements, respiratory and cardiovascular complications, duration of hospitalization, and discharge disposition.

RESULTS: Seven hypothermic patients (12%) could not be cooled to within 1°C of target temperature; three of the seven were obese. Patients randomized to the hypothermic group more frequently required intubation and rewarming for the first 2 hours after surgery. Although not achieving statistical significance, patients with SAH randomized to the hypothermic group, when compared with patients in the normothermic group, had the following: 1) a lower frequency of neurological deterioration at 24 and 72 hours after surgery (21 versus 37-41%), 2) a greater frequency of discharge to home (75 versus 57%), and 3) a greater incidence of good long-term outcomes (71 versus 57%). For patients without acute SAH, there were no outcome differences between the temperature groups. There was no suggestion that hypothermia was associated with excess morbidity or mortality.

CONCLUSION: Mild hypothermia during cerebral aneurysm surgery is feasible in nonobese patients and is well tolerated. Our results indicate that a multicenter trial enrolling 300 to 900 patients with acute aneurysmal SAH will be required to demonstrate a statistically significant benefit with mild intraoperative hypothermia.

The use of moderate systemic hypothermia ([approximately equal to]30°C) to protect the brain during cerebral aneurysm surgery was first described in the mid 1950s (3,4,39). However, by the early 1960s, the benefits of intraoperative hypothermia were questioned (24). This, coupled with the generally poor outcomes associated with deep hypothermia and circulatory arrest (13,45,57), discouraged the use of hypothermia during cerebral aneurysm surgery for the next 2 decades.

During the last 10 years, mild to moderate hypothermia (30-34°C) has been repeatedly demonstrated to reduce neurological injury in animal models of temporary forebrain (8,12,46,52) and focal cerebral ischemia (21,30,50), as well as in animal models of traumatic brain injury (5,10,48). This has led to renewed interest in the application of hypothermia during cerebral aneurysm surgery, as well as in the management of closed head injury (43,44,55). Although mild intraoperative hypothermia is again often used during cerebral aneurysm surgery, clinical efficacy has not been established. This is particularly disturbing in view of several recent clinical studies that demonstrate the multiple adverse effects of very mild intraoperative hypothermia (35.5°C), such as increased intraoperative blood loss (53), delayed emergence from anesthesia (37), and increased rates of postoperative cardiovascular complications (17,18) and wound infection (35). Although none of these later studies were conducted in neurosurgical patients, the neurological benefit of mild intraoperative hypothermia during cerebral aneurysm surgery remains largely theoretical, whereas the potential for harm in other organ systems is better established. Therefore, a clinical trial is needed to demonstrate the neurological benefits and/or associated risks of mild intraoperative hypothermia during cerebral aneurysm surgery.

This report describes the pilot phase of such a study. Our goals were as follows: 1) to assess the practical aspects of inducing

and reversing mild intraoperative hypothermia during cerebral aneurysm surgery; 2) to screen for any major beneficial or adverse effect of hypothermia on outcome; and 3) on the basis of these findings, to establish selection criteria, methodology, and projected sample sizes for future studies.

PATIENTS AND METHODS

The study population consisted of 114 patients undergoing craniotomies for cerebral aneurysm clipping at five academic medical centers during the 17-month period between October 31, 1994, and July 23, 1996. The protocol for this study was approved by the institutional review boards at each institution, and written informed consent was obtained from each patient or a family member.

During the study interval, all patients undergoing craniotomies for cerebral aneurysm surgery were serially evaluated for study eligibility. To be eligible, patients with intracranial aneurysms (with or without acute subarachnoid hemorrhage [SAH]) were required to have a prehospitalization/pre-SAH Rankin disability score of 0 or 1 (58). Patients with acute SAH were required to have a preoperative World Federation of Neurological Surgeons (WFNS) score of I, II, or III (14). Patients were not eligible if any of the following conditions existed: 1) they were endotracheally intubated when evaluated for study enrollment; 2) they had cryoglobulinemia, severe Raynaud's disease, sickle-cell disease, or another disorder considered to contraindicate hypothermia; or 3) they were entered in a blinded trial of any drug that could affect neurological outcome. Cardiovascular disease was not an exclusion criterion. At the time of enrollment, standardized preoperative neurological assessments were conducted; WFNS scores and National Institutes of Health Stroke Scale (NIHSS) scores were obtained (40). The assessments were conducted by examiners trained and certified in the use of the appropriate instruments (see below), who were unaware of any other aspect of the patient's care, including group assignment. Preoperative 12-lead electrocardiograms and blood samples for the measurement of creatinine kinase with MB isoenzymes were also obtained. For patients with acute SAH, preoperative cranial computed tomography reports were reviewed and Fisher scores (16) were assigned post hoc.

The initial operating room temperature was 20 to 22°C, and a cooling/heating mattress on which the patient lay was preset for 37°C. At the time of the patient's arrival to the operating room, a WFNS score of III or less was confirmed and a preinduction tympanic or sublingual temperature was recorded. Standard monitors included a lead II electrocardiograph, pulse oximeter, capnograph, automated blood pressure cuff, and continuous intra-arterial blood pressure monitor. Anesthesia was induced with either intravenous thiopental, etomidate, or propofol and then muscle relaxation and endotracheal intubation. Anesthesia was maintained with fentanyl, isoflurane, and up to 60% nitrous oxide. After intubation, a combination esophageal stethoscope/temperature probe (Mallinckrodt Medical Inc., St. Louis, MO) was placed into the esophagus to monitor the core temperature; this was the primary temperature monitor. Secondary temperature monitors included nasopharyngeal or rectal temperature monitors. After lumbar drain insertion (if used), pin placement, and final positioning, the patient was covered with a forced air cooling/heating blanket (Warm Touch, Mallinckrodt Medical Inc.). At that point, a previously sealed envelope containing group assignment was opened by the anesthesiologist. The envelopes were prepared by the coordinating center (University of Iowa). Each participating center was provided with 30 sequentially numbered envelopes containing cards randomized to allow enrollment of 15 patients to each temperature group

at each center.

In patients assigned to the normothermic group, the following procedures were used to achieve and maintain a target esophageal temperature of 36.5°C: 1) the cooling/heating mattress was set to 38°C, 2) the forced air cooling/heating blanket was set to 36 to 38°C, and 3) intravenous fluids and inspired anesthetic gases were warmed to 37°C. In patients assigned to the hypothermic group, the following procedures were used to achieve a target esophageal temperature of 33.5°C by the time of clip application: 1) the cooling/heating mattress was set to 20°C, 2) the forced air cooling/heating blanket was set to deliver unwarmed (room temperature) air, and 3) intravenous fluids and anesthetic gases were not warmed.

Group assignment and intraoperative temperature were not revealed to the neurosurgical team during surgery. When the dura was opened, a semiquantitative assessment of brain swelling was made by the neurosurgical team. A brain swelling score of 1 denoted no swelling and excellent operative conditions, whereas a score of 4 denoted swelling so severe as to require a delay in surgery until additional therapies improved conditions (e.g., administration of mannitol, cerebro-spinal fluid drainage, altered position, hyperventilation). Although recorded, the use of induced hypotension, temporary clips, and/or pharmacological cerebral protection were not dictated by protocol but were used as deemed appropriate by the neurosurgical and anesthesia teams. The core temperature at the time of clip application was recorded.

At the time of clip application, patients assigned to the hypothermic group were rewarmed as rapidly as possible by the following procedures: 1) the cooling/heating mattress was set to 40°C, 2) the forced air cooling/warming blanket was set to 41°C, and 3) intravenous fluids and anesthetic gases were warmed (39°C). At completion of the head dressing, anesthetics and muscle relaxants were discontinued. Patients with core temperatures less than or equal to 35.5°C typically remained intubated, while forced air warming continued in recovery areas (recovery room or intensive care unit). Extubation criteria were not dictated by protocol, but intubation status as the time of arrival in recovery areas and on postoperative Days 1 through 3 was recorded. Twelve-lead electrocardiograms and creatinine kinase isoenzymes were obtained on postoperative Days 1 through 3, and diagnosis of myocardial infarction was made on the basis of local criteria. All patients were prospectively followed until the time of discharge, and all major perioperative complications, such as death, respiratory failure, reintubation, subsequent bleeding, and reoperation, were recorded.

On postoperative Days 1, 3, and 7, neurological status was again evaluated by a trained examiner who was not aware of group assignment. Both WFNS and NIHSS scores were assigned. All examiners had passed video training examinations (provided by Henry Ford Hospital, Detroit, MI) (40). An increase of 4 or more points on the NIHSS compared with the preoperative score was considered to denote a significant deterioration in neurological status (6,22). Three to 6 months after surgery, a final outcome assessment was made using the Glasgow Outcome Scale (29).

Statistics

All results are expressed as either percentages or median ± interquartile (25-75%) range. Intergroup differences in the incidence of various events were assessed using contingency table analysis. Mann-Whitney testing was used to examine differences in nonparametric data.

RESULTS

One hundred fourteen patients were randomized. One center withdrew from the study after entering 4 patients, and completed records for 20 patients were received from a second center. The three other centers each contributed 30 patients. Fifty-seven patients were randomized to each temperature group. As summarized in Table 1, there were no important differences between temperature groups in age or weight. Prognostic variables and clinical outcomes for patients with (n = 52) and without (n = 62) acute SAH were assessed separately.

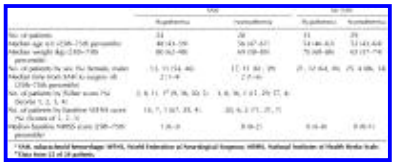

TABLE 1. Demographic and Preoperative Data[a]

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In patients with acute SAH, temperature groups did not differ with respect to the following: 1) interval from SAH to operation, 2) distribution of Fisher scores, and 3) baseline WFNS and NIHSS scores. Although patients without acute SAH (i.e., elective aneurysm repair) had few overt preoperative neurological abnormalities (51 of 62 had a preoperative NIHSS score of zero), many had histories of neurological disease. Specifically, 29% had experienced previous SAH and surgery for either cerebral aneurysms or arteriovenous malformations (median interval from previous surgery to study entry, 4 mo); 10% had histories of non-SAH stroke; and another 10% had histories of seizures. The distribution of these conditions among patients without acute SAH did not differ between temperature groups.

The perioperative data are summarized in Table 2. All patients were normothermic before undergoing anesthetic induction. Not surprisingly, greater brain swelling was noted in patients with acute SAH than in those without. As intended, at the time of clip application, patients assigned to the hypothermia group were significantly colder than those assigned to the normothermia group, with median temperatures of 33.7 versus 36.6°C, respectively ($P < 0.0001$). The core temperatures of 88% of the patients assigned to the normothermia group (SAH and non-SAH patients combined) were within 0.5°C of the target temperature at the time of clip application (i.e., >=36.0°C), and the core temperatures of 95% were within 1.0°C of the target. In contrast, the core temperatures of only 72% of the patients assigned to the hypothermic group were within 0.5°C of the target temperature at the time of clip application (i.e., <=34.0°C), and the core temperatures of 88% were within 1.0°C of the target. The hypothermic and normothermic groups did not differ with respect to the following: 1) use of induced hypotension, 2) use or duration of temporary clipping, and 3) use of supplemental pharmacological cerebral protection. The estimated intraoperative blood loss did not differ between temperature groups.

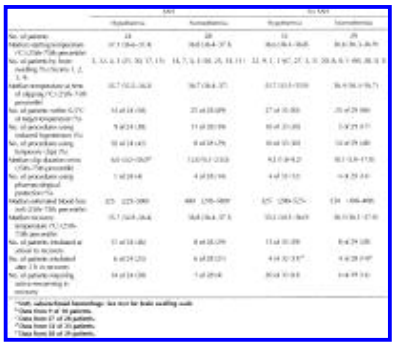

TABLE 2. Perioperative Data[a]

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At the time of the patients' arrival in the recovery areas (recovery room or intensive care unit), patients assigned to the hypothermic group were significantly colder than those assigned to the normothermia group, with median temperatures of 35.6 versus 36.6°C, respectively. Sixty percent of the hypothermic group patients received forced air warming during recovery, compared with 9% of the normothermic group patients. A greater percentage of patients assigned to the hypothermia group required continued mechanical ventilation at the time of their arrival in the recovery areas as compared with patients assigned to the normothermia group (42 versus 28%, respectively) ($P < 0.06$). However, by 2 hours after arrival in the recovery areas, the percentage of intubated patients in the two temperature groups did not differ ([approximately equal to]19%).

Neurological outcomes for patients with acute SAH

Among patients with acute SAH (n = 52), three in-hospital deaths occurred; one patient in the hypothermic group died on postoperative Day 84, and two patients in the normothermic group died on postoperative Days 1 and 9, respectively. These deaths were on a neurological basis, resulting either from cerebral infarction or bleeding from another cerebral aneurysm. As shown in Table 3, temperature groups did not differ at 24 or 72 hours after surgery in median NIHSS scores. However, at both 24 and 72 hours after surgery, a numerically smaller percentage of patients assigned to the hypothermia group had increases in NIHSS scores of 4 points or more than did patients assigned to the normothermia group (21 versus 37-41%, respectively) (P = not significant [NS]). The incidence of delayed ischemic neurological deficit did not differ between temperature groups (50-60%). Nevertheless, a numerically smaller percentage of patients in the hypothermia group were considered to have a resultant neurological deficit at the time of discharge compared with patients in the normothermic group (17 versus 37%, respectively) (P = NS). In addition, patients with acute SAH assigned to the hypothermia group had a numerically greater frequency of discharge to home (as opposed to another acute care hospital or chronic care facility) than those assigned to the normothermia group (75 versus 57%, respectively) (P = NS). None of the patients with acute SAH were lost to follow-up. Two deaths occurred between the time of discharge and the time of the final follow-up examination in patients with acute SAH. One patient, who had been assigned to the hypothermia group, died 6 months after surgery as a result of a new aneurysmal SAH. The other death occurred in a patient who had been assigned to the normothermia group. She suffered an acute cardiopulmonary arrest 2 weeks after surgery, with no evidence of acute intracranial pathological abnormality. At the 3- to 6-month follow-up examinations, patients with acute SAH who had been assigned to the hypothermia group had a numerically greater incidence of good outcomes than did those assigned to the normothermia group (71 versus 57%, respectively)

(*P* = NS).

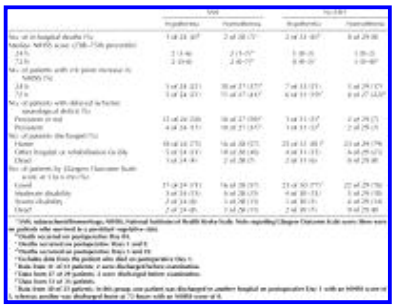

TABLE 3. Neurological Outcomes[a]

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Neurological outcomes for patients without acute SAH

Among patients without acute SAH (n = 62), two in-hospital deaths occurred; each patient had been assigned to the hypothermia group. These two deaths occurred on postoperative Days 5 and 22, respectively, and both resulted from cerebral infarction. There were no difference between temperature groups in NIHSS scores at 24 and 72 hours nor in the percentage of patients with increases in NIHSS of 4 points or more (17-21%) (Table 3). The diagnosis of delayed ischemic neurological deficit was very uncommon in these patients. The frequency of discharge to home (79-81%) was not affected by temperature assignment. There were no known deaths between the time of discharge and the time of the final follow-up examination, but three patients without acute SAH were lost to follow-up (all had been assigned to the hypothermia group and were neurologically normal at the time of discharge). In patients without acute SAH, there was no difference between temperature groups in final outcome, with 76 to 77% experiencing good outcomes.

Other outcomes/complications

As anticipated, both the duration of hospitalization and the frequency of most postoperative complications were greater for patients with acute SAH compared with those without acute SAH (Table 4). Nevertheless, in patients with and without SAH, temperature assignment did not seem to influence the incidence of the following: 1) endotracheal intubation at 24 and 72 hours, 2) need for intensive care at 24 and 72 hours, 3) postoperative pneumonia and/or other respiratory complications, 4) postoperative cardiovascular complications, 5) postoperative hydrocephalus or brain swelling (or need for treatment), or 6) duration of hospitalization. Although 6% of the patients were considered to have evidence of myocardial ischemia, the diagnosis of myocardial infarction was not made in any patient. This study was largely completed before any reports demonstrating an association between hypothermia and wound infection were made. Therefore, wound infections were not prospectively sought in this trial.

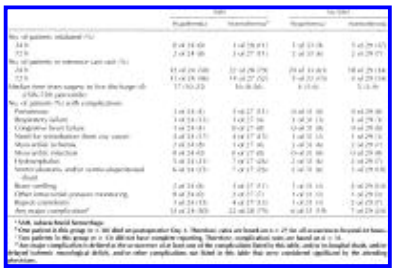

TABLE 4. Other Outcomes/ Complications[a]

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DISCUSSION

This study demonstrates the feasibility and apparent safety of mild intraoperative hypothermia during cerebral aneurysm surgery. There is no suggestion of excess intra- or postoperative morbidity or mortality in patients for whom hypothermia is used. In patients with acute SAH, these preliminary results suggest that intraoperative hypothermia may confer some degree of neurological benefit. Based on these results, we think that performance of a larger, definitive prospective trial is justified in patients with acute aneurysmal SAH.

We anticipated that patients with unruptured aneurysms would have less perioperative morbidity than those with acute aneurysmal SAH. For this reason, we decided a priori to analyze predictive variables and clinical outcomes separately between patients with and without acute SAH. In patients with and without acute SAH, demographic and predictive variables were well matched between patients assigned to normothermia and hypothermia groups. Thus, apparent outcome differences can be reasonably hypothesized as being the result of differences in temperature management.

There were no difficulties in achieving and maintaining the target temperature in the normothermic group. In contrast, induction and reversal of intraoperative hypothermia was less reliable and had some associated drawbacks. With surface cooling and rewarming, thermal exchange is relatively slow and is inhibited by reflex cutaneous vasoconstriction, which limits heat transfer between the core and the periphery, especially once core temperature is less than 34°C (34,54). Using cooling techniques similar to those used this study, Baker et al. (2) achieved a cooling rate of -1.0 ± 0.4°C per hour. In our study, the median time from induction to aneurysm clipping was 270 minutes, and in 90% of the cases, the time from induction to clipping exceeded 180 minutes. Hence, it seems that there should have been sufficient time to attain target hypothermia (33.5°C) in almost all patients before performing aneurysm clipping. Nevertheless, 7 of 57 (12%) patients assigned to the hypothermic group had temperatures greater than 34.5°C at the time of clipping. Of these seven, three were markedly obese: 127, 130, and 150 kg. Obesity decreases the ratio of surface area to mass and increases the size of the peripheral thermal compartment. These properties each diminish the rate of core cooling during surgery (36). However, the weights of the other four patients who failed to cool ranged from 66 to 90 kg, and cooling times ranged between 235 and 375 minutes. In the absence of unreported protocol failures, we cannot readily explain why these patients did not cool, other than to hypothesize that thermoregulatory mechanisms in these patients were better maintained during anesthesia than normal. On the basis of these findings, we recommend that future trials be restricted to patients who weigh less than 110 kg. If such trials demonstrate the protective value of hypothermia, then more effective methods for cooling larger patients will need to be developed.

Although there was usually sufficient time to cool patients before performing aneurysm clipping, rarely was there sufficient time to rewarm them by the time of completion of surgery. In patients assigned to the hypothermia group, the median interval from aneurysm clipping to arrival in recovery was 114 minutes ([approximately equal to]1.9 h). Baker et al. (2) observed that surface rewarming took place even more slowly and more variably than did cooling (+0.7 ± 0.8°C/h). Thus, as might be expected, patients assigned to the hypothermia group arrived in recovery colder and more commonly required postoperative ventilation and forced air warming. However, by 2 hours in recovery, normothermia was restored and the need for intubation did not differ between temperature groups. Even mild hypothermia can impair neurological function (11) and delay emergence from anesthesia (37). Thus, use of intraoperative hypothermia may delay, or make more difficult, postoperative neurological assessment. In our view, this is a potentially significant drawback. Nevertheless, in this study, there were no apparent adverse sequelae of delayed emergence or extubation.

There is no suggestion that hypothermia was associated with excess morbidity or mortality. All in-hospital deaths were unequivocally on a neurological basis. Although we did not standardize criteria for the assessment of cardiovascular complications, they were actively sought by serial electrocardiographic and enzymatic testing for the first 3 days after surgery. Although electrocardiographic abnormalities are common after SAH (7,41), no patient in this study was judged as having sustained an overt myocardial infarction. Studies demonstrating increased postoperative cardiovascular morbidity in patients with intraoperative hypothermia have been conducted in patients who had known, or were at high risk of, coronary artery disease (17,18). Although patients with cerebral aneurysms often have cardiovascular risk factors, they tend to have a low incidence of overt cardiac symptoms before SAH. For example, in the International Cooperative Study on the Timing of Aneurysm Surgery, only 3% of the patients had pre-SAH histories of either angina, congestive heart failure, or myocardial infarction, and the cumulative in-hospital incidence of these complications was also 3% (31). Of 708 patients scheduled for surgery in the North American subset of the aforementioned cooperative study, 88% of the deaths were on a neurological basis, with the remaining 12% of the deaths resulting from "medical therapy complications" or "other" causes (23). Thus, it seems that the overall threat of cardiovascular complications is small relative to the threat of neurological death after SAH, making the detection of hypothermia-related cardiovascular complications difficult. Similarly, we observed no suggestion of increased risk of bleeding or infection (e.g., pneumonia) in patients assigned to the hypothermia group. There was not even a suggestion of increased morbidity in hypothermic patients, as evidenced by an equivalent incidence of postoperative complications and an equivalent number of days of hospitalization from the time of surgery to the time of discharge between groups. Other than cold-associated illnesses (cryoglobulinemia, Raynaud's disease), there did not seem to be an obvious contraindication to intraoperative hypothermia in patients with cerebral aneurysms. This apparent safety suggests that future trials might consider even lower intraoperative temperatures, assuming that lower temperatures may convey even greater cerebral protection and that better cooling and rewarming methods can be devised.

There were no statistically significant differences in short-or long-term neurological outcomes between the temperature groups. For patients without acute aneurysmal SAH, the acute perioperative mortality rate was 3%, and approximately 20% of each temperature group was found to exhibit a new "significant" deterioration in NIHSS score at 24 and 72 hours after surgery. At the time of late follow-up examinations, 20% of the patients without acute SAH had either moderate or severe disabilities.

These outcomes are very similar to those reported by Khanna et al. (33), who reported that 24% of 222 patients undergoing surgery for unruptured cerebral aneurysms had either mild or severe neurological deficits at the time of long-term follow-up examinations and that the perioperative mortality rate was 3%. The cause of these new neurological deficits is rarely known but, in the absence of vasospasm, is generally ascribed to intraoperative brain injury from temporary clips (47,51) and/or acute vessel thrombosis (49), retractor placement (1,59), systemic hypotension, and/or direct surgical trauma (38). Whatever the cause, intraoperative hypothermia did not seem to have a protective effect. With individual exceptions, these new early neurological deficits were generally mild. As a result, 76% of the patients with unruptured aneurysms had good final outcomes and 88% had either good or fair final outcomes.

In patients with acute aneurysmal SAH who were assigned to the hypothermia group, the incidence of new significant neurological deterioration (increased of >=4 points on NIHSS) at 24 and 72 hours after surgery was also approximately 20%. This incidence of new acute postoperative neurological deficits is consistent with that reported in other studies (15,19,20,25,38,42,49). In contrast, in patients with acute SAH assigned to normothermia, the incidence of new significant neurological deterioration was numerically greater (~40% at 24 and 72 h after surgery). This difference between temperature groups seems to carry through to discharge; 75% of the hypothermic patients were discharged to home as opposed to 57% of the normothermic patients. The apparent difference between temperature groups in early neurological status also corresponds to the apparent difference in final neurological outcome in that 71% of the patients assigned to the hypothermia group had good final outcomes versus 57% of those assigned to the normothermia group. We emphasize that none of these apparent neurological outcome differences between temperature groups are statistically significant. Power analysis indicates that randomization of approximately 300 patients with acute aneurysmal SAH would be necessary to achieve statistical significance if the apparent difference in final (good) outcome observed in this study were maintained in a subsequent trial. Obviously, lesser differences in good final outcome would require even more patients to achieve statistical significance. For example, to detect an increase in good outcome from 65 to 75%, a study population of 920 patients is required. Although the current study cannot rule out a protective effect of intraoperative hypothermia in patients undergoing clipping of *un*ruptured aneurysms, our results suggest that many thousands of patients with unruptured aneurysms would be required to demonstrate a neurological benefit.

It is premature to conclude that mild intraoperative hypothermia is protective or to assign a mechanism to the apparent protection observed in patients with acute SAH. It is notable, however, that there is not even a suggestion of neurological benefit with hypothermia in patients with unruptured aneurysms. We wonder therefore, whether hypothermia could improved neurological outcome by decreasing additional (secondary) intraoperative brain injury in patients who have just suffered primary neurological injury as a result of their acute SAH. A substantial body of animal literature indicates that brain tissue that has been subjected to either trauma or ischemia is more susceptible to a subsequent episode of ischemia/hypoxia, even when that second episode is not sufficiently severe to damage normal brain (9,26-28,32,56). This may be compounded in the immediate post-SAH period because of acute brain swelling and blood surrounding feeding vessels and the aneurysms. These later features may increase the need for brain retraction and manipulation of intracranial vessels and increase the risk of regional hypoperfusion in a brain that has already been rendered susceptible to additional secondary injury by the initial SAH. Hypothermia, by virtue of its protective effect against a wide variety of ischemic and traumatic neurological insults,

might limit these secondary injuries. Our observation that the apparent benefit of hypothermia was present at 24 hours after surgery, but only in patients with acute SAH, is consistent with this hypothesis.

In summary, this pilot trial demonstrates the feasibility and apparent safety of a randomized prospective blinded trial of mild intraoperative hypothermia (33.5°C) for cerebral aneurysm surgery. Only markedly obese patients (i.e., >=110 kg) and patients with cold-associated illness should be excluded from future prospective studies. Improved cooling methods will likely increase the percentage of patients who attain target hypothermic temperature. The only disadvantages to intraoperative hypothermia seem to be mild postoperative hypothermia and the need for brief (<2 h) postoperative warming and intubation. There is no suggestion of increased postoperative morbidity or mortality with hypothermia. Only in patients with acute SAH is there any suggestion of neurological benefit with hypothermia. Our results indicate that a multicenter trial with between 300 to 900 patients with acute SAH and WFNS scores of III or less will be necessary to demonstrate a statistically significant benefit of the use of mild intraoperative hypothermia during cerebral aneurysms surgery.

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