ORIGINAL ARTICLE

Mild Intraoperative Hypothermia during Surgery for Intracranial Aneurysm

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ABSTRACT

BACKGROUND

Surgery for intracranial aneurysm often results in postoperative neurologic deficits. We conducted a randomized trial at 30 centers to determine whether intraoperative cooling during open craniotomy would improve the outcome among patients with acute aneurysmal subarachnoid hemorrhage.

METHODS

A total of 1001 patients with a preoperative World Federation of Neurological Surgeons score of I, II, or III ("good-grade patients"), who had had a subarachnoid hemorrhage no more than 14 days before planned surgical aneurysm clipping, were randomly assigned to intraoperative hypothermia (target temperature, 33°C, with the use of surface cooling techniques) or normothermia (target temperature, 36.5°C). Patients were followed closely postoperatively and examined approximately 90 days after surgery, at which time a Glasgow Outcome Score was assigned.

RESULTS

There were no significant differences between the group assigned to intraoperative hypothermia and the group assigned to normothermia in the duration of stay in the intensive care unit, the total length of hospitalization, the rates of death at follow-up (6 percent in both groups), or the destination at discharge (home or another hospital, among surviving patients). At the final follow-up, 329 of 499 patients in the hypothermia group had a Glasgow Outcome Score of 1 (good outcome), as compared with 314 of 501 patients in the normothermia group (66 percent vs. 63 percent; odds ratio, 1.14; 95 percent confidence interval, 0.88 to 1.48; P=0.32). Postoperative bacteremia was more common in the hypothermia group than in the normothermia group (5 percent vs. 3 percent, P=0.05).

CONCLUSIONS

Intraoperative hypothermia did not improve the neurologic outcome after craniotomy among good-grade patients with aneurysmal subarachnoid hemorrhage.

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New neurologic deficits are common after intracranial vascular surgery and are due to factors such as brain retraction, vessel occlusion, and intraoperative hemorrhage. Thus, there have been many efforts to protect the brain from such insults.[1-6] The use of systemic hypothermia as a protective adjunct in neurosurgery was first reported in 1955[7] but was largely abandoned during the 1970s and 1980s. Interest in this approach was rekindled after the demonstration in the laboratory that the induction of mild hypothermia (a temperature of approximately 33 to 35°C) improved the outcome of ischemic and traumatic insults.[8-11] This finding coincided with the use of hypothermia for the treatment of other neurologic disorders, including head trauma, stroke, and cardiac arrest.[12-16] However, despite surveys showing that hypothermia is used in over 50 percent of surgical procedures for aneurysms,[17] several case series,[18-22] and our own pilot trial,[23] little information is available concerning the effect of hypothermia on the outcome of neurovascular surgery.

METHODS

The Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) was a multicenter, prospective, randomized, partially blinded trial designed to determine, in patients with subarachnoid hemorrhage, whether the use of intraoperative hypothermia (target temperature, 33°C) would result in a better outcome, as measured by the score on the Glasgow Outcome Scale[24,25] 90 days after surgery, than would the use of normothermia (target temperature, 36.5°C). The protocol was reviewed by the human-studies committee at each participating institution. Written informed consent was obtained from the patients or their legal representatives. All anesthesiologists, neurosurgeons, coordinators, and neurologic assessors were certified by means of written examinations. Before randomization was allowed at a center, hypothermia was induced in two patients to verify the ability of staff members to comply with the study protocols.

ELIGIBILITY AND RANDOMIZATION

Eligible patients were at least 18 years of age, were not pregnant, had had a subarachnoid hemorrhage from a radiologically demonstrated intracranial aneurysm within 14 days before surgery, and had a World Federation of Neurological Surgeons score of I, II, or III ("good grade")[26] at the time of enrollment, which was verified on arrival in the operating room. Patients were required to have had a Rankin score of 0 (no neurologic disability) or 1 (mild disability) before hemorrhage.[27] Patients were excluded if they had a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 35, had a cold-related disorder, or had an endotracheal tube in place. Nimodipine was started before or after surgery in all but two patients, one in each group.

A permuted-block scheme was used for randomization, with stratification according to the center and the time between subarachnoid hemorrhage and surgery (0 to 7 days or 8 to 14 days). Less than two hours before the planned start of surgery, patients were evaluated and enrolled by means of a telephone-accessed computer system, which directed the anesthesiologist to use a numbered opaque envelope containing the patient's treatment assignment. The envelope was to be opened only after the induction of anesthesia. If, before induction, eligibility criteria were no longer met (owing, for example, to neurologic deterioration), the envelope was not opened and the patient did not undergo randomization. All study personnel, except the anesthesiologists involved in intraoperative care, were unaware of the patients' treatment assignments.

ANESTHESIA AND TEMPERATURE MANAGEMENT

Anesthesia was induced with thiopental or etomidate and maintained with isoflurane or desflurane, fentanyl or remifentanil, and a mix of oxygen and nitrous oxide or of oxygen and air. Standard monitors were used. Other monitors (e.g., those for central venous pressure and evoked potentials) were used according to the preferences at a given center.

Each patient's temperature was monitored in the retrocardiac esophagus (Mon-a-therm Esophageal Stethoscope XL, provided by Tyco Mallinckrodt). After endotracheal intubation and positioning of the patient, the temperature probe was inserted and the patient was covered with a forced-air blanket connected to a heating–cooling unit (PolarAir, provided by Arizant). The use of a circulating water mattress and intravenous cold saline as cooling aids was optional.[28] In patients assigned to hypothermia, esophageal temperature was reduced as quickly as possible, without any delay in the progress of surgery. The goal was to achieve a temperature between 32.5 and 33.5°C by the time the first clip was applied. The temperature of patients assigned to

normothermia was kept between 36 and 37°C. Thiopental or etomidate was permitted for the purpose of cerebral protection, at the discretion of the operating team; this was typically given in conjunction with temporary vessel occlusion. Other medications (e.g., nondepolarizing relaxants, mannitol, and vasoactive agents) were used as needed.

Rewarming of patients assigned to hypothermia began after the last aneurysm clip had been secured. Patients were extubated when deemed ready by the attending physicians. No effort was made to control postoperative care, but detailed daily records were collected until discharge or for 14 days, whichever came first.

OUTCOMES

Patients were seen approximately 90 days after surgery by a certified examiner and a neuropsychologist who were unaware of patients' treatment assignments. Patients were assessed by means of the Glasgow Outcome Scale, the Rankin scale, the Barthel index,[29] the National Institutes of Health (NIH) Stroke Scale,[30] and a battery of neuropsychological examinations. If a patient could not be seen by examiners at the operating center, arrangements were made for him or her to be seen elsewhere by a certified examiner. Twelve patients were interviewed by telephone.

SAFETY AND PROTOCOL MANAGEMENT

A total of 106 predefined adverse events or procedures were monitored. Special attention was paid to events related to neurologic injury, myocardial dysfunction,[31] coagulation,[32,33] and infection.[34] A physician from a nonparticipating institution, who was supplied with information on group assignments but not outcomes, reviewed all intraoperative records. He was empowered to contact participating centers if protocol-compliance issues were identified and to communicate with an unblinded member of the University of Iowa Data Management Center if he noted major problems at a center. This resulted in two centers' being dropped (patient data were retained). Three centers were temporarily restricted from enrolling patients until staff members underwent retraining.

STATISTICAL ANALYSIS

We estimated that the enrollment of 1000 patients would permit the detection of a 10 percent absolute improvement in the fraction of patients with a good outcome, as defined by a score of 1 for the Glasgow Outcome Scale (e.g., 75 percent vs. 65 percent), with a statistical power of 91 percent and a two-sided alpha of 0.05. All data entry and analyses were performed by the Data Management Center at the University of Iowa. Outcomes were analyzed according to the intention-to-treat principle. All analyses were defined before the treatment assignments were revealed. Two planned interim analyses were performed after outcome data had been received for 357 and 655 patients, and the results were reported to the data and safety monitoring board. The interim monitoring method of Lan and DeMets was used with the O'Brien–Fleming spending function for these interim analyses. All results are two-sided, and the P values have not been adjusted for the interim analyses.

Differences between the groups in baseline and intraoperative variables were compared by means of t-tests or the Wilcoxon rank-sum test for interval-scale variables, Fisher's exact tests for two-by-two tables, and the Freeman–Halton extension to the Fisher's exact test for categorical variables with more than two possible outcomes.[35] The primary outcome variable was a score of 1 on the Glasgow Outcome Scale (indicating mild or no disability). The rates of good outcomes were compared in the normothermia and hypothermia groups with the use of the Cochran–Mantel–Haenszel statistic with study site and time from subarachnoid hemorrhage to surgery as stratification variables.[36] We report adjusted odds ratios and 95 percent confidence intervals for differences between rates. Subgroup analyses of the primary outcome were performed according to the method of Grizzle et al.[37] Models included terms for treatment, subgroup, and an interaction between treatment and subgroup.

RESULTS

Between February 2000 and April 2003, 3966 patients underwent aneurysm surgery at 30 participating centers; 2856 had a subarachnoid hemorrhage. A total of 1183 patients were eligible, and 1033 patients were enrolled. Owing to changes in status after enrollment, 32 patients did not undergo randomization, resulting in a total enrollment of 1001 patients. One patient was lost to follow-up, leaving 1000 patients in our efficacy population.

The baseline characteristics of the patients are shown in Table 1. There were no significant differences between the groups in any preoperative factors, except that fever (temperature of at least

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Hypothermia Group (N=499)	Normothermia Group (N=501)
Age (yr)	52±12	51±13
Female sex (%)	65	66
Race or ethnic group (%)		
White	80	80
Black	6	8
Hispanic	5	6
Other	9	6
Current smoker (%)	54	54
WFNS score (%)		
I (GCS score 15, no motor deficit)	67	66
II (GCS score 13 or 14, no motor deficit)	28	30
III (GCS score 13 or 14, any motor deficit)	5	5
Fisher grade on 1st CT scan (%)†		
I (No subarachnoid blood)	6	5
II (Diffuse blood)	35	34
III (Localized clot or thick layer)	47	48
IV (Intraparenchymal or ventricular clot)	12	14
Hydrocephalus on 1st CT scan (%)†	38	41
Time from SAH to surgery (days)		
Mean	3±3	3±3
Median	2	2
Nimodipine treatment (no. of patients)	498	500

* Plus–minus values are means ±SD. Because of rounding, percentages may not total 100.
† Information was from the first computed tomographic (CT) scan obtained after admission, as assessed by the operating surgeon. WFNS denotes World Federation of Neurological Surgeons, GCS Glasgow Coma Scale, and SAH subarachnoid hemorrhage. Results are based on the 1000 patients with follow-up information, according to group assignment (the efficacy population). There were no significant differences between groups.

38.5°C at any time) was more common in the hypothermia group than in the normothermia group (5 percent vs. 2 percent, P=0.005). The median time from subarachnoid hemorrhage to surgery was 2 days; 907 patients underwent surgery 0 to 7 days after hemorrhage, and 93 did so 8 to 14 days after hemorrhage. Ventriculostomy was performed preoperatively in 7 percent of patients in the hypothermia group and 9 percent of patients in the normothermia group.

PERIOPERATIVE CARE

Perioperative characteristics are shown in Table 2. There were no significant differences between groups except in intraoperative and postoperative temperature (P=0.001), the amount of crystalloid administered (P=0.001), and urinary output (P=0.001). There were no significant differences in operating conditions, the incidence and duration of temporary vessel occlusion, the number of patients with severe intraoperative hemorrhage, or other recorded variables.

POSTOPERATIVE COURSE

There were no significant differences in the number of adverse events in the early postoperative period (data not shown). Two hours after surgery, the temperature was lower in the hypothermia group (Table 2), and 25 percent of patients in this group remained intubated, as compared with 13 percent of patients in the normothermia group. Ten percent of patients in both groups were intubated 24 hours after surgery. Excluding patients who were still intubated and sedated, 39 percent of patients in the

Table 2. Characteristics of Intraoperative Care.*

Characteristic	Hypothermia Group (N=499)	Normothermia Group (N=501)	P Value
No. of aneurysms treated (%)†			0.59
0	<1	<1	
1	89	91	
≥2	10	9	
Location of 1st aneurysm treated (%)			0.73
Anterior communicating artery	37	34	
Posterior communicating artery	22	25	
Middle cerebral artery	21	21	
Vertebrobasilar system	6	5	
Other	14	15	
Time from induction of anesthesia to placement of 1st clip (min)	217±101	214±82	0.54
Time from placement of last clip to arrival in recovery area (min)	102±35	100±37	0.20
Total time in operating room (min)	324±120	318±108	0.41
Temperature (°C)			
On arrival in operating room	36.8±0.7	36.8±0.6	0.91
At placement of 1st aneurysm clip	33.3±0.8	36.7±0.5	0.001
2 Hr after surgery	36.4±1.0	37.1±0.7	0.001
Temporary clipping			
Temporary clips applied (%)	42	47	0.13
Temporary clips applied for ≥20 min (%)‡	5	6	1.00
Duration of temporary clipping (min)	11±12	10±9	0.71
Intraoperative conditions and events			
Moderate or severe brain swelling (%)§	36	38	0.56
Aneurysm judged difficult or severely difficult to access (%)¶	36	35	0.95
Intraoperative use of protective drugs (%)	20	23	0.28
Leak or rupture of aneurysm (%)	29	34	0.10
Estimated blood loss (ml)	428±366	417±415	0.29
Blood loss ≥1000 ml (%)	7	6	0.37
Red-cell transfusion (%)	12	13	0.56
Crystalloid administration (ml)	3828±1595	3287±1550	0.001
Urinary output (ml)	2052±1259	1679±1059	0.001
New dysrhythmias (%)‖	4	4	1.00
Intentional (controlled) hypotension (%)	4	5	0.37
Unintended hypotension (%)	2	3	0.24
Vasopressor use (%)**	25	22	0.26

* Plus–minus values are means ±SD. Results are based on the 1000 patients with follow-up information, according to group assignment (the efficacy population). All values were reported by the operating neurosurgeon or attending anesthesiologist.

† Although most aneurysms were clipped, other treatments included trapping and wrapping. In a small fraction of patients, no treatable aneurysm was found.

‡ The values represent the percentage of all patients, not just those with temporary clips.

§ At the time of dural opening, surgeons were asked to rate the degree of brain swelling on a four-point scale in which a score of 0 indicated no swelling, a score of 1 slight swelling (no treatment needed), a score of 2 moderate swelling (treatment needed), and a score of 3 severe swelling (treatment needed, delaying surgery for more than 10 minutes).

¶ Surgeons were also asked to rate the difficulty of gaining access to the aneurysm on a four-point scale, in which a score of 0 indicated that the site was easy to access, a score of 1 moderately difficult, a score of 2 difficult, and a score of 3 severely difficult.

‖ Values include all dysrhythmias, regardless of severity or requirement for treatment.

** Values reflect patients who continuously received any vasopressor (e.g., phenylephrine, norepinephrine, dopamine, or dobutamine) for any reason for at least 15 minutes.

hypothermia group and 42 percent of patients in the normothermia group had an increase from baseline of 4 or more points in the NIH Stroke Scale score when they were examined three to six hours after surgery (there were no significant differences between the groups). These values had decreased to 27 percent and 28 percent, respectively, by 24 hours (again, there were no significant differences between groups). There were no significant differences between the hypothermia group and the normothermia group in the mean (±SD) number of days in the intensive care unit (6±5 for both) or the total duration of hospitalization (16±9 and 16±11 days, respectively). Sixty-one percent of patients in the hypothermia group and 59 percent of those in the normothermia group were discharged directly to their homes. Twenty-four patients in the hypothermia group died in the hospital, as compared with 23 in the normothermia group (P=0.88).

OUTCOME

The median time to the final outcome assessment was 88 days (10th and 90th percentiles, 72 and 113 days) in both groups. Outcome information is presented in Table 3 for the 1000 patients with follow-up data. There were no significant differences between the groups in any measure. There were no significant treatment-related differences in outcomes between high- and low-volume centers (data not shown).

The interaction between the time to surgery and treatment was significant (P=0.04). In the subgroup in which surgery was performed zero to seven days after subarachnoid hemorrhage, 64 percent of patients in the hypothermia group (289 of 452) were classified as having a good outcome, as compared with 63 percent of patients in the normothermia group (287 of 455; odds ratio, 1.06; 95 percent confidence interval, 0.81 to 1.40). In the subgroup in which surgery was performed 8 to 14 days after subarachnoid hemorrhage, 83 percent of patients in the hypothermia group were classified as having a good outcome, as compared with 61 percent of patients in the normothermia group (39 of 47 vs. 28 of 46; odds ratio, 2.70; 95 percent confidence interval, 1.00 to 7.30). However, the difference was no longer significant when outcomes were adjusted for differences in factors present before randomization (smoking status, presence or absence of alcohol abuse, and the incidence of Fisher grade III on computed tomography) between the subgroups.

The interaction between sex and treatment was also significant (P=0.03). In the hypothermia group, 120 of 174 men had a good outcome, as compared with 97 of 171 men in the normothermia group (69 percent vs. 57 percent; odds ratio, 1.78; 95 percent confidence interval, 1.12 to 2.84). However, like the interaction between the time to surgery and treatment assignment, this difference disappeared after adjustment for covariates (in particular, age). Among women, 209 of 325 patients in the hypothermia group had a good outcome, as compared with 217 of 330 in the normothermia group (64.3 percent vs. 65.8 percent); this difference was not significant. Increasing age, increasing World Federation of Neurological Surgeons scores at baseline, increasing Fisher grade at baseline, severe intraoperative hemorrhage, and placement of a temporary clip for at least 20 minutes were associated with worse outcomes, but without any temperature-related interactions.

OUTCOMES ACCORDING TO COMPLIANCE WITH THE PROTOCOL

We expected that the assigned temperatures would not be achieved in some patients. We therefore compared the outcomes in patients whose intraoperative temperatures reached the defined target range of no more than 33.5°C in the hypothermia group (373 patients) and at least 36°C in the normothermia group (467 patients). There were no significant differences between the groups.

ADVERSE EVENTS

There were no significant differences in the incidence of any event after randomization, except for a higher rate of bacteremia in the hypothermia group than in the normothermia group (25 patients [5 percent] vs. 13 patients [3 percent], P=0.05) (Table 4).

DISCUSSION

Studies in animals have demonstrated the protective or therapeutic value of mild hypothermia for insults including global cerebral ischemia, permanent or temporary focal ischemia, trauma, and subarachnoid hemorrhage.[8-11,38-42] Accordingly, we wished to evaluate hypothermia for the purpose of improving the outcome of neurosurgery. Patients undergoing a craniotomy for the placement of aneurysm clips after subarachnoid hemorrhage seemed to be the optimal study population, since a substantial fraction of such patients awaken with new or worsened neurologic deficits. For example,

Table 3. Outcomes.*

Outcome	Hypothermia Group		Normothermia Group		P Value†	Odds Ratio (95% CI)‡
	No. Analyzed	No. with Score (%)	No. Analyzed	No. with Score (%)		
Score for Glasgow Outcome Scale	499		501			
1 (Minor or no disability)§		329 (66)		314 (63)	0.32	1.14 (0.88–1.48)
2 (Moderate disability)		105 (21)		108 (22)		
3 (Severe disability)		35 (7)		47 (9)		
4 (Vegetative state)		1 (<1)		0		
5 (Death)¶		29 (6)		32 (6)		
Rankin score	499		501			
Score 0 or 1 (mild or no neurologic disability)		333 (67)		318 (63)	0.32	1.14 (0.88–1.49)
Score for Barthel's index‖	469		468			
95–100		416 (89)		403 (86)	0.23	1.27 (0.86–1.87)
60–90		29 (6)		35 (7)		
0–55		24 (5)		30 (6)		
Score for NIH Stroke Scale**	461		452			
0 (No deficit)		306 (66)		291 (64)	0.60	1.08 (0.82–1.42)
1–7 (Mild deficit)		139 (30)		138 (31)		
8–14 (Moderate deficit)		7 (2)		17 (4)		
15–42 (Severe deficit)		9 (2)		6 (1)		

* All information was obtained from examinations performed approximately 90 days after surgery. Unless otherwise specified, results are based on the 1000 patients with follow-up information, according to group assignment (the efficacy population).
† P values were obtained by means of the Cochran–Mantel–Haenszel test of association, with adjustment for study site and the time from subarachnoid hemorrhage to surgery.
‡ Odds ratios have been adjusted for study site and the time from subarachnoid hemorrhage to surgery. CI denotes confidence interval.
§ This good outcome was the prespecified primary outcome.
¶ One additional patient in the hypothermia group died after completing the final outcome assessment. This patient was included in the safety population.
‖ Scores for the Barthel index range from 0 to 100, with higher scores indicating increasing ability to perform the activities of daily living independently. Only surviving patients were included in the analysis. The examination was not performed in one patient in each group.
** There were 4 patients with missing data, 5 patients with incomplete examinations, and 29 deaths in the hypothermia group. There were 11 patients with missing data, 6 patients with incomplete examinations, and 32 deaths in the normothermia group.

a review of data on the 2922 surgical patients in the International Study on the Timing of Aneurysm Surgery indicated that 32.5 percent had a decline in neurologic status 24 hours after surgery (Torner J: unpublished data). These values are very similar to the incidence of worsened values on the NIH Stroke Scale 3 to 6 hours and 24 hours postoperatively in our patients.

Although subarachnoid hemorrhage alone damages the brain, neurosurgery carries its own risks. In patients with unruptured aneurysms who were neurologically normal before surgery, the combined rate of postoperative complications and death in one study was 15.7 percent.[43] The causes of such complications are unclear but include brain retraction,[44] temporary arterial occlusion,[45] intraoperative rupture,[46] and other ischemic insults that may be amenable to amelioration by hypothermia.

In our patients, unlike patients with stroke, head trauma, or cardiac arrest, cooling could be instituted before the likely time of injury. On the basis of a pilot study,[23] we defined the study population as one in which the chances of demonstrating a benefit appeared to be maximal. Eligibility was restrict-

Table 4. Selected Adverse Events and Procedures.*

Event	Hypothermia Group (N=499)	Normothermia Group (N=502)	P Value
	percent		
Neurologic event			
Intraparenchymal hemorrhage	3	4	0.17
Epidural or subdural hemorrhage	5	5	0.89
Delayed ischemic neurologic deficit	23	22	0.82
Cerebral infarction	26	30	0.23
Brain swelling	24	26	0.56
Seizure	7	6	0.61
Cardiovascular event			
Myocardial ischemia or infarction	2	1	0.30
Congestive heart failure or pulmonary edema	10	12	0.42
Ventricular fibrillation or tachycardia	1	1	0.34
Supraventricular dysrhythmia	4	5	0.43
Coagulation			
Severe hemorrhage (≥1000 ml in 24 hr)†	7	6	0.37
Red-cell transfusion at any time	34	31	0.25
Coagulopathy	1	1	0.22
Infection			
Incision or bone-flap infection	2	2	0.81
Meningitis or ventriculitis	6	4	0.31
Bacteremia	5	3	0.05
Pneumonia	7	7	0.90
Urinary tract infection	15	18	0.31

* Results are based on the entire population of 1001 patients, according to the actual treatment received (the safety population). Values represent the percentage of patients who had at least one episode of the described event at any time between randomization and the final follow-up evaluation, except as noted otherwise.

† All episodes of severe hemorrhage occurred in the operating room or shortly thereafter.

ed to those with World Federation of Neurological Surgeons scores of I, II, or III, because we expected the rates of complications and death to be high among patients with scores of IV or V, regardless of the therapy used. Obese patients were excluded because they are difficult to cool.[23] Cooling was restricted to the intraoperative period, because the use of longer periods of hypothermia could increase risk and would limit clinicians' ability to assess patients' neurologic status immediately after surgery. A target temperature of 33°C was chosen as low enough to be potentially protective yet practically achievable with the use of surface cooling methods without delaying the progress of surgery.

Our results demonstrate that the use of mild hypothermia in the intraoperative period has no beneficial effects on the outcome in this patient population. The 95 percent confidence intervals for the difference between groups in the percentage of patients with a good outcome rule out the clinically meaningful difference that the trial was designed to detect. We do not think that the observed lack of effect was due to procedural difficulties; the groups were well matched, there was a high degree of compliance with the protocol, and the rate of follow-up was nearly perfect. The lack of effect was also not due to a paucity of surgically related insults, since the neurologic condition was worse in nearly 30 percent of our patients 24 hours after surgery.

There were suggestions of a benefit from hypothermia in two predefined subgroups: patients undergoing surgery 8 to 14 days after subarachnoid hemorrhage and male patients. These findings must be viewed with great caution, since these were secondary analyses. We stratified the analyses according to the time after subarachnoid hemorrhage only to ensure balance between treatment groups; patients did not undergo randomization according to whether surgery was early or late. Delayed surgery was not planned but, rather, was usually the result of delayed referral or diagnosis. The numbers of patients in the normothermia and hypothermia groups who underwent surgery 8 to 14 days after subarachnoid hemorrhage are small (46 and 47 patients, respectively), and randomization did not result in the near-perfect balance in preoperative characteristics seen in the overall study population. The apparent benefit in male patients is subject to the same concerns. Nevertheless, these subgroups may deserve further study.

Our study has limitations. Patients were cooled to approximately 33°C and only for the intraoperative period. The use of colder temperatures for longer periods might have resulted in different outcomes. However, since we saw no differences when we examined only the patients with the coldest temperatures, we do not think that the chosen temperature was critical. It is possible that the relatively slow rate of cooling in our study may have resulted in inadequate protection during the early stage of retractor placement, or exposure of the aneurysm. However, a review of anesthesia records indicated that the temperature of 50 percent of patients in the

hypothermia group reached 34.5°C or lower more than an hour before clipping. We controlled esophageal rather than brain temperatures, and there may be discrepancies between these two measurements. However, the patterns of brain and core temperatures are similar,[47] and direct measurement of brain temperature during surgery was not deemed practical. We also did not control any aspects of postoperative care. Nevertheless, we were unable to identify any systematic differences in numerous postoperative variables.

We used a relatively crude, albeit widely used outcome assessment. However, we found no significant differences between the groups when other outcome measures were used. (We are still evaluating the outcome on the basis of the results of neuropsychological examinations.) Finally, we included only patients with a relatively good preoperative grade. We recognized that restricting the study to such patients would reduce the incidence of poor outcomes. However, we thought that, given a sufficiently large number of patients, treatment effects, if present, would be detectable. Moreover, the incidence of new or worsened postoperative deficits was high, as was the fraction of patients with outcomes that were less than good. Thus, there is no reason to believe that any clinically meaningful beneficial effects of hypothermia on either the short- or long-term outcome were missed. In summary, we have demonstrated that intraoperative cooling has no overall benefit in this group of neurosurgical patients.

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APPENDIX

The members of IHAST were as follows: **University of Iowa — Steering Committee:** M. Todd, B. Hindman, W. Clarke, K. Chaloner, J. Torner, P. Davis, M. Howard, D. Tranel, S. Anderson; **Clinical Coordinating Center:** M. Todd, B. Hindman, J. Weeks, L. Moss, J. Winn; **Data Management Center:** W. Clarke, K. Chaloner, M. Wichman, R. Peters, M. Hansen, D. Anderson, J. Lang, B. Yoo; **Physician Safety Monitor:** H. Adams; **Project Advisory Committee** — G. Clifton (University of Texas, Houston), A. Gelb (University of California, San Francisco), C. Loftus (Temple University, Philadelphia), A. Schubert (Cleveland Clinic, Cleveland); **Physician Protocol Monitor** — D. Warner (Duke University, Durham, N.C.); **Data and Safety Monitoring Board** — W. Young, chair (University of California, San Francisco), R. Frankowski (University of Texas Health Science Center at Houston School of Public Health, Houston), K. 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