

LACK OF EFFECT OF INDUCTION OF HYPOTHERMIA AFTER ACUTE BRAIN INJURY

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ABSTRACT

Background Induction of hypothermia in patients with brain injury was shown to improve outcomes in small clinical studies, but the results were not definitive. To study this issue, we conducted a multicenter trial comparing the effects of hypothermia with those of normothermia in patients with acute brain injury.

Methods The study subjects were 392 patients 16 to 65 years of age with coma after sustaining closed head injuries who were randomly assigned to be treated with hypothermia (body temperature, 33°C), which was initiated within 6 hours after injury and maintained for 48 hours by means of surface cooling, or normothermia. All patients otherwise received standard treatment. The primary outcome measure was functional status six months after the injury.

Results The mean age of the patients and the type and severity of injury in the two treatment groups were similar. The mean (\pm SD) time from injury to randomization was 4.3 \pm 1.1 hours in the hypothermia group and 4.1 \pm 1.2 hours in the normothermia group, and the mean time from injury to the achievement of the target temperature of 33°C in the hypothermia group was 8.4 \pm 3.0 hours. The outcome was poor (defined as severe disability, a vegetative state, or death) in 57 percent of the patients in both groups. Mortality was 28 percent in the hypothermia group and 27 percent in the normothermia group ($P=0.79$). The patients in the hypothermia group had more hospital days with complications than the patients in the normothermia group. Fewer patients in the hypothermia group had high intracranial pressure than in the normothermia group.

Conclusions Treatment with hypothermia, with the body temperature reaching 33°C within eight hours after injury, is not effective in improving outcomes in patients with severe brain injury. (N Engl J Med 2001; 344:556-63.)

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TREATMENT with moderate, systemic hypothermia reduces the rates of cerebral edema and death after injury to the cerebral cortex in laboratory animals.¹⁻⁴ The results of early studies of hypothermia in humans with brain injury were inconclusive.⁵⁻⁹ Subsequent testing established 32°C as the safe limit for hypothermia in humans with brain injury.¹⁰ In two 1993 reports of trials in patients with brain injury, moderate hypothermia maintained for 48¹¹ and 24¹² hours resulted in a 15

percent and an 18 percent increase (i.e., difference between the hypothermia and normothermia groups), respectively, in the percentage of patients who had a favorable outcome. On the basis of these data, we initiated a larger trial of moderate hypothermia in patients with severe brain injury in October 1994 through May 1998 and report the results here.

METHODS

Study Subjects

The National Acute Brain Injury Study: Hypothermia was a prospective, multicenter, randomized trial with a planned sample size of 500 patients. The protocol and consent procedures were approved by the institutional review board of each participating center. In the second year of the trial, a waiver of consent, implemented in compliance with federal regulations,^{13,14} was approved for use if the family of a patient with brain injury could not be located. Written informed consent was obtained from legally authorized representatives for 62 percent of the patients, and consent was waived for 38 percent of the patients. A patient safety and monitoring board reviewed data on complications and mortality each month and evaluated the data every six months against preset rules for stopping the trial.

A total of 392 patients were enrolled, with 193 patients randomly assigned to standard treatment and 199 to standard treatment plus hypothermia. Eighty-eight percent of the patients were enrolled at 5 of the 11 centers participating in the trial: the University of Texas–Houston Health Science Center, St. Louis University, the University of California at Davis, the University of Pittsburgh, and Indiana University at Indianapolis. Enrollment was stopped in May 1998 by the patient safety and monitoring board on the basis of an interim analysis showing that the probability of detecting a treatment effect was less than 0.01 if the trial expanded to include 500 patients.

The criteria for inclusion in the trial were an age of 16 to 65 years, a nonpenetrating head injury, and a score on the Glasgow Coma Scale of 3 to 8 after resuscitation. A score on the Glasgow Coma Scale of 15 signifies normal mental status, and a score of 8 or less signifies coma. A score of 5 to 8 denotes flexor withdrawal or purposeful response to pain, 4 denotes extensor posturing, and 3 de-

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notes no motor response. Patients were excluded if they had a score of 3 with unreactive pupils, a life-threatening injury to an organ other than the brain, a systolic blood pressure of less than 90 mm Hg after resuscitation, oxygen saturation of less than 94 percent after resuscitation, bleeding, pregnancy, or known preexisting medical conditions (e.g., severe heart disease) or if the examiners were unable to initiate cooling within six hours after injury. Enrolled patients were stratified at randomization according to study center and initial score on the Glasgow Coma Scale.

Patient Care

Intracranial pressure was monitored in all patients. All patients received 5 to 10 mg of intravenous morphine each hour for at least 72 hours. Intravenous vecuronium was administered to patients in the normothermia group as needed for respiratory management and for 72 hours to all patients in the hypothermia group to prevent shivering. Patients who had hypothermia on admission were not actively rewarmed. Increased intracranial pressure (a level of more than 20 mm Hg) was treated sequentially with intravenous vecuronium, ventricular drainage, hyperventilation with the arterial pressure of carbon dioxide maintained at more than 30 mm Hg, and mannitol until serum osmolality reached 315 mOsm per kilogram. Barbiturate coma was induced according to a published protocol¹⁵ in patients whose intracranial pressure remained high. Cerebral perfusion pressure (the difference between mean arterial pressure and intracranial pressure) was maintained at or above 70 mm Hg by intracranial-pressure control and the administration of intravenous fluids and vasopressors to increase blood pressure. Dehydration was avoided; the use of arterial and Foley catheters was specified, and central lines were optional. Temperature was measured continuously in the urinary bladder through the use of Foley catheters with thermistors. Overall treatment was consistent with the recommendations of Bullock et al.¹⁶ A loading dose of 18 mg of intravenous phenytoin per kilogram of body weight was followed by 300 mg of phenytoin administered once a day for seven days. Potassium was given as needed to maintain normal serum concentrations during the period of hypothermia. Fluids containing glucose were used only for parenteral nutrition. Nutritional support by either the enteral or the parenteral route was started 48 hours after injury in the normothermia group and 72 hours after injury in the hypothermia group.

For the patients in the hypothermia group, cooling began immediately after randomization; the goal was to achieve a target bladder temperature of 33°C within eight hours after injury. Cooling procedures included the application of ice, gastric lavage with iced fluids, and the use of room-temperature air in the ventilator circuit. After the target temperature was reached, temperature-control pads incorporated into a kinetic treatment table (Roto-Rest, Kinetic Concepts, San Antonio, Tex.) were used to maintain a temperature of 32.5°C to 34.0°C for 48 hours. A rate of rewarming no faster than 0.5°C per two-hour period was used. The body temperatures of the patients in the normothermia group were maintained at 37.0°C.

Study Outcome

The primary outcome measure was the assessment of patients according to the five-category Glasgow Outcome Scale,¹⁷ which was conducted six months after the injury by examiners who were unaware of the patients' treatment-group assignments. Good recovery and moderate disability were designated as favorable outcomes; severe disability, a vegetative state, and death were designated as poor outcomes. Good recovery according to the Glasgow Outcome Scale is defined as functional independence with minor disability, and moderate disability is defined as functional independence with more substantial disability. Severe disability is defined as functional dependence. Patients in a vegetative state are awake but noncommunicative. The results of nine neurobehavioral and neuropsychological tests recommended for brain-injury trials (the Neurobehavioral Rating Scale-Revised, the Disability Rating Scale, the Galveston Orientation and Amnesia Test, the Selective Reminding Test, the Rey-Osterrieth Complex Figure Test, the Symbol Digit Modalities Test, Trail Making Test B, the Controlled Oral Word Association

Test, and the Grooved Pegboard Test) were also determined six months after the injury.¹⁸

Data Collection

Temperature, heart rate, mean arterial pressure, intracranial pressure, cerebral perfusion pressure, urine output, volumes and types of intravenous fluid administered, laboratory values, and doses of selected medications were recorded for 96 hours after admission. All patients were evaluated daily, and 67 complications were recorded. The results of the Therapeutic Intervention Scoring System,¹⁹ which quantifies the number and intensity of interventions in patients in intensive care units, were recorded daily so that any bias in the clinical management could be detected.

Statistical Analysis

The primary outcomes were analyzed by the intention-to-treat method. Data on acute care and outcomes were transmitted to the Biostatistics Center at the Medical College of Virginia. Only the study biostatistician was aware of each patient's treatment-group assignment, but the patient safety and monitoring board had access to data grouped according to treatment.

Post-randomization variables were analyzed for differences between the hypothermia and normothermia groups with the use of multivariate analysis with adjustment for age, and Glasgow coma scores on admission when appropriate. Some simple categorical data were analyzed by two-sided chi-square or Fisher's exact tests. Comparisons for some simple continuous variables were performed with two-sided t-tests. All data are expressed as means \pm SD.

RESULTS

The characteristics of the patients in the hypothermia and normothermia groups were similar at the time of enrollment (Table 1).²⁰⁻²⁴

Temperature

Cooling was begun in the hypothermia group immediately after randomization. The mean time from injury to randomization was 4.3 ± 1.1 hours in the hypothermia group and 4.1 ± 1.2 hours in the normothermia group. The mean time from injury to the achievement of the target body temperature of 33°C in the hypothermia group was 8.4 ± 3.0 hours, and the mean temperature in this group during the first 48 hours was 33.2 ± 1.0 °C. Hypothermia was maintained for 47.2 ± 3.0 hours, and the rewarming period was 18.1 ± 7.0 hours. Nine patients assigned to the hypothermia group did not receive hypothermia, in violation of the protocol. The mean body temperature after 96 hours in the normothermia group was 37.2 ± 0.8 °C; 35 percent of the patients in this group had a temperature of 35.0°C or less at some time during the first 16 hours after injury.

There was no significant relation between the time to reach the target temperature and the outcome. The effect on outcome of the length of time required to reach the target temperature was examined according to quartiles. In the first (lowest) quartile, the mean time to reach the target temperature was 5.3 ± 1.2 hours, and the proportion of patients with poor outcomes was 64 percent. Later initiation of cooling was not associated with a higher proportion of poor outcomes (second quartile, 7.1 ± 0.3 hours and 62 percent;

TABLE 1. KNOWN PROGNOSTIC FACTORS IN PATIENTS WITH HEAD INJURY ASSIGNED TO INDUCTION OF HYPOTHERMIA OR TO NORMOTHERMIA.*

PROGNOSTIC FACTOR	NORMOTHERMIA (N=193)	HYPOTHERMIA (N=199)	P VALUE
Age — yr	32±13	31±12	0.36
Score on Glasgow Coma Scale†	5.8±1.3	5.6±1.3	0.26
Glasgow coma score of 5–8 — no. (%)	145 (75)	142 (71)	0.81
Glasgow coma score of 3–4 — no. (%)	38 (20)	50 (25)	0.17
Unreactive pupil or pupils — no. (%)	50 (26)	48 (24)	0.76
Surgical lesion on admission — no. (%)	69 (36)	68 (34)	0.75
Prehospital hypoxemia — no. (%)‡	67 (35)	57 (29)	0.08
Prehospital hypotension — no. (%)	24 (12)	32 (16)	0.42
Injury Severity Score§	28±8	28±9	0.56

*Plus-minus values are means ±SD.

†The Glasgow Coma Scale is a descriptive numerical system for classifying the degree of responsiveness of patients with impaired consciousness. The scoring system for brain injury classifies scores of 13 to 15 as mild, 9 to 12 as moderate, and 8 or less as severe. Patients with scores of 3 to 4 have the most severe injuries, with no motor response or extensor posturing. Those with scores of 5 to 8 withdraw or localize purposefully to pain (i.e., physically identify the location of the painful stimulus).

‡Hypoxemia was detected by arterial blood gas measurements or pulse oximetry.

§The Injury Severity Score provides an overall score for patients with multiple injuries. Each injury is assigned a score on the Abbreviated Injury Scale, on which injury is ranked from 1 to 6, with 1 being minor and 6 fatal. To calculate the Injury Severity Score, the scores of the three most severe injuries are squared and summed. Values range from 0 to 75 and correlate with mortality, morbidity, and length of hospital stay.

third quartile, 8.9±0.7 hours and 51 percent; fourth quartile, 12.7±2.5 hours and 47 percent; P=0.28).

Medical Treatment

The doses of study medications, cumulative fluid balance, nutritional support, Therapeutic Intervention scores, and percentage of days with complications are shown in Table 2. The hypothermia group had a higher cumulative fluid balance, a greater use of vasopressors, a lower dose of vecuronium, and a higher percentage of days with complications than the normothermia group. Also, in the hypothermia group, mean arterial pressure was lower on days 3 and 4 during and after rewarming, the number of patients with a mean arterial pressure of less than 70 mm Hg was higher on day 4, mean cerebral perfusion pressure was higher on day 1 and lower on days 3 and 4, and the proportion of patients with a cerebral perfusion pressure of less than 50 mm Hg was lower on day 1 and higher on day 4 than in the normothermia group (Table 3).

Mean intracranial pressure did not differ significantly between the two treatment groups on any day.

TABLE 2. FACTORS RELATED TO MEDICAL TREATMENT AFTER HOSPITALIZATION IN PATIENTS WITH HEAD INJURY ASSIGNED TO INDUCTION OF HYPOTHERMIA OR TO NORMOTHERMIA.*

VARIABLE	HYPOTHERMIA	NORMOTHERMIA	P VALUE
Morphine (mg)†	8.2±4.3	8.3±4.8	0.82
Vecuronium (mg)†	6.9±2.8	8.3±3.8	0.003
Mannitol (g)	43.1±27.3	47.3±32.9	0.21
Phenytoin (mg)	273±203	279±175	0.51
Potassium (mmol)	25.0±12.6	28.0±32.5	0.61
Patients receiving vasopressors (%)	80	69	0.01
Hours of vasopressor therapy‡	48.5±33.9	41.0±37.8	0.05
Patients receiving two or more vasopressors (%)	51	39	0.43
Food intake by day 6 (kcal/day)	1569±840	1480±831	0.37
Daily mean TISS score in the ICU§	48.4±7.1	46.8±8.3	0.05
TISS score at hospital discharge§	17.4±12.6	16.1±11.9	0.41
Cumulative fluid balance during first 96 hours (ml)	3061±5946	1947±4586	0.04
Hospital days with complications per patient (%)¶	78±22	70±29	0.005

*Plus-minus values are means ±SD.

†Values are mean hourly doses during the first 96 hours after injury.

‡Values are hours of vasopressor treatment during the first 96 hours after injury.

§TISS denotes Therapeutic Intervention Scoring System, and ICU intensive care unit. This system permits quantitative comparison of the number and intensity of interventions in patients receiving intensive care. Forty-nine interventions are scored with a range of 1 to 4 points per intervention, with higher scores indicating a greater number and intensity of interventions. A typical score for a general intensive care unit is 27 to 30.

¶Values are the means of the percentages of all hospital days on which any complication was present for each patient.

Throughout the first 96 hours, the percentage of patients with an intracranial pressure of more than 30 mm Hg was lower in the hypothermia group (P=0.02). The percentage of patients with very high intracranial pressures (more than 30 mm Hg) was lower on day 2 (P=0.002) and day 3 (P=0.03) in the hypothermia group, but this difference did not persist through day 4. The Therapy Intensity Level,²⁵ which measures the intensity of therapy for high intracranial pressure, was slightly but significantly higher in the hypothermia group than in the normothermia group on day 3 during rewarming (Table 3).

Laboratory Data

There were small but statistically significant differences in the mean values for certain laboratory tests during the first 96 hours after randomization. Patients assigned to hypothermia had higher arterial blood pH values, hemoglobin concentrations, and hematocrit values. There was also a slight prolongation of prothrombin and partial-thromboplastin times and lower platelet counts in the hypothermia group. The patients

in the normothermia group had higher mean serum potassium concentrations and white-cell counts. Significantly more patients in the hypothermia group had serum creatinine concentrations of more than 2.5 mg per deciliter (221 μ mol per liter; 8 percent vs. 0.3 percent, $P=0.05$). There were no differences between groups for any other laboratory value. All mean values were within their respective normal ranges.

Complications

Ten percent of the patients in the hypothermia group and 3 percent of those in the normothermia group had critical hypotension (a mean arterial pressure of less than 70 mm Hg associated with organ failure) for two or more consecutive hours ($P=0.01$). Bradycardia associated with hypotension for two or more consecutive hours occurred in 16 percent of the patients in the hypothermia group and 4 percent of the patients in the normothermia group ($P=0.04$). The percentage of hospital days on which any complication was recorded was 78 ± 22 percent for patients in the hypothermia group and 70 ± 29 percent for patients in the normothermia group ($P=0.005$).

Outcome

Outcome data were obtained for 385 patients (98 percent). However, data on age or Glasgow coma score were missing or inaccurate for 17 patients, and therefore outcome data adjusted for age and Glasgow coma score were analyzed for 368 patients. There were no

differences between the hypothermia and normothermia groups in the primary outcome measure; 57 percent of the patients in both groups had a poor outcome (severe disability, vegetative state, or death) (Table 4). Mortality was 28 percent in the hypothermia group and 27 percent in the normothermia group. The outcome data unadjusted for age and Glasgow coma score in 385 patients were no different from the outcome data adjusted for age and Glasgow coma score in 368 patients. There were no significant differences between the two groups in the results of the neurobehavioral and neuropsychological tests at six months (data not shown).

The effects of hypothermia were evaluated in subgroups of patients for all independent variables present on admission and known to influence outcome (older age, low Glasgow coma score, compressed cisterns on computed tomographic scans, and surgical hematoma).²⁰⁻²⁴ For patients in the two treatment groups with Glasgow coma scores of 3 or 4 and 5 to 8, there were no differences in rates of poor outcome or death. In both treatment groups, the outcome was more often poor in patients over 45 years of age than in those who were 45 or younger ($P=0.001$). There were more poor outcomes in patients over 45 years of age in the hypothermia group than in patients over 45 in the normothermia group (88 percent in the hypothermia group vs. 69 percent in the normothermia group, $P=0.08$), but mortality was not higher (Table 4). The patients over 45 years of age in the hypothermia group also had more days with complications while they

TABLE 4. RATES OF POOR OUTCOME AND DEATH SIX MONTHS AFTER SEVERE BRAIN INJURY IN PATIENTS TREATED WITH INDUCTION OF HYPOTHERMIA OR NORMOTHERMIA.

TREATMENT GROUP	TOTAL No.	No. (%) WITH POOR OUTCOME*	RELATIVE RISK (95% CI)†	P VALUE	No. (%) WHO DIED	RELATIVE RISK (95% CI)†	P VALUE
All patients‡	368		1.0 (0.8–1.2)	0.99		1.0 (0.7–1.4)	0.79
Hypothermia	190	108 (57)			53 (28)		
Normothermia	178	102 (57)			48 (27)		
Patients with Glasgow coma scores of 3–4 on admission	87		1.1 (0.8–1.4)	0.64		1.4 (0.4–2.4)	0.35
Hypothermia	50	39 (78)			22 (44)		
Normothermia	37	27 (73)			13 (35)		
Patients with Glasgow coma scores of 5–8 on admission	281		0.9 (0.7–1.2)	0.55		1.0 (0.6–1.5)	0.71
Hypothermia	140	69 (49)			30 (21)		
Normothermia	141	75 (53)			32 (23)		
Patients >45 years old	52		1.3 (1.0–1.7)	0.08		1.0 (0.3–2.0)	1.00
Hypothermia	26	23 (88)			10 (38)		
Normothermia	26	18 (69)			10 (38)		

*Poor outcome was defined as severe disability, vegetative state, or death and was adjusted for age and Glasgow coma score on admission.

†Values indicate the relative risk in the hypothermia group as compared with the normothermia group. CI denotes confidence interval.

‡Data are presented for 368 patients because outcome data were missing for 7 patients and Glasgow coma score on admission, age, or both were missing for 17 patients.

were hospitalized (82 ± 21 percent of days in the hypothermia group vs. 55 ± 29 percent of days in the normothermia group, $P=0.002$).

Effect of Hypothermia at the Time of Hospitalization

Retrospective analysis of body temperature on admission showed that temperatures of 35.0°C or less had an adverse effect on outcome; however, temperatures above 35.0°C had no effect (Table 5). Factors that adversely affect outcome in patients with severe brain injury were more prevalent in the subgroup with hypothermia on admission than in the subgroup with normothermia on admission; these factors included a higher mean age, a higher Injury Severity Score, and a higher percentage of patients with prehospital hypotension. Other factors not known to affect the outcome after brain injury that were associated with hypothermia on admission were a positive test for blood alcohol, a higher volume of fluid administered before hospitalization, and admission in the winter (Table 5). The mean length of time from injury to admission was the same in both groups.

There were differences in the pattern of body tem-

perature between the subgroups with hypothermia on admission and with normothermia on admission. The body temperature of patients who had hypothermia on admission increased slowly and spontaneously. It took 14.4 ± 10.9 hours for the body temperature of patients who had hypothermia on admission and were assigned to the normothermia group to reach 37°C , as compared with 5.8 ± 4.1 hours for patients in the same group who had normothermia on admission ($P<0.001$). Patients who had hypothermia on admission and were assigned to the hypothermia group did not reach 33°C sooner than those who had normothermia on admission, because the body temperature in 39 percent of them spontaneously increased by $1.4 \pm 0.7^\circ\text{C}$ before randomization. The mean temperature in the first eight hours after hospitalization was $36.5 \pm 0.9^\circ\text{C}$ in the patients who had normothermia on admission and were assigned to the hypothermia group and $33.6 \pm 1.3^\circ\text{C}$ in the patients who had hypothermia on admission and were assigned to the hypothermia group ($P<0.001$).

Among the patients who had hypothermia on admission and were treated with hypothermia, 61 percent had poor outcomes, as compared with 78 percent of those with hypothermia on admission who were in the normothermia group ($P=0.09$) (Table 6). Among patients 45 years of age or younger who had hypothermia on admission, 52 percent of those assigned to the hypothermia group had poor outcomes, as compared with 76 percent in the normothermia group ($P=0.02$). However, the outcome was poor in 86 percent of patients over 45 years of age in the normothermia group and in 93 percent of patients over 45 in the hypothermia group (Table 6). Among the patients who had normothermia on admission, the outcomes were similar in the two treatment groups. The incidence of intracranial pressure of more than 30 mm Hg was lower in patients assigned to hypothermia both among patients who had hypothermia on admission (37 percent in the hypothermia group vs. 55 percent in the normothermia group, $P=0.10$) and among patients who had normothermia on admission (44 percent in the hypothermia group vs. 61 percent in the normothermia group, $P=0.007$).

DISCUSSION

Our findings regarding the outcomes of induced hypothermia for the treatment of severe brain injury are different from those of two earlier phase 2 trials. In 1993, Clifton et al.¹¹ reported a 15 percent improvement in outcome at six months in 46 patients whose body temperatures were cooled to 32°C for 48 hours, beginning within 6 hours after injury. In 1997, Marion et al.²⁶ reported a statistically significant improvement in outcome by 38 percent in 46 patients with Glasgow coma scores of 5 to 7 among 82 patients cooled to 32°C . The differences in results between these studies and the present one may relate to the dif-

TABLE 5. CHARACTERISTICS AT THE TIME OF HOSPITALIZATION OF PATIENTS WITH BRAIN INJURY ASSIGNED TO INDUCTION OF HYPOTHERMIA OR TO NORMOTHERMIA.*

CHARACTERISTIC	INITIAL BODY TEMPERATURE		P VALUE
	$\leq 35^\circ\text{C}$ (N=102)	$> 35^\circ\text{C}$ (N=264)	
Temperature on admission ($^\circ\text{C}$)	33.7 ± 1.2	36.5 ± 0.9	<0.001
Age (yr)	34 ± 12	31 ± 12	0.05
Glasgow coma score of 3–4 (%)†	28	22	0.22
Glasgow coma score of 5–8 (%)†	72	78	0.22
Hematoma requiring surgery (%)	35	28	0.21
Prehospital hypoxemia (%)‡	37	31	0.27
Prehospital hypotension (%)	22	13	0.05
Injury Severity Score§	30.7 ± 9.2	27.2 ± 8.2	<0.001
Admission in winter, from 10/1 to 4/1 (%)	62	50	0.05
Positive test for blood alcohol (%)	49	39	0.03
Prehospital fluid volume (ml)	958 ± 981	705 ± 790	0.02
Hours from injury to admission	1.3 ± 0.9	1.3 ± 0.9	0.83

*Plus-minus values are means \pm SD.

†The Glasgow Coma Scale is a descriptive numerical system for classifying the degree of responsiveness of patients with impaired consciousness. The scoring system for brain injury classifies scores of 13 to 15 as mild, 9 to 12 as moderate, and 8 or less as severe. Patients with scores of 3 or 4 have the most severe injuries, with no motor response or extensor posturing. Those with scores of 5 to 8 withdraw or localize purposefully to pain.

‡Hypoxemia was detected by arterial blood gas measurements or pulse oximetry.

§The Injury Severity Score provides an overall score for patients with multiple injuries. Each injury is assigned a score on the Abbreviated Injury Scale, on which injury is ranked from 1 to 6, with 1 being minor and 6 fatal. To calculate the Injury Severity Score, the scores of the three most severe injuries are squared and summed. Values range from 0 to 75 and correlate with mortality, morbidity, and length of hospital stay.

TABLE 6. BODY TEMPERATURE ON ADMISSION AND OUTCOME SIX MONTHS AFTER SEVERE BRAIN INJURY IN PATIENTS TREATED WITH INDUCTION OF HYPOTHERMIA OR NORMOTHERMIA.

TREATMENT GROUP	No. WITH BODY TEMPERATURE $\leq 35.0^{\circ}\text{C}$ ON ADMISSION	No. (%) WITH POOR OUTCOME*	RELATIVE RISK (95% CI)†	P VALUE	No. WITH BODY TEMPERATURE $> 35.0^{\circ}\text{C}$ ON ADMISSION	No. (%) WITH POOR OUTCOME*	RELATIVE RISK (95% CI)†	P VALUE
All patients‡	102		0.8 (0.6–1.0)	0.09	264		1.1 (0.8–1.3)	0.7
Hypothermia	62	38 (61)			127	69 (54)		
Normothermia	40	31 (78)			137	71 (52)		
Patients ≤ 45 years old	81		0.7 (0.5–1.0)	0.02	233		1.0 (0.8–1.3)	0.84
Hypothermia	48	25 (52)			115	59 (51)		
Normothermia	33	25 (76)			118	59 (50)		
Patients > 45 years old	21		1.1 (0.8–1.5)	0.60	31		1.3 (0.9–2.0)	0.23
Hypothermia	14	13 (93)			12	10 (83)		
Normothermia	7	6 (86)			19	12 (63)		

*Poor outcome was defined as severe disability, vegetative state, or death and was adjusted for age and Glasgow coma score on admission.

†Values indicate the relative risk in the hypothermia group as compared with the normothermia group. CI denotes confidence interval.

‡Data are presented for 366 patients because temperature on admission was missing for 2 patients, outcome data were missing for 7 patients, and Glasgow coma score on admission, age, or both were missing for 17 patients.

ferent percentages of patients who had hypothermia on admission, differences in the protocols for rewarming, and possible imbalances in randomization.

In the 1997 study, 66 percent of the patients in the normothermia group who had Glasgow coma scores of 5 to 7 had poor outcomes — an unexpectedly high rate — as compared with 52 percent in the same group of patients in our trial. The patients with hypothermia on admission who were assigned to the normothermia group were actively rewarmed in the 1997 study (Marion DW: personal communication), whereas in our study the body temperature of these patients rose spontaneously over a period of 24 hours. The discrepancies in results, therefore, could be explained by the inclusion of a high percentage of patients with hypothermia on admission and by worsened neurologic outcomes due to rapid rewarming of such patients in the normothermia group in the 1997 study.

The effect of hypothermia on high intracranial pressure²⁶⁻²⁸ is beneficial but probably unrelated to its effect on outcome. The effect on intracranial pressure was evident both in patients who had normothermia on admission and whose outcome did not improve with induced hypothermia and in patients who had hypothermia on admission and whose outcome did improve with continued hypothermia.

One interpretation of the variable effects of treatment in patients with different body temperatures on admission is that the induction of hypothermia in patients who have normothermia on admission is not beneficial, but that rewarming of patients who have hypothermia on admission is detrimental. Supporting this argument is the finding that hypothermia on admission was associated with a greater severity of injury and worse outcomes than was normothermia on admission. This finding might suggest that spontaneous hypothermia is a result of more severe brain injury.

An alternative interpretation is that the very early cooling in patients who have hypothermia on admission is crucial to achieving a neuroprotective effect. In the hypothermia group, the time from the injury to the achievement of the target temperature was only slightly less in the patients who had hypothermia on admission. These patients, however, had significantly lower temperatures in the first eight hours than the patients who had normothermia on admission. The results indicate that brain-injured patients who have hypothermia on admission should not be rewarmed, but that induced hypothermia that reaches a target temperature eight hours after injury did not prevent a poor outcome in patients with severe head injury.

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REFERENCES

1. Clasen RA, Pandolfi S, Russell J, Stuart D, Hass GM. Hypothermia and hypotension in experimental cerebral edema. *Arch Neurol* 1968;19:472-86.
2. Laskowski EJ, Klatzo I, Baldwin M. Experimental study of the effects of hypothermia on local brain injury. *Neurology* 1960;10:499-505.
3. Rosomoff HL, Gilbert R. Brain volume and cerebrospinal fluid pressure during hypothermia. *Am J Physiol* 1955;183:19-22.
4. Rosomoff HL, Shulman K, Raynor R, Grainger W. Experimental brain injury and delayed hypothermia. *Surg Gynecol Obstet* 1960;110:27-32.
5. Drake CG, Jory TA. Hypothermia in the treatment of critical head injury. *CMAJ* 1962;87:887-91.

6. Hendrick EB. The use of hypothermia in severe head injuries in childhood. *Arch Surg* 1959;79:362-4.
7. Lazorthes G, Campan L. Hypothermia in the treatment of craniocerebral traumatism. *J Neurosurg* 1958;15:162-7.
8. Sedzimir CB. Therapeutic hypothermia in cases of head injury. *J Neurosurg* 1959;16:407-14.
9. Shapiro HM, Wyte SR, Loeser J. Barbiturate-augmented hypothermia for reduction of persistent intracranial hypertension. *J Neurosurg* 1974;40:90-100.
10. Clifton GL, Allen SJ, Berry J, Koch SM. Systemic hypothermia in treatment of brain injury. *J Neurotrauma* 1992;9:Suppl 2:S487-S495.
11. Clifton GL, Allen S, Barrodale P, et al. A phase II study of moderate hypothermia in severe brain injury. *J Neurotrauma* 1993;10:263-71.
12. Marion DW, Obrist WD, Carlier PM, Penrod LE, Darby JM. The use of moderate therapeutic hypothermia for patients with severe head injuries: a preliminary report. *J Neurosurg* 1993;79:354-62.
13. Action related to emergency research activity. *Fed Regist* 1995; 60(143):38353.
14. Waiver of informed consent requirements in certain emergency research. *Fed Regist* 1996;61(192):51531.
15. Eisenberg HM, Frankowski RF, Contant CF, Marshall LF, Walker MD. High-dose barbiturate control in elevated intracranial pressure in patients with severe head injury. *J Neurosurg* 1988;69:15-23.
16. Bullock R, Chesnut RM, Clifton G, et al. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma* 2000;17:451-553.
17. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet* 1975;1:480-4.
18. Clifton GL, Hayes RL, Levin HS, Michel ME, Choi SC. Outcome measures for clinical trials involving traumatically brain-injured patients: report of a conference. *Neurosurgery* 1992;31:975-8.
19. Myles GL, Perry AG, Malkoff MD, Shatto BJ, Scott-Killmade MC. Quantifying nursing care in barbiturate-induced coma with the Therapeutic Intervention Scoring System. *J Neurosci Nurs* 1995;27:35-42.
20. Chesnut RM, Marshall SB, Piek J, Blunt BA, Klauber MR, Marshall LF. Early and late systemic hypotension as a frequent and fundamental source of cerebral ischemia following severe brain injury in the Traumatic Coma Data Bank. *Acta Neurochir Suppl (Wein)* 1993;59:121-5.
21. Choi SC, Narayan RK, Anderson RL, Ward JD. Enhanced specificity of prognosis in severe head injury. *J Neurosurg* 1988;69:381-5.
22. Vollmer DG, Torner JC, Jane JA, et al. Age and outcome following traumatic coma: why do older patients fare worse? *J Neurosurg* 1991;75: Suppl:S37-S49.
23. Marshall LF, Marshall SB, Klauber MR, et al. A new classification of head injury based on computerized tomography. *J Neurosurg* 1991;75: Suppl:S14-S20.
24. Gennarelli TA, Spielman GM, Langfitt TW, et al. Influence of the type of intracranial lesion on outcome from severe head injury. *J Neurosurg* 1982;56:26-32.
25. Maset AM, Marmarou A, Ward JD, et al. Pressure-volume index in head injury. *J Neurosurg* 1987;67:832-40.
26. Marion DW, Penrod LE, Kelsey SF, et al. Treatment of traumatic brain injury with moderate hypothermia. *N Engl J Med* 1997;336:540-6.
27. Shiozaki T, Sugimoto H, Taneda M, et al. Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. *J Neurosurg* 1993;79:363-8.
28. Shiozaki T, Sugimoto H, Taneda M, et al. Selection of severely head-injured patients for mild hypothermia therapy. *J Neurosurg* 1998;89:206-11.

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