ORIGINAL ARTICLE

Hypothermia Therapy after Traumatic Brain Injury in Children

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ABSTRACT

BACKGROUND

Hypothermia therapy improves survival and the neurologic outcome in animal models of traumatic brain injury. However, the effect of hypothermia therapy on the neurologic outcome and mortality among children who have severe traumatic brain injury is unknown.

METHODS

In a multicenter, international trial, we randomly assigned children with severe traumatic brain injury to either hypothermia therapy (32.5°C for 24 hours) initiated within 8 hours after injury or to normothermia (37.0°C). The primary outcome was the proportion of children who had an unfavorable outcome (i.e., severe disability, persistent vegetative state, or death), as assessed on the basis of the Pediatric Cerebral Performance Category score at 6 months.

RESULTS

A total of 225 children were randomly assigned to the hypothermia group or the normothermia group; the mean temperatures achieved in the two groups were 33.1±1.2°C and 36.9±0.5°C, respectively. At 6 months, 31% of the patients in the hypothermia group, as compared with 22% of the patients in the normothermia group, had an unfavorable outcome (relative risk, 1.41; 95% confidence interval [CI], 0.89 to 2.22; P=0.14). There were 23 deaths (21%) in the hypothermia group and 14 deaths (12%) in the normothermia group (relative risk, 1.40; 95% CI, 0.90 to 2.27; P=0.06). There was more hypotension (P=0.047) and more vasoactive agents were administered (P<0.001) in the hypothermia group during the rewarming period than in the normothermia group. Lengths of stay in the intensive care unit and in the hospital and other adverse events were similar in the two groups.

CONCLUSIONS

In children with severe traumatic brain injury, hypothermia therapy that is initiated within 8 hours after injury and continued for 24 hours does not improve the neurologic outcome and may increase mortality. (Current Controlled Trials number, ISRCTN77393684.)

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Hypothermia therapy significantly improves survival and the neurologic outcome in rodent models of traumatic brain injury.[1,2] An early case series involving 18 children suggested that hypothermia therapy could improve survival and the neurologic outcome among children with traumatic brain injury.[3] These observations led to two randomized trials involving children.[4,5]

In these two trials, investigators analyzed a total of 96 children with severe traumatic brain injury and reported that hypothermia therapy appeared to be safe and caused no significant increase in serious adverse events; however, these trials were not powered to detect significant improvements in survival or neurologic recovery.[4,5] In a single-center, randomized trial reported in 1997, Marion et al.[6] found that 24 hours of hypothermia therapy decreased the risk of a poor outcome, defined as death, a persistent vegetative state, or severe disability, in a subgroup of adults with a score of 5 to 7 on the Glasgow Coma Scale on admission after traumatic brain injury. These data provided a rationale for a trial of 24 hours of hypothermia therapy in children, and we began our study shortly after publication of these findings.[6] We hypothesized that, as compared with normothermia (36.5 to 37.5°C), treatment with hypothermia (32 to 33°C) for 24 hours, started within 8 hours after severe traumatic brain injury, would reduce the risk of an unfavorable outcome at 6 months.

METHODS

PATIENTS AND SITES

We conducted this study at 17 centers in three countries (see the Appendix). Patients were eligible if they were 1 to 17 years of age and had traumatic brain injury, a score on the Glasgow Coma Scale of 8 or less at the scene of the accident or in the emergency room, a computed tomographic (CT) scan that showed an acute brain injury, and a need for mechanical ventilation. We excluded patients who were screened more than 8 hours after injury, as well as patients with refractory shock, suspected brain death, nonaccidental injury, prolonged cardiac arrest at the scene of the accident, high cervical spinal cord injury, severe neurodevelopmental disability before the injury, brain injury due to a gunshot wound, acute isolated epidural hematoma, or pregnancy. The study was approved by the research ethics board at each participating institution. Written informed consent was obtained from the parents or guardians; deferred consent was obtained when parents or guardians were not available within 8 hours after injury.[7]

After each patient had been assessed and the patient's condition had been stabilized, a study physician randomly assigned the patient to a treatment group with the use of a central telephone-based system that was available 24 hours a day. The randomization, prepared by an independent statistician, was blocked in groups of four (participating centers were unaware of the block size) and included two stratification variables: center and age (less than 7 years of age and 7 years of age or more). The rationale for stratification by age at the time of injury was based on several studies that showed less recovery in IQ scores, attention, and executive functions among children who sustained severe injuries earlier in childhood, as compared with those who were injured later in childhood.[8-10]

TREATMENT GUIDELINES

Guidelines for cooling, rewarming, and management of intracranial pressure and cerebral perfusion pressure were established by consensus of the participating investigators, after a review of all relevant evidence.[11] Patients were cooled with the use of surface cooling techniques. Esophageal temperature was maintained at a mean (±SD) of 32.5±0.5°C for 24 hours.[11] For rewarming, the temperature was increased at a rate of 0.5°C every 2 hours. After rewarming in the hypothermia group, and beginning immediately in the normothermia group, temperature was maintained at 37±0.5°C until intracranial hypertension resolved. We documented baseline characteristics, including demographic and injury data, the score on the Glasgow Coma Scale, and Pediatric Trauma Score.[12]

STUDY OUTCOMES

The primary outcome for the study was the proportion of patients who had an unfavorable outcome — defined as severe disability, a persistent vegetative state, or death — at 6 months, which was assessed without knowledge of the treatment assignments. With the use of a scripted telephone interview, a trained site psychologist assessed each patient according to the six-point Pediatric Cerebral Performance Category scale (with a score of 1 representing normal performance, 2 mild dis-

ability, 3 moderate disability, 4 severe disability, 5 a persistent vegetative state, and 6 death).[13,14] A score on this scale was also assessed by means of an interview of the parents or guardians 1 week after the head injury, in which they were asked to estimate the child's level of function before the injury, and 1, 3, and 12 months after the injury. In addition, measures of intelligence,[15-17] memory functioning,[18,19] and speed of information processing were assessed in all of the children who were able to participate in testing 3 and 12 months after the injury; at these time points, parents were also interviewed with the use of an instrument that assesses a child's executive functions.[20] Blood pressure, intracranial pressure, cointerventions, lengths of stay in the intensive care unit (ICU) and in the hospital, and the rates of adverse events, including hypotension, infection, bleeding, arrhythmias, and electrolyte abnormalities, were also recorded.

STATISTICAL ANALYSIS

We estimated that enrolling 202 children would allow us to detect a reduction of 20 percentage points in the absolute risk[21] of an unfavorable outcome, from 50%[22] in the control (normothermia) group to 30% in the hypothermia group, with a two-sided alpha level of 0.05 and a statistical power of 80%. Assuming a 10% rate of loss to follow-up, our estimated sample size was 222 children.

Two planned interim analyses of the safety and efficacy of the study treatment were reviewed by a blinded, independent data and safety monitoring committee after 33% and 66% of the patients had been enrolled and followed for 6 months after injury.[23] The rates of an unfavorable outcome, death, and adverse events were compared between groups, with $P<0.001$ designated as the threshold for stopping the trial if there was compelling evidence of significant benefit or harm in either one of the study groups. There were no plans to stop the trial early if there appeared to be no evidence of unequal benefit or harm. At each interim analysis, the data and safety monitoring committee recommended the continuation of the trial.

The statistical analysis of the primary outcome was conducted with the use of the chi-square test according to the intention-to-treat principle and then according to the treatment received. Sensitivity analyses were performed to account for patients with missing data for primary outcomes. We planned eight a priori subgroup analyses, including one for children less than 7 years of age as compared with children 7 years of age or older. Exploratory analyses were performed with the use of logistic-regression models to adjust for the effects of clinical factors that may be associated with the outcome in children with traumatic brain injury — intervention group (hypothermia vs. normothermia), an age of less than 7 years as compared with an age of 7 years or more, score on the Glasgow Coma Scale (scores range from 3 to 15, with higher scores indicating better function) on admission to the hospital (3 or 4 vs. 5 to 8), temperature on admission of less than 35°C versus 35°C or more, intracranial pressure of more than 20 mm Hg versus 20 mm Hg or less, hypotension or hypoxia present or absent on admission, number of therapies used to control intracranial pressure (0 to 3 vs. 4 or 5), hypertonic saline used or not used to control intracranial pressure, and three variables that were noted on CT scans (presence or absence of extradural hematoma, cerebral edema, and midline shift). Mortality was analyzed by means of chi-square tests. Further exploratory analyses of mortality were performed with the use of Cox proportional-hazards models, with unadjusted and adjusted analyses of the time to death in the two groups. Scores on the Pediatric Cerebral Performance Category scale were also compared over time, with the use of an analysis of variance with repeated measures.

All secondary outcomes were analyzed according to the intention-to-treat principle. Continuous variables were analyzed first with independent Student's t-tests and then with generalized linear models. Categorical variables, including rates of adverse events, were analyzed with the use of the chi-square test. Additional analyses of variables related to the process of care, including lengths of stay in the ICU and hospital, were performed by means of nonparametric procedures (the Wilcoxon rank-sum test).

RESULTS

PATIENTS AND TREATMENT ASSIGNMENT

From February 1999 to October 2004, a total of 1441 consecutive patients with traumatic brain injury were admitted to the pediatric ICUs that participated in the study (see the figure in the Supplementary Appendix, available with the full text of this article at www.nejm.org). Three hundred twenty-seven of the 1441 patients (23%) met the eligibility criteria. Of the 327 eligible patients, 69

were not identified and their parents or guardians were not approached for consent within 8 hours after injury, 33 had parents or guardians who declined consent, and 225 (69% of eligible patients) were enrolled. One hundred eight patients were randomly assigned to hypothermia therapy, and 117 patients to normothermia. A total of 7 patients (3% of enrolled patients) did not have a monitor inserted to measure intracranial pressure — 3 of 108 patients (3%) in the hypothermia group and 4 of 117 (3%) in the normothermia group. Baseline characteristics of the patients who were enrolled in the study are presented in Table 1.

INTERVENTION AND MONITORING

One hundred two of the 108 patients (94%) who were assigned to hypothermia therapy received the intervention (mean temperature, 33.1±1.2°C for 24

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Hypothermia Group (N=108)	Normothermia Group (N=117)
Age — yr	9.8±4.9	10.2±4.8
Male sex — no. (%)	70 (65)	71 (61)
Weight — kg	39.4±21.2	40.3±21.1
GCS on admission — median (IQR)	5 (4–6)	5 (3–6)
Pediatric Trauma Score — median (IQR)	3 (2–5)	3 (2–5)
Cause of injury — no. (%)		
Motor vehicle	70 (65)	64 (55)
Passenger	30 (43)	32 (51)
Pedestrian	40 (57)	31 (49)
Bicycle	12 (11)	18 (15)
Fall	17 (16)	21 (18)
Other	9 (8)	14 (12)
Initial presentation — no. (%)		
Hypotension on admission	8 (7)	3 (3)
Hypoxia on admission	3 (3)	0
Transfer from another institution	62 (57)	79 (68)
CT findings — no. (%)		
Extradural hematoma	10 (9)	22 (19)
Intracerebral hematoma	62 (57)	62 (53)
Cerebral edema	85 (79)	83 (71)
Midline shift	33 (31)	27 (23)
Skull fracture	59 (55)	59 (50)
Other injuries — no. (%)†		
Spinal cord injury	1 (1)	1 (1)
Thoracic injury	38 (35)	36 (31)
Cardiovascular injury	4 (4)	1 (1)
Abdominal injury	10 (9)	13 (11)
Genitourinary injury	11 (10)	10 (9)
Major fracture or dislocation	25 (23)	22 (19)

* Plus–minus values are means ±SD. GCS denotes Glasgow Coma Scale, and IQR interquartile range.
† Thoracic injuries included major airway trauma, hemothorax, pulmonary contusion, pulmonary laceration, and ruptured diaphragm. Cardiovascular injuries included major-vessel injuries, cardiac lacerations, and myocardial contusion. Abdominal injuries included injuries to the liver, spleen, bowel, and pancreas. Major fractures and dislocations included facial, spinal, pelvic, and long-bone fractures and dislocation of major joints.

hours). The mean time to initiation of cooling was 6.3±2.3 hours (range, 1.6 to 19.7) after injury, the mean time to attainment of the target temperature range was 3.9±2.6 hours (range, 0.0 to 11.8), and the mean time to completion of rewarming after the 24-hour period at the target temperature was 18.8±14.9 hours (range, 2.5 to 148.0) (Fig. 1). In 114 of the 117 patients (97%) in the normothermia group, a normal temperature (36.9±0.5°C) was maintained for 24 hours. No patient who was assigned to the normothermia group was treated with hypothermia. Any failures to follow the temperature protocol and treatment guidelines were reviewed by a clinical care committee, and rapid feedback was given to the principal and site investigators to improve compliance with the protocol.

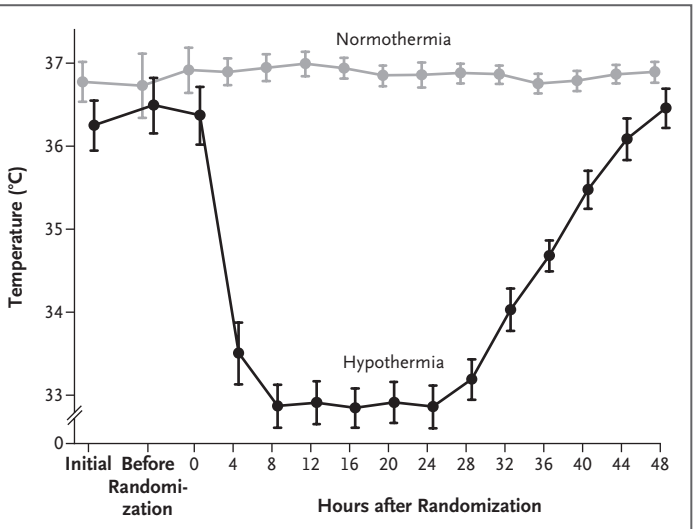

Figure 1. Temperature of Patients in the Hypothermia and Normothermia Groups.

Data are shown as means and 95% confidence intervals.

COINTERVENTIONS

A significantly higher proportion of patients in the normothermia group than in the hypothermia group received hypertonic saline to control intracranial pressure during the first 24 hours (Table 2). A significantly higher proportion of patients in the hypothermia group than in the normothermia group received vasoactive drugs for hypotension during the rewarming period (Table 2). Otherwise, there were no significant imbalances in the rate at which therapies were used to treat intracranial hypertension or in the fluid balance between the groups.

STUDY OUTCOMES

Data on primary outcomes were available for 205 patients (91%). Overall, 20 of the 225 patients (9%) were lost to follow-up at 6 months — 6 of 108 patients (6%) in the hypothermia group and 14 of 117 (12%) in the normothermia group. Thirty-two of 102 patients (31%) in the hypothermia group and 23 of 103 (22%) in the normothermia group had an unfavorable outcome at 6 months (relative risk of an unfavorable outcome with hypothermia therapy, 1.41; 95% confidence interval [CI], 0.89 to 2.22; P=0.14) (Table 3). In a sensitivity analysis that accounted for the 20 patients who were lost to follow-up at 6 months and assuming the worst case in the hypothermia group and the best case in the normothermia group, hypothermia therapy was associated with an unfavorable outcome (P=0.001); with the opposite scenario (best case and worst case in the two groups, respectively), there was no increased risk of an unfavorable outcome with hypothermia therapy (P=0.82). With logistic-regression models adjusted for clinical factors that may be associated with the outcome in children with traumatic brain injury, the adjusted odds ratio for an unfavorable outcome with hypothermia therapy was 2.33 (95% CI, 0.92 to 5.93; P=0.08).

We also performed an analysis of the primary outcome according to the treatment received, but we noted no major differences from the intention-to-treat analysis. In a subgroup analysis of patients 7 years of age or older, the risk of an unfavorable outcome was higher with hypothermia therapy than with normothermia (relative risk, 1.71; 95% CI, 0.96 to 3.06; P=0.06). The relative risk of an unfavorable outcome was also higher with hypothermia therapy in the subgroup that included patients whose recorded measurements of intracranial pressure were all less than 20 mm Hg (relative risk, 2.12; 95% CI, 1.07 to 4.19; P=0.03). There were no significant differences in the other subgroups that were analyzed. The Pediatric Cerebral Performance Category scores improved with time after the injury in both groups; the improvement was greater in the normothermia group than in the hypothermia group 1, 3, 6, and 12 months after the injury, although the difference was not significant (P=0.07).

There were 23 deaths (21%) in the hypothermia group, as compared with 14 deaths (12%) in the normothermia group (relative risk of death with

Table 2. Cointerventions to Manage Intracranial Pressure and Support Blood Pressure.*

Therapy	Hypothermia Group (N=108)	Normothermia Group (N=117)	P Value
0–24 Hr			
Cerebrospinal fluid drainage — no. (%)	45 (42)	55 (47)	0.42
Mannitol — no. (%)	54 (50)	70 (60)	0.14
Hypertonic saline (3%) — no. (%)	34 (31)	54 (46)	0.02
Hyperventilation — no. (%)			0.99
$PaCO_2$, 30–35 mm Hg	11 (10)	12 (10)	
$PaCO_2$, <30 mm Hg	47 (44)	50 (43)	
Barbiturates — no. (%)	15 (14)	22 (19)	0.32
Dopamine, epinephrine, or norepinephrine — no. (%)	59 (55)	56 (48)	0.31
Transfusions of packed cells — no. (%)	38 (35)	30 (26)	0.12
Fluid balance — ml/24 hr			0.78
Median	700	750	
Interquartile range	250–1700	300–1500	
25–72 Hr			
Cerebrospinal fluid drainage — no. (%)	52 (48)	56 (48)	0.97
Mannitol — no. (%)	61 (56)	67 (57)	0.91
Hypertonic saline (3%) — no. (%)	54 (50)	64 (55)	0.48
Hyperventilation — no. (%)			0.09
$PaCO_2$, 30–35 mm Hg	6 (6)	9 (8)	
$PaCO_2$, <30 mm Hg	48 (44)	35 (30)	
Barbiturates — no. (%)	23 (21)	26 (22)	0.87
Dopamine, epinephrine, or norepinephrine — no. (%)	92 (85)	66 (56)	<0.001
Transfusions of packed cells — no. (%)	33 (31)	36 (31)	0.97
Fluid balance — ml/24 hr			0.8
Median	828	617	
Interquartile range	380–1550	500–1300	

* The guidelines that were used for the management of intracranial pressure and cerebral perfusion pressure are outlined in Hutchison et al.[11] If the intracranial pressure was greater than 20 mm Hg and if reversible causes had been ruled out or treated, therapies were given in the following order: cerebrospinal fluid drainage if an external ventricular drain was present, mannitol, hypertonic saline, hyperventilation, and barbiturates; patients were treated with the next listed therapy only if the previous therapy was ineffective. Therapies for cerebral perfusion pressure were given if cerebral perfusion was less than 60 mm Hg for patients 10 years of age or older or less than 50 mm Hg for those less than 10 years of age. $PaCO_2$ denotes partial pressure of arterial carbon dioxide.

hypothermia therapy, 1.40; 95% CI, 0.90 to 2.27; P=0.06) (Table 3 and Fig. 2). In the unadjusted Cox proportional-hazards model, the hazard ratio for death with hypothermia therapy was 1.84 (95% CI, 0.95 to 3.58; P=0.07), whereas in the model adjusted for clinical factors that may be associated with the outcome in children with traumatic brain injury, the hazard ratio for death was 2.36 (95% CI, 1.04 to 5.37; P=0.04).

There were no significant differences in the durations of intracranial pressure monitoring, mechanical ventilation, or stays in the pediatric ICU or the hospital between the two groups (Table 3). Intracranial pressures were lower during the cooling period and higher during the rewarming period in the hypothermia group, as compared with the normothermia group; the difference was significant at 16 hours (P=0.02), 24 hours (P=0.01),

Table 3. Primary and Secondary Outcomes.*

Outcome	Hypothermia Group (N=108)	Normothermia Group (N=117)	Relative Risk or Absolute Difference (95% CI)	P Value
Primary				
PCPC score 4–6 — no./total no. (%)	32/102 (31)	23/103 (22)	1.41 (0.89 to 2.22)	0.14
Secondary				
Overall mortality — no. (%)	23 (21)	14 (12)	1.40 (0.90 to 2.27)	0.06
Duration of care — days				
ICP monitoring	6.4±4.0	6.0±3.0	0.4 (–0.6 to 1.3)	0.45
Mechanical ventilation	9.5±6.1	8.9±5.7	0.7 (–0.9 to 2.2)	0.41
Intensive care unit	11.5±7.1	11.3±7.2	0.2 (–1.7 to 2.1)	0.85
Hospital	30.2±31.7	28.3±24.2	1.9 (–5.8 to 9.5)	0.63
Physiological variables at 0 to 24 hr				
ICP — mm Hg (95% CI)	14.7±10.7 (12.7 to 16.8)	17.1±11.1 (15 to 19.1)		0.12
CPP — mm Hg (95% CI)	66.4±12 (64.1 to 68.8)	64.3±11.5 (62.2 to 66.5)		0.19
Mean blood pressure — mm Hg (95% CI)	80.6±9.8 (78.7 to 82.5)	81.4±10.1 (79.5 to 83.2)		0.56
Heart rate — beats/min (95% CI)	81.5±16.7 (78.3 to 84.7)	108.1±19.1 (104.6 to 111.6)		<0.001
Physiological variables at 25 to 72 hr				
ICP — mm Hg (95% CI)	17.1±7.1 (15.6 to 18.5)	17.4±10.7 (15.4 to 19.4)		0.77
CPP — mm Hg (95% CI)	60.8±7.8 (59.2 to 62.4)	66±10.8 (64 to 68.1)		<0.001
Mean blood pressure — mm Hg (95% CI)	77.7±7.6 (76.2 to 79.2)	83.4±8 (81.9 to 84.9)		<0.001
Heart rate — beats/min (95% CI)	100.7±18.3 (97.1 to 104.3)	105.3±18.2 (101.9 to 108.6)		0.07
Adverse events — no. (%)				
Hypotension				
0–24 hr	27 (25)	18 (15)		0.07
25–72 hr	49 (45)	38 (32)		0.047
Ventricular tachycardia	1 (1)	0		0.48
Ventricular fibrillation	0	1 (1)		0.52
ARDS	8 (8)	6 (5)		0.47
Pneumonia	39 (36)	51 (44)		0.25
Septic shock	2 (2)	2 (2)		0.38
Other infections	16 (15)	19 (16)		0.81
Bleeding				
Late intracranial	3 (3)	5 (4)		0.72
Extracranial	1 (1)	1 (1)		0.96

* Plus–minus values are means ±SD. Relative risks are given for the Pediatric Cerebral Performance Category (PCPC) score and for overall mortality. Absolute differences between the values for the hypothermia and normothermia groups are given for the duration of ICP monitoring and of mechanical ventilation and for the length of the intensive care unit and hospital stays. The primary outcome was the proportion of patients with an unfavorable outcome, defined as severe disability, a persistent vegetative state, or death (PCPC score of 4 to 6) at 6 months. ARDS denotes acute respiratory distress syndrome, CPP cerebral perfusion pressure, and ICP intracranial pressure.

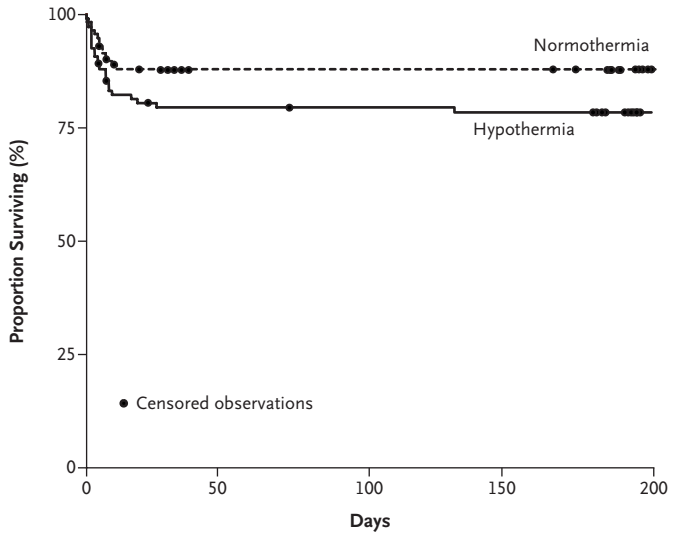

Figure 2. Kaplan–Meier Estimates of Survival.

The causes of death in the hypothermia group were brain death (4 patients), brain trauma (12), brain ischemia (1), hypoxia resulting from severe lung injury (3), and septic shock (1), with unknown causes in 2 patients. The causes of death in the normothermia group were brain death (2 patients), brain trauma (9), and brain ischemia (2), with an unknown cause in 1 patient.

48 hours (P=0.01), and 72 hours (P=0.03). The heart rate was significantly lower in patients who were undergoing hypothermia therapy than in those in the normothermia group (P<0.001) (Table 3). During rewarming after hypothermia therapy, we noted significantly more episodes of hypotension (P=0.047) and lower mean blood pressures and cerebral perfusion pressures (P<0.001 for both comparisons) (Table 3). Hypotension was treated with boluses of intravenous fluids and vasopressors according to the study treatment guidelines. No other serious adverse events were significantly associated with the use of hypothermia therapy (Table 3).

We performed neuropsychological follow-up for 59% of the survivors at 3 months and for 63% of the survivors at 12 months. Patients were not assessed if they were too young to participate in testing (generally, younger than 5 years of age) or had severe functional or physical impairment that made assessment impossible, or if their parents or guardians could not be contacted or refused follow-up. Scores on assessments of long-term visual memory were significantly worse in the hypothermia group than in the normothermia group 12 months after injury (P=0.05) (see the table in the Supplementary Appendix). There were no other differences in neuropsychological outcomes between the groups.

In the hypothermia group, as compared with the normothermia group, the mean serum glucose level was significantly higher in the first 24 hours (171.2±91.9 mg per deciliter [9.5±5.1 mmol per liter] vs. 138.7±46.8 mg per deciliter [7.7±2.6 mmol per liter], P=0.002), the platelet count was significantly lower (174,900±61,000 per cubic millimeter vs. 192,000±67,200 per cubic millimeter, P=0.05), and the prothrombin time and serum lactate level were significantly higher between 25 and 72 hours (prothrombin time, 15.3±2.6 seconds vs. 14.3±2.5 seconds; P=0.03; lactate level, 11.7±7.2 mg per deciliter vs. 9.0±5.4 mg per deciliter; P=0.03).

DISCUSSION

In this multicenter, randomized, controlled trial, we found that among children with major head injury, moderate hypothermia therapy (32 to 33°C), initiated within 8 hours after the injury and maintained for 24 hours, did not improve the functional outcome at 6 months. We observed a trend toward increased mortality in the hypothermia group and found no evidence of a benefit with respect to any secondary outcomes, including functional and neuropsychological outcomes at 3 and 12 months, length of stay in the ICU or hospital, and adverse events.

While we were conducting this trial, the results of a large study of hypothermia therapy in 392 adults with severe traumatic brain injury were published.[24] This study, conducted by Clifton et al., did not show meaningful benefits in the rate of survival or in functional outcomes and documented more complications, such as critical hypotension, in adults who were treated with hypothermia for 48 hours than in those who were treated with normothermia.[24] Three of four systematic reviews that pooled trial data on hypothermia, including 1130 adults in the four systematic reviews, also noted the absence of a benefit from hypothermia therapy after traumatic brain injury.[25-28] Hypothermia therapy appears to be of benefit in some adults and newborns with a hypoxic–ischemic brain injury[29-33] but not in adults with traumatic brain injury.[24]

A potential limitation of our trial is that the mean time to the initiation of hypothermia was 6.3 hours. It is plausible that hypothermia therapy might be more effective if it were initiated earlier, as was reported in an animal model of traumatic

brain injury, in which hypothermia was instituted within 15 minutes[34]; however, there would be great logistical challenges to conducting such a trial. We did not detect a benefit in our subgroup of patients who were treated early (data not shown). Another limitation of our trial is that more prolonged therapy might have resulted in beneficial outcomes. We chose to treat patients for 24 hours on the basis of evidence from studies of adults.[6] However, in one systematic review, a subgroup analysis suggested that hypothermia therapy given for more than 48 hours reduced the risks of death and a poor neurologic outcome (relative risk, as compared with normothermia, 0.70 [95% CI, 0.56 to 0.87] and 0.65 [95% CI, 0.48 to 0.89], respectively).[28] Hypothermia, with adjustment of degree and depth according to intracranial pressure, may be of benefit as a therapy for refractory intracranial hypertension in many children with severe traumatic brain injury.[4,5] Another potential limitation of our study is the small sample. Future studies should be powered to detect smaller treatment effects.

This study has several strengths. We used a similar approach to control intracranial hypertension and to manage fluid balance in the two groups.[11] We found no evidence that cointerventions such as the management of intracranial pressures and fluids or other aspects of care contributed to the failure of hypothermia therapy. The rate of loss to follow-up at 6 months was less than 10%.

On the basis of the results of this multicenter trial, we conclude that the use of this hypothermia protocol is not warranted for the treatment of severe head injury in children. Further research may elucidate whether earlier implementation of hypothermia therapy or more prolonged hypothermia therapy would improve the outcome in children with severe traumatic brain injury.

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APPENDIX

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