TREATMENT OF TRAUMATIC BRAIN INJURY WITH MODERATE HYPOTHERMIA

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ABSTRACT

Background Traumatic brain injury initiates several metabolic processes that can exacerbate the injury. There is evidence that hypothermia may limit some of these deleterious metabolic responses.

Methods In a randomized, controlled trial, we compared the effects of moderate hypothermia and normothermia in 82 patients with severe closed head injuries (a score of 3 to 7 on the Glasgow Coma Scale). The patients assigned to hypothermia were cooled to 33°C a mean of 10 hours after injury, kept at 32 to 33°C for 24 hours, and then rewarmed. A specialist in physical medicine and rehabilitation who was unaware of the treatment assignments evaluated the patients 3, 6, and 12 months later with the use of the Glasgow Outcome Scale.

Results The demographic characteristics and causes and severity of injury were similar in the hypothermia and normothermia groups. At 12 months, 62 percent of the patients in the hypothermia group and 38 percent of those in the normothermia group had good outcomes (moderate, mild, or no disabilities). The adjusted risk ratio for a bad outcome in the hypothermia group was 0.5 (95 percent confidence interval, 0.2 to 1.2). Hypothermia did not improve the outcomes in the patients with coma scores of 3 or 4 on admission. Among the patients with scores of 5 to 7, hypothermia was associated with significantly improved outcomes at 3 and 6 months (adjusted risk ratio for a bad outcome, 0.2; 95 percent confidence interval, 0.1 to 0.9 at both intervals), although not at 12 months (risk ratio, 0.3; 95 percent confidence interval, 0.1 to 1.0).

Conclusions Treatment with moderate hypothermia for 24 hours in patients with severe traumatic brain injury and coma scores of 5 to 7 on admission hastened neurologic recovery and may have improved the outcome. (N Engl J Med 1997;336:540-6.)

THE therapeutic use of hypothermia in a patient with traumatic brain injury was first reported in 1943.[1] However, since neither this report nor several subsequent reports provided comparative data on patients kept at normal temperatures, they failed to establish the efficacy of therapeutic hypothermia.[2-5] Moreover, the degree and duration of cooling and the interval between the injury and the initiation of treatment varied both within and among the studies.

In 1993, preliminary reports on three clinical trials of moderate hypothermia (a temperature of 32 or 33°C) in patients with traumatic brain injury were published, including our report on the first 40 patients in this study.[6-8] The largest trial included 46 patients. The studies differed slightly in terms of the duration of cooling (one day or two days) and when it was initiated (within hours after the injury or only after conventional therapy had failed to control intracranial pressure). In each study, there was a trend toward improved outcomes among the patients treated with hypothermia, as compared with those kept at a normal temperature. On the basis of these results, we continued our study. We also assessed the effects of hypothermia on post-traumatic cerebral physiology and ventricular cerebrospinal fluid concentrations of excitatory amino acids and interleukin-1β. This report describes the results in 82 patients, including the 40 patients described in our preliminary report.[8]

METHODS

From February 1991 through September 1994, 155 patients with closed head injuries who had a score of 3 to 7 on the Glasgow Coma Scale[9] were admitted to our trauma center. The Glasgow Coma Scale is based on patients' ability to open their eyes, speak, and use their arms or legs. Patients with a score of 7, for example, usually attempt to remove a painful stimulus with an arm but do not speak or open their eyes in response to the stimulus.

The predetermined entry criteria, in addition to a closed head injury and a Glasgow coma score of 3 to 7, were an age of 16 to 75 years, admission within six hours after the injury, and an inability to follow commands. Patients were excluded for the following reasons: clinical brain death (a score of 3 on the Glasgow Coma Scale and no brain-stem reflexes), prolonged hypoxia or hypotension, a gunshot wound, pregnancy, an undetermined time of injury, or normal findings on a computed tomographic (CT) scan of the head (class I according to the classification described by Marshall et al.[10]).

Eighty-two of the 155 patients met the entry criteria and were randomly assigned to hypothermia or normothermia within six hours after injury. Using a block-randomization scheme, we assigned patients with a Glasgow coma score of 3 or 4 to a treatment group separately from those with a score of 5 to 7 by choosing among equal numbers of sealed envelopes containing the group assignments. This procedure and the study protocol were approved by the University of Pittsburgh investigational review board. If family members were available within six hours after the injury, we obtained written informed consent before randomization. Otherwise, patients were enrolled in the study,

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and consent was obtained when family members arrived at the hospital.

Treatment Protocol

We began to cool the 40 patients assigned to the hypothermia group immediately after enrollment, using cooling blankets (Blanketrol II, Cincinnati Sub-Zero, Cincinnati) placed above and below the patient and nasogastric lavage with iced saline. Once the rectal temperature reached 33°C (a mean of 10 hours after the injury), it was kept between 32 and 33°C for 24 hours. During the next 12 hours, the patients were passively rewarmed to a temperature of 37 to 38.5°C, at a rate no greater than 1°C per hour, by a gradual adjustment of the blanket thermostat. In the 42 patients in the normothermia group, the temperature was kept between 37 and 38.5°C during the entire five-day monitoring period. The patients in the normothermia group who had rectal temperatures below 37°C at admission were passively rewarmed over a period of 12 hours. To prevent shivering, the patients in the hypothermia group received continuous infusions of a paralytic drug (vecuronium bromide, 10 mg per hour) and a narcotic agent (fentanyl citrate, 50 to 100 μg per hour) for the first 36 hours after the injury. The patients in the normothermia group received similar doses of these drugs during that time.

To determine how accurately rectal temperatures reflected brain temperatures, we compared the results of simultaneous rectal and brain measurements in the first 40 patients. Brain temperatures were measured directly with a microthermistor placed 2 cm from the tip of an external ventricular-drainage catheter (PMT, Chanhassen, Minn.). In 95 percent of over 4000 simultaneous measurements, rectal and brain temperatures did not vary by more than 0.5°C. We therefore used the rectal temperature as a reliable, easily measured indication of the brain temperature.

To monitor cerebral oxygen extraction, we determined the difference between arterial and jugular venous oxygen content every 4 hours for the first 24 hours and every 6 hours thereafter. A jugular venous catheter was inserted into the jugular bulb, and the oxygen content of blood samples obtained from this catheter was subtracted from the oxygen content of simultaneously obtained samples of radial arterial blood. Cerebral blood flow was measured every 12 hours for five days with the xenon-133 technique.[11]

The patients were treated according to the principles described in "Guidelines for the Management of Severe Head Injury."[12] We rapidly evacuated large subdural and epidural hematomas and hemorrhagic contusions. Intravascular volumes were maintained at nearly normal values by keeping central venous pressures between 6 and 15 cm of water. The cerebral perfusion pressure (the mean arterial pressure minus the intracranial pressure) was maintained at a level higher than 70 mm Hg at all times by keeping the mean arterial pressure at a level between 90 and 110 mm Hg and the intracranial pressure at a level below 20 mm Hg. A ventriculostomy catheter, with a closed column of cerebrospinal fluid coupled to a strain-gauge transducer, was inserted to provide continuous measurement of intracranial pressure. Ventricular cerebrospinal fluid was drained intermittently and bolus intravenous infusions of mannitol (25 to 50 g every three to four hours) were administered to reduce intracranial hypertension. If these measures were unsuccessful and follow-up CT scans showed no mass lesions that should be resected, pentobarbital was infused at a dose that resulted in the suppression of bursts on the electroencephalogram (60 to 120 mg per hour). Corticosteroids were not used. If the intracranial pressure remained high, we administered intravenous dopamine to increase the mean arterial pressure and maintain the cerebral perfusion pressure at a level above 70 mm Hg. Dopamine infusions were required in 22 patients in the hypothermia group and in 17 in the normothermia group. We used hypocapneic therapy (partial pressure of carbon dioxide, $<$33 mm Hg at 37°C) only to manage otherwise uncontrollable intracranial hypertension. All patients received phenytoin (300 mg per day) intravenously for seven days.

Cerebrospinal Fluid Analysis

We withdrew specimens of cerebrospinal fluid (3 to 4 ml) from the ventriculostomy catheter every 4 hours for the first 24 hours and every 6 hours for the next four days. Immediately before the samples were assayed, they were filtered to remove proteinaceous and particulate material. Aspartate and glutamate concentrations were measured by high-pressure liquid chromatography with the use of a fluorescence detector after precolumn derivation of amino acids with *o*-phthaldialdehyde.[13] Interleukin-1β was measured with a highly sensitive enzyme-linked immunosorbent assay (Cistron Biotechnology, Pine Brook, N.J.).

Assessment of Neurologic Outcome

A specialist in physical medicine and rehabilitation who was unaware of the patients' treatment assignments determined the neurologic outcome 3, 6, and 12 months after the injury. The neurologic outcome was scored according to the Glasgow Outcome Scale,[14] as follows: 1, death; 2, vegetative state — unable to interact with the environment; 3, severe disability — unable to live independently but able to follow commands; 4, moderate disability — capable of living independently but unable to return to work or school; and 5, mild or no disability — able to return to work or school.

Statistical Analysis

The base-line characteristics, complications, and outcomes in the two groups were compared with the use of chi-square tests, Fisher's exact tests, Wilcoxon rank-sum tests, or t-tests as appropriate. To compare values for pressure (intracranial pressure, cerebral perfusion pressure, and mean arterial pressure), cerebrospinal fluid neurochemical concentrations, and hematologic variables, we tested the differences in mean values with the use of generalized-linear-regression analysis. Because we performed multiple measurements of each variable in each patient and assumed that the values were correlated, we used a generalized linear model that adjusts for intraclass correlation.[15] An interim analysis of the outcomes at three and six months for the first 40 patients in the study, reported elsewhere, slightly reduces the power of this final analysis.[8]

Most of the demographic and clinical characteristics of the two groups were similar. On the basis of the CT class, the injuries were slightly less severe in the hypothermia group, but the difference was not statistically significant (Table 1). To adjust for a possible confounding effect of the CT class, we performed logistic-regression analyses with a dichotomous outcome variable (death, vegetative state, or severe disability vs. normal or moderate disability). The explanatory variables were treatment group, initial Glasgow coma score, and CT class.

RESULTS

Characteristics of the Patients

Most of the patients were men, and the most common cause of head injury was a motor vehicle accident (Table 1). The two groups did not differ significantly in terms of age; numbers of patients with abdominal or chest injuries or arm, leg, or pelvic fractures; or the initial Glasgow coma score, although a slightly higher percentage of patients in the normothermia group had a coma score of 5 to 7.

The mean stay in the trauma center was similar in the two groups: 38 days (range, 2 to 267) in the hypothermia group and 35 (range, 1 to 138) in the normothermia group. Eight patients in the hypothermia group and nine in the normothermia group died during this time. Among the surviving patients, 25 (78 percent) in the hypothermia group and 29

TABLE 1. CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF 82 PATIENTS WITH TRAUMATIC BRAIN INJURY ASSIGNED TO HYPOTHERMIA OR NORMOTHERMIA.*

CHARACTERISTIC	HYPOTHERMIA (N=40)	NORMOTHERMIA (N=42)
Age (yr)	31±12	35±15
	no. of patients (%)	
Male sex	36 (90)	33 (79)
Cause of injury		
Motor vehicle accident	30 (75)	25 (60)
Assault	2 (5)	1 (2)
Fall	4 (10)	14 (33)
Other	3 (8)	1 (2)
Unknown	1 (2)	1 (2)
Initial Glasgow coma score		
3 or 4	18 (45)	16 (38)
5–7	22 (55)	26 (62)
Pupillary abnormalities†	33 (82)	35 (83)
CT class‡		
I	1 (2)	1 (2)
II	15 (38)	9 (21)
III	10 (25)	8 (19)
IV	1 (2)	4 (10)
V	13 (32)	20 (48)
Abdominal injuries	4 (10)	6 (14)
Chest injuries	12 (30)	10 (24)
Pelvic or leg fractures	7 (18)	7 (17)
Arm fractures	6 (15)	4 (10)

*Plus–minus values are means ±SD. Percentages may not add to 100 because of rounding.

†Pupillary abnormalities were defined as abnormalities in size or the reaction to light in one or both pupils.

‡The CT class was determined according to the following classification: class I, no visible evidence of injury; class II, cisterns present, with a midline shift of ≤5 mm and no lesions >25 ml; class III, cisterns compressed or absent; class IV, a midline shift of >5 mm; and class V, a lesion requiring surgical evacuation.[14] All CT scans were reviewed by a neuroradiologist, and the CT classification was based on that review. The neuroradiologists interpreted the CT scans of two patients (one in each group) as normal (class I) after the neurosurgeon responsible for randomization had interpreted the scans as showing diffuse swelling (class II).

(88 percent) in the normothermia group were transferred to a head-injury rehabilitation hospital, where the average length of stay for each group was 69 days. The rates of incidence of delayed post-traumatic intracranial hematomas, infections, deep venous thrombosis, and pulmonary, renal, and cardiac complications were similar in the two groups.

Neurologic Outcome

Three months after injury, 15 (38 percent) of the patients in the hypothermia group had a score on the Glasgow Outcome Scale of 4 or 5, as compared with 7 patients (17 percent) in the normothermia group ($P=0.03$) (Table 2). At 12 months, 24 (62 percent) of the patients in the hypothermia group and 16 (38 percent) of those in the normothermia group had a score of 4 or 5 ($P=0.05$). The efficacy of hypothermia was related to the severity of the injury as indicated by the Glasgow coma score on admission. Patients with initial coma scores of 3 or 4 did not benefit from hypothermia, whereas those with scores of 5 to 7 did. Among these patients with higher scores, 16 (73 percent) in the hypothermia group and 9 (35 percent) in the normothermia group had a good outcome (a Glasgow outcome score of 4 or 5) at six months ($P=0.008$).

Logistic-regression analysis of the results in all patients revealed that the CT class and initial Glasgow coma score confounded the treatment effects ascribed to hypothermia (Table 3). When the logistic-regression analysis was adjusted to account for these two variables, the risk ratios were higher than the unadjusted ratios at 6 and 12 months. For the subgroup of patients with an initial Glasgow coma score of 5 to 7, the analysis adjusted for CT class also revealed that this variable may have confounded the treatment effect ascribed to hypothermia at 12 months. However, the unadjusted and adjusted risk ratios at three and six months did not change, and the 95 percent confidence intervals excluded 1 at both points in time. Thus, in the subgroup with an initial Glasgow coma score of 5 to 7, the significant improvement at three and six months in the patients treated with hypothermia could not be attributed to the slight difference between the groups in the CT-based classification of the severity of the injury.

Cerebral and Systemic Characteristics

During the first 36 hours after the injury (when the patients in the hypothermia group underwent cooling and rewarming), the hypothermia group had a lower mean intracranial pressure, cerebral blood flow, and heart rate and a higher mean cerebral perfusion pressure (Table 4). During the period after rewarming, the mean cerebral perfusion pressure was significantly lower in the hypothermia group than in the normothermia group, although it remained above 70 mm Hg. The mean intracranial pressure in the hypothermia group increased but did not significantly exceed that in the normothermia group.

Moderate hypothermia was not associated with significant changes in serum glucose, amylase, or creatinine concentrations or hematocrit values. The partial-thromboplastin times during the first 36 hours after the injury were slightly higher and the serum potassium concentrations were slightly lower in the hypothermia group, but these values were still within the normal range. Platelet counts and prothrombin times did not differ significantly between the two groups.

Cerebrospinal Fluid Analysis

Among the patients with an initial Glasgow coma score of 5 to 7, those in the hypothermia group had

TABLE 2. GLASGOW OUTCOME SCORES IN THE HYPOTHERMIA AND NORMOTHERMIA GROUPS AT 3, 6, AND 12 MONTHS.*

GLASGOW OUTCOME SCORE	AT 3 MONTHS		AT 6 MONTHS		AT 12 MONTHS	
	HYPOTHERMIA	NORMOTHERMIA	HYPOTHERMIA	NORMOTHERMIA	HYPOTHERMIA†	NORMOTHERMIA
	number of patients (percent)					
All patients						
1 (Death)	8 (20)	9 (21)	8 (20)	10 (24)	9 (23)	10 (24)
2 (Vegetative state)	6 (15)	11 (26)	3 (8)	7 (17)	3 (8)	8 (19)
3 (Severe disability)	11 (28)	15 (36)	7 (18)	11 (26)	3 (8)	8 (19)
4 (Moderate disability)	8 (20)	4 (10)	7 (18)	8 (19)	9 (23)	5 (12)
5 (Mild or no disability)	7 (18)	3 (7)	15 (38)	6 (14)	15 (38)	11 (26)
Total	40	42	40	42	39	42
P value‡	0.12		0.05		0.18	
Patients with coma score of 5 to 7						
1 (Death)	2 (9)	5 (19)	2 (9)	6 (23)	2 (9)	6 (23)
2 (Vegetative state)	2 (9)	7 (27)	1 (5)	3 (12)	1 (5)	4 (15)
3 (Severe disability)	6 (27)	9 (35)	3 (14)	8 (31)	3 (14)	6 (23)
4 (Moderate disability)	6 (27)	3 (12)	4 (18)	6 (23)	5 (23)	2 (8)
5 (Mild or no disability)	6 (27)	2 (8)	12 (55)	3 (12)	11 (50)	8 (31)
Total	22	26	22	26	22	26
P value‡	0.01		0.01		0.04	

*Percentages may not add to 100 because of rounding.

†One patient was lost to follow-up.

‡P values are for comparisons of all five outcomes in the hypothermia and normothermia groups.

TABLE 3. EFFECT OF HYPOTHERMIA ON THE GLASGOW OUTCOME SCORE AT 3, 6, AND 12 MONTHS.*

LOGISTIC-REGRESSION ANALYSIS	AT 3 MONTHS	AT 6 MONTHS	AT 12 MONTHS
	risk ratio (95% CI)		
All patients			
Unadjusted			
Hypothermia (yes vs. no)	0.3 (0.1–0.8)	0.4 (0.2–1.0)	0.4 (0.2–0.9)
Adjusted			
Hypothermia (yes vs. no)	0.3 (0.1–1.0)	0.5 (0.2–1.2)	0.5 (0.2–1.2)
CT class (as compared with next lower class)	1.4 (0.8–2.1)	1.7 (1.1–2.3)	1.4 (1.1–2.2)
Coma score (5 to 7 vs. 3 or 4)	0.3 (0.1–1.0)	0.4 (0.2–1.2)	0.7 (0.2–1.7)
Patients with coma score of 5 to 7			
Unadjusted			
Hypothermia (yes vs. no)	0.2 (0.1–0.7)	0.2 (0.1–0.7)	0.2 (0.1–0.8)
Adjusted			
Hypothermia (yes vs. no)	0.2 (0.1–0.9)	0.2 (0.1–0.9)	0.3 (0.1–1.0)
CT class (as compared with next lower class)	1.7 (0.9–3.3)	1.4 (0.9–2.5)	1.7 (0.9–2.5)

*The risk ratios derived in the logistic-regression analysis were for a Glasgow outcome score of 1, 2, or 3 (death, vegetative state, or severe disability, respectively), as compared with a score of 4 (moderate disability) or 5 (mild or no disability). CI denotes confidence interval.

TABLE 4. EFFECT OF HYPOTHERMIA ON SYSTEMIC AND INTRACRANIAL PHYSIOLOGIC CHARACTERISTICS IN THE HYPOTHERMIA AND NORMOTHERMIA GROUPS.

CHARACTERISTIC	HYPOTHERMIA		NORMOTHERMIA		P VALUE*
	NO. OF PATIENTS/ NO. OF OBSERVATIONS	MEAN VALUE	NO. OF PATIENTS/ NO. OF OBSERVATIONS	MEAN VALUE	
0–36 hours†					
Intracranial pressure (mm Hg)	40/813	15.4	41/853	19.7	0.01
Cerebral perfusion pressure (mm Hg)	40/756	82.4	41/778	77.4	0.05
Difference between arterial and jugular venous oxygen content (ml/dl)	40/260	5.1	40/252	4.6	0.11
Cerebral blood flow (ml/100 g of tissue/min)	30/62	28.8	29/55	35.7	0.05
Arterial pressure (mm Hg)	40/732	97.2	41/757	96.4	0.49
Heart rate (beats/min)	32/627	67.4	33/629	82.1	<0.001
37–60 hours					
Intracranial pressure (mm Hg)	40/676	19.2	37/577	17.4	0.10
Cerebral perfusion pressure (mm Hg)	40/604	73.5	37/516	84.1	<0.001
Difference between arterial and jugular venous oxygen content (ml/dl)	38/152	4.0	38/153	3.8	0.48
Cerebral blood flow (ml/100 g of tissue/min)	19/28	40.5	21/29	42.1	0.53
Arterial pressure (mm Hg)	40/599	92.6	37/516	101.4	<0.001
Heart rate (beats/min)	32/494	92.3	29/436	87.4	0.30

*P values are for differences between the values in the hypothermia group and those in the normothermia group; a generalized-linear-regression analysis was used to adjust for intraclass correlation.

†During this period, patients in the hypothermia group underwent cooling.

TABLE 5. VENTRICULAR CEREBROSPINAL FLUID CONCENTRATIONS OF ASPARTATE, GLUTAMATE, AND INTERLEUKIN-1β IN THE HYPOTHERMIA AND NORMOTHERMIA GROUPS.*

VARIABLE	HYPOTHERMIA		NORMOTHERMIA		P VALUE†
	NO. OF PATIENTS/NO. OF SAMPLES	MEAN (±SD) VALUE	NO. OF PATIENTS/NO. OF SAMPLES	MEAN (±SD) VALUE	
Patients with coma score of 3 or 4					
Aspartate (mg/dl)	3/19	0.02±0.016	3/17	0.013±0.02	0.50
Glutamate (mg/dl)	3/19	0.046±0.03	3/17	0.031±0.03	0.46
Interleukin-1β (pg/ml)	3/14	6.7±5.5	4/19	20.6±2.4	0.21
Patients with coma score of 5 to 7					
Aspartate (mg/dl)	8/46	0.025±0.02	6/37	0.036±0.03	0.45
Glutamate (mg/dl)	8/46	0.04±0.02	6/37	0.071±0.05	<0.001
Interleukin-1β (pg/ml)	9/45	3.1±3.5	3/21	21.5±3.9	0.03

*Mean values are for all specimens obtained in each group during the first 36 hours after injury (the period of cooling for patients in the hypothermia group). To convert the values for aspartate to micromoles per liter, multiply by 75.13; to convert the values for glutamate to micromoles per liter, multiply by 67.97; to convert the values for interleukin-1β to picomoles per liter, multiply by 0.059.

†P values are for the difference between the values in the hypothermia group and those in the normothermia group; a generalized-linear-regression analysis was used to adjust for intraclass correlation.

a significantly lower mean cerebrospinal fluid concentration of interleukin-1β and glutamate than did those in the normothermia group during the first 36 hours after injury (Table 5). In patients with the higher Glasgow coma scores, the mean interleukin-1β concentration remained significantly lower in the hypothermia group after rewarming (6.6 pg per milliliter [0.39 pmol per liter], vs. 41.4 pg per milliliter [2.44 pmol per liter] in the normothermia group; $P = 0.003$).

DISCUSSION

Several clinical characteristics of severe traumatic brain injury influence patients' outcome. The most important characteristics are the patient's age, the initial Glasgow coma score, the presence or absence

of pupillary abnormalities, and to a lesser extent, CT-based classification of the severity of the injury.[10,16] In our study, the hypothermia and normothermia groups were similar with regard to these characteristics, but the Glasgow coma scores were slightly higher in the normothermia group and the CT class was slightly lower in the hypothermia group. The results of a logistic-regression analysis adjusted for the effects of these clinical characteristics suggest but do not establish conclusively that hypothermia improves the outcome for patients with a Glasgow coma score of less than 8. In the subgroup of patients with an initial Glasgow coma score of 5 to 7, however, hypothermia was associated with a significant improvement in the outcome three and six months after the injury, even after adjustment for the CT class.

In animals with global ischemia and traumatic brain injury, moderate hypothermia (a temperature of 32 to 34°C) reduces secondary brain injury and improves the behavioral outcome.[17-20] The specific effects of hypothermia include reducing cerebral ischemia, edema, and tissue injury and preserving the blood–brain barrier.[21-25] The mechanisms by which hypothermia limits secondary brain injury are ill defined. In uninjured primates, a reduction in the brain temperature from 37 to 22°C caused a linear decrease in cerebral metabolism and preserved high-energy phosphate stores.[26] In rats and primates with experimentally induced cerebral ischemia, however, reducing cerebral activity with inhalation anesthetics did not decrease brain-tissue injury.[27,28] In most of these studies, the cerebral effects of the anesthetics were measured according to the degree of suppression of electrical activity. However, anesthetics may depress only the rate of energy use associated with electrophysiologic activity, whereas hypothermia may reduce the rate of energy use associated with both electrophysiologic activity and the homeostatic functions required to maintain cellular integrity (basal metabolism).[29]

Alternatively, hypothermia may mitigate brain injury by reducing the extracellular concentrations of excitatory neurotransmitters, particularly glutamate.[30] We found that hypothermia significantly lowered ventricular cerebrospinal fluid glutamate concentrations in our patients with an initial Glasgow coma score of 5 to 7. The patients who had no benefit from hypothermia (those with a score of 3 or 4) had cerebrospinal fluid glutamate concentrations similar to those in the corresponding normothermia group. On the basis of these findings, we believe that glutamate is one potential mediator of hypothermia's beneficial effects.

Hypothermia may also reduce secondary brain injury by suppressing the post-traumatic inflammatory response. Extravasation of polymorphonuclear leukocytes in the injured area has been documented very early after several types of experimentally induced brain injury.[31,32] Hypothermia may reduce the infiltration of cells into the injured area by either preserving the blood–brain barrier[24] or reducing the amount of cytokines released. Interleukin-1β is one of several cytokines that appear in the ventricular cerebrospinal fluid soon after traumatic brain injury in humans.[33,34] Because it promotes the adhesion of leukocytes to endothelium and increases capillary endothelial permeability, interleukin-1β is undoubtedly important in initiating the post-traumatic inflammatory response.[35,36] We found that the mean ventricular cerebrospinal fluid concentration of interleukin-1β was significantly lower in the hypothermia group, both during cooling and after rewarming, than in the normothermia group. As with glutamate, this effect occurred only in the patients with an initial Glasgow coma score of 5 to 7.

Treatment with moderate hypothermia for 24 hours did not increase the incidence of complications in these critically ill patients. Although other investigators have documented a hypothermia-related increase in the incidence of infections (particularly pulmonary infection), coagulation disorders, and cardiac arrhythmias, these complications can be attributed to the use of temperatures below 30°C or a cooling period longer than 24 hours.[37,38] The partial-thromboplastin time, though not the prothrombin time, increased slightly during cooling in our patients treated with hypothermia, but we found no indication of clinically important hypothermia-induced coagulopathies[39] or bleeding.

We conclude that treatment with moderate hypothermia (a temperature of 32 or 33°C) for 24 hours, initiated soon after severe traumatic brain injury, significantly improved the outcomes at three and six months in patients without flaccidity or decerebrate rigidity (those with Glasgow coma scores of 5 to 7) on initial evaluation. Our results also suggest an improved outcome 12 months after the injury in this group of patients.

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