ILD-to-moderate hypothermia as a treatment for brain injury has been a major area of research during the last decade. Laboratory studies have shown that mild-to-moderate hypothermia provides significant protective effects, diminishes the degree of neurological damage, reduces the rate of mortality, and improves neurological outcome.\textsuperscript{2,4,5,8–10,14,29,30} It is believed that the beneficial effects of mild-to-moderate hypothermia act through metabolic and biochemical processes. Such mechanisms include temperature-dependent reduction of cerebral oxygen metabolism,\textsuperscript{11,12} decreased free-radical production,\textsuperscript{15,25} limitation of blood–brain barrier disruption\textsuperscript{15,25} and brain edema,\textsuperscript{20} attenuation of ionic disruption,\textsuperscript{30} decreased excitatory amino acid releases,\textsuperscript{3,23} reduced cerebral lactate accumulation,\textsuperscript{18} reduced hyperglycemia,\textsuperscript{17} and inhibition of excessive calcium entry into neurons and intracellular calcium overload\textsuperscript{22} following brain injury.

Recently, several clinical trials have demonstrated that a short duration (24–48 hours) of mild-to-moderate hypothermia may have improved outcome in patients suffering from brain injury.\textsuperscript{5,7,19,25} Other medical centers have found that a 3- to 14-day-long period of induced mild hypothermia may significantly improve outcome and reduce high ICP in patients with severe TBI.\textsuperscript{5,24} We performed a randomized study of long-term mild hypothermia in 87 patients with severe TBI. Forty-four patients received standard treatment under normothermic conditions (37–38°C). Forty-three patients received long-term mild hypothermia therapy, which was induced using a cooling blanket. These patients were maintained at 33 to 35°C for 3 to 14 days until the individual patient’s intracranial pressure (ICP) returned to the normal level, after which the patient was returned to normothermia. In this report we describe the results in 87 patients at 1 year postinjury.

Effect of long-term mild hypothermia therapy in patients with severe traumatic brain injury: 1-year follow-up review of 87 cases

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Object. The goal of this study was to investigate the protective effects of long-term (3–14 days) mild hypothermia therapy (33–35°C) on outcome in 87 patients with severe traumatic brain injury (TBI) (Glasgow Coma Scale score \leq 8).

Methods. In 43 patients assigned to a mild hypothermia group, body temperatures were cooled to 33 to 35°C a mean of 15 hours after injury and kept at 33 to 35°C for 3 to 14 days. Rewarming commenced when the individual patient’s intracranial pressure (ICP) returned to the normal level. Body temperatures in 44 patients assigned to a normothermia group were maintained at 37 to 38°C. Each patient’s outcome was evaluated 1 year later by using the Glasgow Outcome Scale. One year after TBI, the mortality rate was 25.58% (11 of 43 patients) and the rate of favorable outcome (good recovery or moderate disability) was 46.51% (20 of 43 patients) in the mild hypothermia group. In the normothermia group, the mortality rate was 45.45% (20 of 44 patients) and the rate of favorable outcome was 27.27% (12 of 44 patients) \(p < 0.05\). Induced mild hypothermia also markedly reduced ICP \(p < 0.01\) and inhibited hyperglycemia \(p < 0.05\). The rates of complication were not significantly different between the two groups.

Conclusions. The data produced by this study demonstrate that long-term mild hypothermia therapy significantly improves outcomes in patients with severe TBI.

KEY WORDS • hypothermia • traumatic brain injury • outcome

MILD-TO-MODERATE hypothermia as a treatment for brain injury has been a major area of research during the last decade. Laboratory studies have shown that mild-to-moderate hypothermia provides significant protective effects, diminishes the degree of neural damage, reduces the rate of mortality, and improves neurological outcome.\textsuperscript{2,4,5,8–10,14,29,30} It is believed that the beneficial effects of mild-to-moderate hypothermia act through metabolic and biochemical processes. Such mechanisms include temperature-dependent reduction of cerebral oxygen metabolism, decreased free-radical production,\textsuperscript{11,12} limitation of blood–brain barrier disruption\textsuperscript{15,25} and brain edema,\textsuperscript{20} attenuation of ionic disruption,\textsuperscript{30} decreased excitatory amino acid releases,\textsuperscript{3,23} reduced cerebral lactate accumulation,\textsuperscript{18} reduced hyperglycemia,\textsuperscript{17} and inhibition of excessive calcium entry into neurons and intracellular calcium overload\textsuperscript{22} following brain injury.

Recently, several clinical trials have demonstrated that a short duration (24–48 hours) of mild-to-moderate hypothermia may have improved outcome in patients suffering from brain injury.\textsuperscript{5,7,19,25} Other medical centers have found that a 3- to 14-day-long period of induced mild hypothermia may significantly improve outcome and reduce high ICP in patients with severe TBI.\textsuperscript{5,24} We performed a randomized study of long-term mild hypothermia in 87 patients with severe TBI. Forty-four patients received standard treatment under normothermic conditions (37–38°C). Forty-three patients received long-term mild hypothermia therapy, which was induced using a cooling blanket. These patients were maintained at 33 to 35°C for 3 to 14 days until the individual patient’s ICP returned to the normal level, after which the patient was returned to normothermia. In this report we describe the results in 87 patients at 1 year postinjury.

Clinical Material and Methods

Patient Population

From May 1992 through May 1998, 87 patients with severe TBI (GCS\textsuperscript{27} score \leq 8) were admitted to our hospital and randomly assigned to either the normothermia control group (44 patients) or the mild hypothermia group (43 patients). Most of the patients were men, and the most common cause of head injury was a motor vehicle accident. The two groups did not differ significantly in patient age; initial GCS score; pathological findings on CT scans, which included intracranial hematoma, cerebral contusion, and tSAH; pupillary abnormalities; or performance of a craniotomy (Table 1).

Treatment Protocol

We induced hypothermia in the 43 patients assigned to the mild hypothermia group immediately after admission.
Protection provided by long-term mild hypothermia

by placing cooling blankets (model MTA-4702; Gaymar Industries, Inc., Orchard Park, NY) beneath the patients’ bodies. All patients underwent tracheotomy and received ventilation (Aridyne 3600; Timeter Corp., St. Louis, MO). The patients in the hypothermia group received continuous infusions of a paralytic drug (Tracrium 10–40 mg/hour) and chlorpromazine (5–10 mg/hour) administered using an infusion pump to prevent shivering. The dosage was given according to each patient’s temperature, blood pressure, heart rate, and muscular tone. Once the patient’s rectal temperature reached 33˚C (a mean of 15 hours after injury), it was kept at approximately that temperature (33–35˚C) 3 to 14 days, depending on the individual patient’s ICP. When the patient’s ICP returned to a normal level (ICP < 15 mm Hg), hypothermia was discontinued. The patients were passively rewarmed to a temperature of 37 to 38.3˚C at a rate no greater than 1˚C/hour, by gradual adjustment of the blanket thermostat. In the 44 patients assigned to the normothermia group, body temperature was maintained between 37˚C and 38˚C throughout the entire 14-day monitoring period.

The patients were treated according to guidelines for the management of severe TBI set forth by the Joint Section on Neurotrauma and Critical Care of the Brain Trauma Foundation and the American Association of Neurological Surgeons. We rapidly evacuated large intracranial hematomas and hemorrhagic contusions. Each patient’s cerebral perfusion pressure was maintained at a level higher than 70 mm Hg at all times by keeping mean arterial blood pressure between 90 and 120 mm Hg, and the ICP at a level below 25 mm Hg. A fiberoptic catheter was inserted to provide continuous measurement of ICP (model 3000; Camino Laboratories, San Diego, CA). Bolus intravenous infusions of mannitol (25–50 g every 6–8 hours) and furosemide (20–40 mg every 6–8 hours) were administered to reduce intracranial hypertension. Corticosteroid medications were not used. The patient’s temperature, respiratory rate, heart rate, blood pressure, cardiac rhythm, and oxygen saturation were continuously monitored (Hewlett Packard, Palo Alto, CA). Serum glucose, blood gases, and serum electrolytes were regularly measured.

Assessment of Neurological Outcome

A specialist in physical medicine and rehabilitation, who was unaware of the patients’ treatment group assignments, determined neurological outcomes 1 year postinjury. The patients’ neurological outcomes were scored according to the Glasgow Outcome Scale13 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

Baseline characteristics, complications, ICP, blood glucose values, serum electrolyte levels, and outcomes in the two groups were compared using chi-square tests, Fisher’s exact tests, or t-tests, as appropriate. A probability value less than 0.05 was considered significant. Results for groups are presented as the means ± standard deviation.

### Results

At 1 year post-TBI in the mild hypothermia group, the mortality rate was 25.58% (11 of 43 patients) and the rate of favorable outcome (good recovery or moderate disability) was 46.51% (20 of 43 patients). In the normothermia group, the mortality rate was 45.45% (20 of 44 patients) and the rate of favorable outcome was 27.27% (12 of 44 patients) (p < 0.05).

Within 24 hours after injury, the mean ICP was 29.63 ± 2.25 mm Hg in the hypothermia group and 30.3 ± 3 mm Hg in the normothermia group (p > 0.05). However, on the 7th day postinjury the mean ICP was 18.9 ± 2.25 mm Hg in the hypothermia group and 30.3 ± 3 mm Hg in the normothermia group (p < 0.01). Within 72 hours after injury the mean serum glucose level was 10.2 ± 2.4 mmol/L in the hypothermia group and 9.1 ± 3.9 mmol/L in the normothermia group (p > 0.05). However, on the 7th day postinjury the mean serum glucose level was 5.6 ± 1.4 mmol/L in the hypothermia group and 8.6 ± 1.1 mmol/L in the normothermia group (p < 0.05).

Within 24 hours after injury in the hypothermia group, pH, PaO₂, and PaCO₂ were 7.43 ± 0.06, 75.98 ± 25.05 mm Hg, and 33.45 ± 7.58 mm Hg, respectively. At that time in the normothermia group, pH, PaO₂, and PaCO₂ were 7.44 ± 0.06, 82.88 ± 42.83 mm Hg, 33.68 ± 4.05 mm Hg, respectively (p > 0.05). Table 2 provides details on serum levels of potassium, sodium, chloride, and calcium in the two groups. There was no difference between the two groups either before hypothermia was induced or after body temperature was normalized (p > 0.05).

At 1 year postinjury, the number of complications in these patients, including pneumonia, cardio-arrhythmia, hypotension, posttraumatic seizure, stress ulcer, diarrhea, and urinary infection, were not significantly different between the mild hypothermia and the normothermia groups (p > 0.05; Table 3).

### TABLE 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mild Hypothermia Group (43 patients)</th>
<th>Normothermia Group (44 patients)</th>
</tr>
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<tr>
<td>age (yrs)</td>
<td>42.2</td>
<td>40.6</td>
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<tr>
<td>sex (M/F)</td>
<td>35/8</td>
<td>37/7</td>
</tr>
<tr>
<td>cause of injury</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
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<td>5</td>
<td>6</td>
</tr>
<tr>
<td>other</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>initial GCS score</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>pathological findings on CT scan</td>
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<td>32</td>
</tr>
<tr>
<td>hematoma</td>
<td>26</td>
<td>29</td>
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<tr>
<td>contusion</td>
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<td>16</td>
</tr>
<tr>
<td>tSAH</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>pupillary abnormalities</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>cranotomy</td>
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Discussion

We have found that long-term mild hypothermia (33–35°C) significantly reduces the incidence of mortality and improves the favorable outcome in patients with severe TBI. Furthermore, we have demonstrated that mild hypothermia markedly decreases ICP and inhibits hyperglycemia in patients with severe TBI. Our findings are consistent with those of previous reports.24

Mild-to-moderate hypothermia therapy has been tested clinically in patients with severe TBI in the United States, Europe, Japan, and China. Several clinical trials have demonstrated that a short duration (24–48 hours) of mild-to-moderate hypothermia may improve outcomes in patients with severe TBI.3,23,24 Marion, et al.19 compared the effects of moderate hypothermia and normothermia in 82 patients with severe closed-head injuries (GCS Score 3–7). At 12 months postinjury, 62% of patients in the hypothermia group and only 38% of those in the normothermia group had good outcomes. Shiozaki and colleagues24 reported that mild hypothermia significantly increased survival rates (50% in the hypothermia group compared with 18% in the normothermia group) in patients with severe head injury (p < 0.05). Metz and associates21 reported that moderate hypothermia therapy was applied to 10 patients with severe head injury, including seven patients with GCS Score 3, two with GCS Score 4, and one with GCS Score 6. Eight patients survived and seven had a good recovery.

There still is inconsistency in the duration of hypothermia prescribed for treatment of severe TBI in different trauma centers. Some head-trauma centers insist that the length of hypothermia therapy should be shorter than 48 hours to prevent complications resulting from long-term hypothermia.21,22 Other centers recommend that hypothermia be maintained until ICP returns to the normal range, which usually occurs within 3 to 14 days postinjury.23,24 Traumatic brain edema and high ICP usually last more than 7 days in patients with severe TBI, especially in those who have massive cerebral contusion and brain hernia. The difference in duration of hypothermia may be the reason for differences in outcomes in patients treated with hypothermia in different trauma centers. Therefore, we suggest that mild-to-moderate hypothermia should be maintained until the patient’s ICP returns to the normal range as long as complications, such as pneumonia or other systemic infections, do not develop.

Our data showed that pathological findings on CT scans do not affect the protective effects provided by long-term mild hypothermia in patients with severe TBI. Patients with TBI who had GCS scores of 8 or lower randomly entered our clinical trial regardless of whether there was evidence of intracranial hematoma, cerebral contusion, or SAH on the initial CT scan obtained after admission. Actually, we used CT findings as well as continuous ICP monitoring to help us determine the duration of mild hypothermia to be used in individual patients. If results of CT scanning demonstrated narrowing or disappearance of the patient’s basal cisterns and ventricular systems or evidence of massive brain edema and cerebral contusion, we usually prescribed a relatively longer period of mild hypothermia. Conversely, if results of CT scanning demonstrated normal-sized basal cisterns and ventricular systems or mild brain edema and cerebral contusion, we prescribed a relatively shorter period of mild hypothermia therapy.

The mechanisms of hypothermic protection observed after brain injury have not been elucidated. However, recent experimental studies have demonstrated a number of possible mechanisms. Mild hypothermia: 1) reduces cerebral glucose metabolism and cerebral oxygen metabolism and decreases cerebral lactate content following brain injury;12,18,28 2) prevents disruption of the blood–brain barrier after ischemia or TBI and reduces brain edema following TBI;15,20,25 3) diminishes levels of endogenous toxic neurotransmitters, including glutamate, glycine, aspartate, acetylcholine, and norepinephrine, into the brain after TBI;1,23 4) inhibits excessive calcium entry into neurons and intracellular calcium overload following brain injury;25 5) protects membrane structural proteins in neurons, such as microtubule-associated protein-2, after TBI;26 and 6) may prevent diffuse axonal injury following TBI.20

Systemic cooling was induced using a cooling blanket and the patients were given a muscle relaxant and controlled or assisted ventilation to prevent shivering. Patients remained in a state of mild hypothermia for 3 to 14 days without exhibiting significant side effects or complications. We believe that systemic mild hypothermia induced and maintained using a cooling blanket with administration of a muscle relaxant is a safe and effective measure for management of severe TBI. However, when neurosurgeons decide to treat a patient with mild hypothermia, the following concerns should be borne in mind: 1) The combination of mild hypothermia and muscle relaxant therapy may inhibit the cough reflex, which may increase the possibility of respiratory infections. To de-

### TABLE 2

<table>
<thead>
<tr>
<th></th>
<th>Mild Hypothermia Group (43 patients)</th>
<th>Normothermia Group (44 patients)</th>
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<tbody>
<tr>
<td>K+</td>
<td>3.93 ± 0.45</td>
<td>3.87 ± 0.42</td>
</tr>
<tr>
<td>Na+</td>
<td>141.60 ± 5.11</td>
<td>140.20 ± 4.81</td>
</tr>
<tr>
<td>Cl–</td>
<td>105.72 ± 7.70</td>
<td>112.78 ± 7.90</td>
</tr>
<tr>
<td>Ca++</td>
<td>2.21 ± 0.21</td>
<td>2.35 ± 0.23</td>
</tr>
</tbody>
</table>

* Values are expressed in millimoles per liter as the means ± standard deviation. Abbreviation: elec = electrolyte.

### TABLE 3

<table>
<thead>
<tr>
<th>Complication</th>
<th>Mild Hypothermia Group (43 patients)</th>
<th>Normothermia Group (44 patients)</th>
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</thead>
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<tr>
<td>pneumonia</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>cardio-arhythmia</td>
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<td>5</td>
</tr>
<tr>
<td>hypotension</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>stress ulcer</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>diarrhea</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>urinary infection</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>seizure</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Protection provided by long-term mild hypothermia

crease the occurrence of pneumonia in our study, all patients with severe TBI received a tracheotomy instead of tracheal intubation as soon as possible after hospital admission, because long-term tracheal intubation may easily cause respiratory obstruction of blood, sputum, and gastric contents, possibly resulting in pneumonia. Nurses were instructed to turn the patient over and slap the back of the chest as well as to perform tracheal suction every 15 minutes to keep the respiratory tract clean. Sputum bacteriologic cultures and antibody sensitivity tests were performed every 2 days to assist the physician in finding the most sensitive antibody. Tracheoscopy was used to clean out sputum and secretions of the trachea and to administer intratracheal medication. 2) The dosage and speed of action of the muscle relaxant must be controlled by an infusion pump, depending on the patient’s physiological condition including temperature, blood pressure, heart rate, and muscle tone. The purpose and favorable dosage of a muscle relaxant was only designed to prevent shivering during hypothermia; the coughing reflex must continue to exist. 3) Patients with cardiovascular diseases or traumatic shock, and patients younger than 15 years or older than 65 years of age should not receive hypothermia therapy.

References


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