Selection of severely head injured patients for mild hypothermia therapy

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Object. The authors have analyzed the efficacy of inducing mild hypothermia (34°C) in 62 severely head injured patients to control fulminant intracranial hypertension.

Methods. All 62 patients fulfilled the following criteria: 1) persistent intracranial pressure (ICP) greater than 20 mm Hg despite fluid restriction, hyperventilation, and high-dose barbiturate therapy; 2) an ICP lower than the mean arterial pressure; and 3) a Glasgow Coma Scale (GCS) score of 8 or less on admission. The patients were divided into three groups based on computerized tomography findings: extracerebral hematoma (34 patients with subdural and/or epidural hematoma), focal cerebral lesion (20 patients with localized brain contusion and/or intracerebral hematoma), and diffuse swelling (eight patients with no focal mass lesion). Mild hypothermia prevented ICP elevation in 35 (56.5%) of the 62 patients whose ICP was greater than 20 mm Hg despite conventional therapies. Among those 35 patients whose ICP was controlled by mild hypothermia, 12 (34.3%) achieved functional recovery (good outcome or moderate disability). However, functional recovery was observed in only five (10.9%) of the 46 patients whose ICP was greater than 40 mm Hg after conventional therapies. Of 40 patients with an admission GCS score of 5 to 8, there were 11 (27.5%) who achieved functional recovery. On the contrary, mild hypothermia was not effective in 22 patients with an admission GCS score of 3 or 4. In the patients with focal cerebral lesions, ICP was controlled by mild hypothermia in 17 patients (85%) and patient outcome was intimately related to the extent of the damage. Among 18 patients with extracerebral hematoma who had a midline shift of 9 to 12 mm, raised ICP could be successfully controlled by mild hypothermia in 16 patients (88.9%) and three (16.7%) achieved functional recovery. However, ICP could not be controlled in patients with extracerebral hematoma who had a midline shift of 13 mm or more. In patients with diffuse swelling, ICP elevation could not be prevented at all by mild hypothermia.

Conclusions. The authors conclude that mild hypothermia is effective for preventing ICP elevation in patients without diffuse brain swelling in whom ICP remains higher than 20 mm Hg but less than 40 mm Hg after conventional therapies.

KEY WORDS • head injury • intracranial hypertension • mild hypothermia • computerized tomography classification

It has been reported in numerous clinical studies on head injury that elevated intracranial pressure (ICP) is clearly related to increased death rates.\textsuperscript{5,10,12,13,17} The single most frequent cause of death in severely head injured patients is uncontrollable intracranial hypertension.\textsuperscript{9,11} Although a critical ICP level has not been definitely identified, an ICP of 30 to 40 mm Hg has been considered to be lethal.\textsuperscript{15,17} Thus, reduction of ICP is one of the major goals when treating severely head injured patients.

In 1993, we published a preliminary report in which we showed that mild hypothermia (34°C) was effective for controlling intracranial hypertension that is refractory to conventional ICP reduction therapies.\textsuperscript{14} On the basis of this study, we have continued to use mild hypothermia therapy in patients whose ICP cannot be controlled by conventional ICP reduction therapies. In the present study, we analyzed clinical profiles and pathological findings in 62 severely head injured patients who required mild hypothermia to control fulminant intracranial hypertension. We also assessed the ability of mild hypothermia to decrease ICP and to improve outcome in these patients.

Clinical Material and Methods

Patient Population and Management

From 1990 to 1997, a total of 137 severely head injured patients who required continuous infusion of barbiturate medication to control intracranial hypertension were admitted to the Department of Traumatology of Osaka University Hospital. Patients younger than 10 years were
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excluded from this study. In 25 of the 137 patients, ICP was controlled with high-dose barbiturate therapy alone; these patients were excluded from this study. Thirty-eight additional patients were excluded because their ICP equaled their mean arterial blood pressure before mild hypothermia could be initiated. Twelve patients with severe life-threatening injury to another organ were also excluded. We induced mild hypothermia (34°C) in the remaining 62 patients to control intracranial hypertension. These 62 patients (36 males and 26 females) ranged in age from 15 to 71 years, with a mean age of 40 years. Of the 62 patients, 58 were brought to our hospital directly from the scene of their accident within 40 minutes after injury occurred. The remaining four patients were referred from other hospitals within 2 hours after injury occurred. The cause of the injury was a traffic accident in 49 cases, falls in 12, and assault in one. Glasgow Coma Scale (GCS) scores of all patients on admission were 8 or less. In each case, informed consent was obtained from the patient’s family to participate in the study.

All patients were initially intubated, continuously hyperventilated with PaCO₂ between 25 to 30 mm Hg, and treated with fluid restriction at 1 ml/kg/hour. If cerebral perfusion pressure (CPP = mean arterial blood pressure – ICP) was less than 60 mm Hg, adequate amounts of albumin were given. To maintain urine output above 0.5 ml/kg/hour, adequate amounts of colloid fluids and/or continuous infusion of dopamine at 3 to 5 μg/kg/minute were given during the study period as needed. No corticosteroid medication or mannitol was administered during the study. After initial resuscitation, all patients immediately underwent computerized tomography (CT) scanning of the head. Subsequently, an intraventricular catheter was inserted in each patient for continuous ICP and intracranial temperature monitoring. If necessary, intracranial mass lesions associated with midline displacement more than 5 mm were evacuated operatively.

In all patients, intracranial hypertension was initially managed by using conventional ICP reduction therapies such as fluid restriction, hyperventilation, and high-dose barbiturate medications. Barbiturate therapy was initiated by an intravenous injection of thiopental at 4 to 6 mg/kg followed by a continuous infusion at 6 to 8 mg/kg/hour to maintain a burst-suppression pattern on electroencephalography. After high-dose barbiturate therapy, we induced mild hypothermia (34°C) in patients in whom ICP remained higher than 20 mm Hg.

Mild hypothermia (intracranial temperature 34°C) was induced by surface cooling, which was accomplished by placing water-circulating blankets above and below the patient. The intracranial temperature, measured in the lateral ventricle, was maintained at 33.5 to 34.5°C. Mild hypothermia therapy was continued for 2 days or until it was considered not to be effective. When the therapy was discontinued, the patient was rewarmed slowly and intracranial temperature was maintained between 35.5°C and 36.5°C for 24 hours. If ICP increased above 20 mm Hg during rewarming, the patient was recooled to 34°C. If the ICP remained below 20 mm Hg for at least 24 hours, the patient was rewarmed spontaneously to above 37°C, with continuous infusion of barbiturates at 2 mg/kg/hour to prevent shivering. When rewarmed was complete, the barbiturates were gradually withheld.

Classification Based on CT Scans

Before mild hypothermia therapy was initiated, the patients were divided into three groups based on CT findings: 1) the extracerebral hematoma group (Fig. 1), composed of patients whose primary mass lesion was a subdural and/or epidural hematoma; 2) the focal cerebral lesion group (Fig. 2), composed of patients whose primary mass lesion was brain contusion and/or intracerebral hematoma; and 3) the diffuse swelling group (Fig. 3), composed of patients who had compressed or obliterated basal cisterns and/or the third ventricle without a significant intracranial mass lesion. To evaluate the supratentorial extension of damage in the focal cerebral lesion group, the number of damaged cerebral lobes was calculated. Each hemispheric lobe was calculated as one lobe (left frontal lobe, right temporal lobe, and so forth). Brainstem and cerebellum were not included in this evaluation.

Patient Outcome

The outcome of each patient was assessed 6 months after injury according to the Glasgow Outcome Scale (GOS), as follows: 1, death; 2, vegetative state; 3, severe disability; 4, moderate disability; 5, mild or no disability. For statistical comparison, patients with a GOS score of 4
or 5 were classified as having a favorable outcome. Unfavorable outcome was assigned to those with a GOS score of 1, 2, or 3. Each survivor received a personal follow-up interview either by clinic visit or telephone interview.

Statistical Analysis

All values are expressed as the mean ± standard deviation. Physiological measurements within groups were analyzed by using one-way analysis of variance followed by Scheffe’s test. Clinical characteristics and outcomes in the three groups were compared using chi-square tests. Significance was assigned when probability was less than 0.05.

Results

Table 1 shows the correlation between the GCS score on admission and the GOS score 6 months after injury in all patients. Twelve patients (19.4%) had a favorable outcome (a GOS score of 4 or 5). Forty patients (64.5%) died during the study; 27 (43.5%) of whom died of uncontrollable intracranial hypertension. The effectiveness of mild hypothermia was strongly related to the severity of head injury as indicated by the GCS score on admission. Among 40 patients with an admission GCS score of 5 to 8, 11 patients (27.5%) had favorable outcomes. However, among 22 patients with an admission GCS score of 3 or 4, only one patient had a favorable outcome.

<table>
<thead>
<tr>
<th>GOS Score 6 Mos After Injury</th>
<th>GCS Score on Admission (no. of patients)</th>
<th>Total No. of Patients</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>good</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>moderate disability</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>severe disability</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>vegetative</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>death</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>totals</td>
<td>10</td>
<td>12</td>
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</table>

Figure 4 illustrates outcome in relation to ICP before induction of mild hypothermia. Mild hypothermia controlled ICP elevation in 35 patients (56.5%). Seven (43.8%) of 16 patients with ICP lower than 40 mm Hg before induction of mild hypothermia had favorable outcomes. However, only five (10.9%) of 46 patients with ICP greater than 40 mm Hg before induction of mild hypothermia had favorable outcomes. Of the 21 patients with ICP greater than 60 mm Hg before initiation of mild hypothermia, all died, with the exception of one vegetative patient. Seventeen (85%) of these died of uncontrollable intracranial hypertension. These results clearly demonstrate a significant relationship between raised ICP and increased incidence of mortality.

Patient Characteristics and Outcomes in the Three CT Groups

Clinical characteristics in the three groups are summarized in Table 2. More than 50% of patients were included in the extracerebral hematoma group. The three groups did not differ significantly in age, neurological status, or levels of ICP and CPP before mild hypothermia therapy (Table 2). On initial CT scans, the incidence of traumatic subarachnoid hemorrhage and obliteration of the basal cisterns did not differ among the three groups.

Figure 5 shows the relationship between GCS score on admission and GOS score 6 months after injury in the three groups. Among patients in the focal cerebral lesion group, mild hypothermia successfully controlled intracranial hypertension in 17 patients (85%) and eight (40%) had a favorable outcome. Only three patients (15%) died as a result of uncontrollable ICP. All patients in the focal cerebral lesion group had contusionsal hemorrhage; subdural hematoma was an associated lesion in eight of these patients. Ten patients (50%) needed surgical evacuation of mass lesions before mild hypothermia therapy was initiated. Patient outcome in the focal cerebral lesion group was strongly related to the numbers of damaged cerebral lobes. With the exception of one patient in the vegetative state, all patients with four or five injured lobes died.

Twenty-two (64.7%) of the 34 patients in the extracerebral hematoma group died; 16 (47.1%) of these died as a result of uncontrollable intracranial hypertension. Four patients (11.8%) were left in a vegetative state, and four (11.8%) were severely disabled. Overall, outcome in the extracerebral hematoma group was worse than that in the focal cerebral lesion group; only four patients (11.8%) had favorable outcomes. Acute subdural hematoma, found in 32 patients (94.1%), accounted for an overwhelming majority of the primary mass lesions in this group. Epidural hematoma was the primary lesion in only two patients: one achieved a good recovery, but the other patient was found to be neurologically dead due to uncontrollable ICP on the 5th hospital day. Surgical evacuation of the hematoma was required in 24 patients (70.6%) before induction of mild hypothermia in this group. In the extracerebral hematoma group, patient outcome clearly depended on the degree of midline displacement. Among 18 patients with a midline shift of 9 to 12 mm, we successfully controlled raised ICP in 16 patients (88.9%); three (16.7%) achieved functional recovery. However, we failed to control intracranial hypertension in all patients who ex-
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Hibited a midline shift of 13 mm or greater before induction of mild hypothermia.

Outcome in the diffuse swelling group was the worst of the three groups. Regardless of the GCS score on admission, all eight patients died of uncontrollable intracranial hypertension. Six (75%) of the eight patients succumbed to neurological death within 48 hours after injury: one on the 4th hospital day and another on the 6th hospital day.

Discussion

In 1993 three clinical trials of mild hypothermia therapy in severely head injured patients were published. These preliminary studies demonstrated that mild hypothermia (33-34°C) could be useful in improving outcome and neurological recovery in patients with severe head injury. These trials, however, differed with respect to the time at which mild hypothermia therapy was initiated. We induced mild hypothermia only after conventional ICP reduction therapies failed to control intracranial hypertension. As the number of our patients who received mild hypothermia therapy increased, we became aware of the fact that mild hypothermia could successfully control ICP in some patients, whereas it failed to control ICP in others. To clarify the differences in ICP response to mild hypothermia, we examined GCS score on admission, ICP levels, and CT findings so that we could assess in which category of patients mild hypothermia could control ICP.

It has been reported that admission GCS score is closely associated with patient outcome. According to the Traumatic Coma Data Bank (TCDB), mortality rates progressively decreased with increases in GCS scores; a GCS score of 3 resulted in 78.4% mortality; a score of 4 resulted in 55.9%; 5 in 40.2%; 6 in 21.2%; 7 in 17.6%; and a score of 8 in 11.3% mortality. In the present study, the mortality rate in each GCS score group was as follows: 3, 90%; 4, 75%; 5, 64.3%; 6, 54.5%; 7, 37.5%; and 8, 57.1%.

Our results are in reasonably good agreement with the results of the TCDB. It must be considered as inevitable that in our patients the mortality rate for each GCS score was higher than that of the TCDB because the severity of injuries in our patients was much higher than that in the TCDB patients. Our present study clearly demonstrated that mild hypothermia provided little benefit to patients with an initial GCS score of 3 or 4, which is consistent with the results of Marion, et al. The lack of significant benefit to these patients indicates the therapeutic limit of mild hypothermia in severely head injured patients.

Lobato and colleagues reported that only one (3.8%) of 26 patients with an ICP over 40 mm Hg survived after severe head injury. Of 46 patients with ICP higher than 40 mm Hg before mild hypothermia in our study, 12 patients (26.1%) survived, five (10.9%) with functional recovery. Wilberger and associates reported that no survivor of severe head injury who achieved a functional recovery had postoperative ICP higher than 45 mm Hg. Among our 35 patients who exhibited ICP greater than 45 mm Hg before mild hypothermia, three patients (8.6%) had favorable outcomes 6 months after injury (Fig. 4). Although there were a few differences in patient population between our study and those of Lobato and colleagues and Wilberger and associates, our success with mild hypothermia used in conjunction with conventional therapies may cast light on the treatment of raised ICP in severely head injured patients. When ICP could not be maintained below 60 mm Hg by conventional therapies, mild hypothermia was useless against the ICP elevation. Until more effective therapeutic approaches become available, the mortality rate will likely remain high in patients with ICP greater than 60 mm Hg.

The efficacy of mild hypothermia was clearly related to the type of intracranial lesion on CT findings. In the focal cerebral lesion group, mild hypothermia successfully prevented progressively elevating ICP that was refractory to

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conventional therapies. Moreover, eight (40%) of the 20 patients with focal cerebral lesions recovered functionally. These results offer definite hope for the treatment of patients with focal cerebral lesions. Mild hypothermia, therefore, should be actively used in patients of this type.

In the extracerebral hematoma group, the efficacy of mild hypothermia was strongly related to the degree of midline displacement. Lobato and colleagues reported that among 28 patients who had a midline shift of 9 to 12 mm only four patients (14.3%) survived. However, of 18 patients with a midline shift of 9 to 12 mm, 10 patients (55.6%) survived in our study and three (16.7%) achieved functional recovery. The differences between our results and those of Lobato and colleagues demonstrate the outstanding efficacy of mild hypothermia to control raised ICP in severely head injured patients. In our present study, no survivor had a midline shift equal to or greater than 13 mm before mild hypothermia therapy. Lobato and colleagues also reported quite similar results: no patient with a midline shift of more than 12 mm survived. A midline shift of 13 mm very likely is the irreversible point for cerebral function.

In patients with diffuse swelling, however, our results clearly demonstrated that mild hypothermia was useless in preventing the rise in ICP. The CT finding of diffuse swelling implies direct injury to the whole brain, including the brainstem (Fig. 3). It is reasonable, therefore, that mild hypothermia is ineffective against ICP elevation in cases of diffuse swelling because the beneficial effects of mild hypothermia have been thought to prevent mainly secondary brain injury by reducing cerebral ischemia, blood-brain barrier disruption, and release of glutamate.

Because mild hypothermia therapy for severe head injury has been the subject of clinical trials in many institutes, debate still continues regarding the best procedures to use, such as time of initiation, duration, target temperature, and so forth. Although there are many problems to be solved concerning the therapeutic use of mild hypothermia, our results demonstrated that functional recovery can be expected in one-third of patients whose ICP is controlled by mild hypothermia after conventional therapies.

Our present study also indicates that, at the present time, mild hypothermia with conventional therapies is the most effective therapy in controlling fulminant intracranial hypertension after severe head injury.

**Conclusions**

We conclude that mild hypothermia therapy is effective for preventing ICP elevation in patients whose ICP is higher than 20 mm Hg but less than 40 mm Hg after con-

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**TABLE 2**

*Clinical characteristics of three groups of severely head injured patients*

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Extracerebral Hematoma Group</th>
<th>Focal Cerebral Lesion Group</th>
<th>Diffuse Swelling Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>34</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>male/female ratio</td>
<td>22:12</td>
<td>10:10</td>
<td>4:4</td>
</tr>
<tr>
<td>mean age (yrs)</td>
<td>42 ± 17</td>
<td>40 ± 18</td>
<td>32 ± 15</td>
</tr>
<tr>
<td>pupil abnormalities on admission†</td>
<td>27 (79.4%)</td>
<td>15 (70%)</td>
<td>7 (87.5%)</td>
</tr>
<tr>
<td>hypoxia on admission‡</td>
<td>11 (32.4%)</td>
<td>6 (30%)</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>hypotension on admission§</td>
<td>10 (29.4%)</td>
<td>5 (25%)</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>mean ICP (mm Hg) before mild hypothermia</td>
<td>52 ± 14</td>
<td>49 ± 16</td>
<td>59 ± 14</td>
</tr>
<tr>
<td>mean CPP (mm Hg) before mild hypothermia</td>
<td>46 ± 22</td>
<td>53 ± 19</td>
<td>39 ± 28</td>
</tr>
<tr>
<td>mean brain temperature (°C) before mild hypothermia</td>
<td>38.1 ± 1.2</td>
<td>38.3 ± 1.2</td>
<td>37.8 ± 1.3</td>
</tr>
<tr>
<td>SAH on initial CT scan</td>
<td>24 (70.6%)</td>
<td>15 (75%)</td>
<td>7 (87.5%)</td>
</tr>
<tr>
<td>obliterated basal cisterns on initial CT scan</td>
<td>28 (82.4%)</td>
<td>12 (60%)</td>
<td>8 (100%)</td>
</tr>
</tbody>
</table>

* There were no significant differences between groups. Mean values are expressed as mean ± standard deviation. Abbreviation: SAH = subarachnoid hemorrhage.

† Pupil abnormalities were defined as abnormalities in size and/or reaction to light in one or both pupils.
‡ Hypoxia was defined as \( \text{PaO}_2 \) less than 60 mm Hg.
§ Hypotension was defined as a sustained fall in systolic blood pressure to 100 mm Hg.

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**FIG. 5.** Charts showing outcome 6 months after injury in relation to GCS score on hospital admission in the three groups. Twenty-seven patients (closed circles) died of uncontrollable ICP. In 35 patients (open circles), mild hypothermia was used successfully to control ICP. Abbreviations: D = death; G = mild or no disability; MD = moderate disability; SD = severe disability; V = vegetative state.
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Cervical therapies. Patients with diffuse swelling did not respond to mild hypothermia, whereas patients with focal lesions did quite well.

References


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