Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury

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Recent experimental studies have demonstrated that mild hypothermia at about 34°C can be effective in the control of intracranial hypertension. A randomized controlled study of mild hypothermia was carried out in 33 severely head-injured patients. All 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 blood pressure; and 3) a Glasgow Coma Scale score of 8 or less. The patients were divided into two groups: one received mild hypothermia (16 patients) and one served as a control group (17 patients).

Mild hypothermia significantly reduced the ICP and increased the cerebral perfusion pressure. Eight patients (50%) in the hypothermia group and three (18%) in the control group survived (p < 0.05), while five (31%) in the hypothermia group and 12 (71%) in the control group died of uncontrollable intracranial hypertension (p < 0.05). In five patients in the hypothermia group, cerebral blood flow was measured by the hydrogen clearance method and arteriojugular venous oxygen difference was evaluated before and during mild hypothermia. Mild hypothermia significantly decreased the cerebral blood flow, arteriojugular venous oxygen difference, and cerebral metabolic rate of oxygen (p < 0.01). The results of this preliminary investigation suggest that mild hypothermia is a safe and effective method to control traumatic intracranial hypertension and to improve mortality and morbidity rates.

Key Words: head injury - cerebral blood flow - cerebral metabolism - intracranial pressure - mild hypothermia - prognosis

It is well known that conventional hypothermia (body temperature less than 30°C) decreases a patient's intracranial pressure (ICP), cerebral blood flow (CBF), and cerebral metabolic rate of oxygen (CMRO₂). Cerebral protective effects of conventional hypothermia have also been employed in the treatment of brain swelling and intracranial hypertension. Shapiro, et al., showed that the combined therapy of barbiturates and conventional hypothermia might effectively control intracranial hypertension in some patients with severe head injury. During the last decade, however, the use of conventional hypothermia has been abandoned because of the unconvincing clinical outcome, management problems, and the presence of clinical toxicity such as cardiovascular instability. Mild hypothermia at 34° to 35°C, on the other hand, is not associated with cardiovascular instability and other untoward side effects in experimental models.

We have performed a randomized controlled trial of mild hypothermia (34°C) in patients with head injury in whom the ICP could not be controlled despite high-dose barbiturate and hyperventilation therapy. The effect on ICP of induced mild hypothermia combined with high-dose barbiturate and hyperventilation therapy was evaluated clinically. To assess the circulatory and metabolic effects of mild hypothermia, CBF and arteriojugular venous oxygen difference (AVDO₂) were measured in some of the patients undergoing hypothermia.

Clinical Material and Methods

Patient Population

From May, 1987, to April, 1992, 67 consecutively treated severely head-injured patients who required continuous infusion of barbiturates to control intracranial hypertension were admitted to the Department of Traumatology at Osaka University Hospital. Patients below the age of 10 years were excluded from study. Of the 67 patients, 62 were admitted within 40 minutes directly from the scene of their accident. The remaining five patients were referred from other hospitals within
2 hours of injury. The Glasgow Coma Scale scores of all patients on admission were 8 or less. The cause of injury was traffic accidents in 53, falls in 13, and assault in one.

All patients were initially intubated, continuously hyperventilated with PaCO₂ between 25 to 30 mm Hg, and treated with fluid restriction at 1 ml/kg/hr. Computerized tomography (CT) of the head was performed as soon as possible after admission. Follow-up CT scans were scheduled on Days 2, 4, 7, and 14 after admission. After initial CT, an intraventricular catheter was inserted in all patients for continuous monitoring of the ICP. If possible, patients with focal intracranial mass lesions associated with significant midline displacement underwent surgical treatment immediately after CT.

In all 67 patients, intracranial hypertension was initially managed with conventional ICP reduction therapy, such as fluid restriction, hyperventilation, and high-dose barbiturates. 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/hr to maintain a burst-suppression pattern on electroencephalography. In order to maintain a urine output above 0.5 ml/kg/hr, adequate amounts of colloid fluids and/or continuous infusion of dopamine at 3 to 5 μg/kg/min were given during the study period as needed. Neither corticosteroids nor mannitol were administered during the study.

Patients in whom the ICP remained higher than 20 mm Hg at 5 to 6 hours after induction of high-dose barbiturate therapy were eligible for inclusion in this study. In 21 of the 67 patients, ICP was controlled with high-dose barbiturate therapy alone; these patients were excluded from this study. Among the other 46 patients, 13 were excluded because their ICP equaled the mean arterial blood pressure (MABP) before the study could be initiated. Thus, 33 patients (17 females and 16 males) were included in this investigation, with a mean age of 35 years (range 17 to 67 years). In each case, informed consent was obtained from the patient's family prior to entry into the study.

### Study Groups

The 33 patients in the study were randomly divided into two groups: patients receiving mild hypothermia (16 patients) and a control group (17 patients). The clinical data of the two groups are described in Table 1. Both groups were similar with respect to patient age, neurological status (Fig. 1), type of intracranial lesion (Fig. 2), and level of ICP.

**Mild hypothermia** in 16 patients (core temperature 34°C) was induced by surface cooling with water-circulating blankets above and below the patient. The core temperature, measured in the bladder, was maintained at 33.5°C to 34.5°C. Mild hypothermia 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 the core 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 patients were rewarmed spontaneously to above 37°C, with continuous infusion of barbiturates at 2 mg/kg/hr to prevent shivering. When rewarming was complete, the barbiturates were gradually withheld.

**Blood Pressure and ICP Monitoring**

After initial CT, an intraventricular catheter was inserted in all patients for continuous monitoring of the ICP; ICP recordings were made every hour. Arterial blood pressure was monitored through an indwelling radial or femoral artery catheter. Cerebral perfusion pressure (CPP) was calculated as the difference between the MABP and the ICP.

**Cerebral Blood Flow Measurement**

In five of the 16 patients treated with mild hypothermia, the mean hemispheric CBF was measured at the bedside within 48 hours after injury. At first, the CBF was measured under normothermic conditions (36.5°C to 37.5°C). If the initial core temperature was above 37.5°C, the CBF was measured 2 or 3 hours after cooling to 37°C. The CBF was again measured 2 or 3 hours after the patients were cooled to between 33.5°C and 34.5°C.

### Table 1

<table>
<thead>
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<th>Patient characteristics for the two study groups*</th>
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<td>Factor</td>
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<td>surgical mass†</td>
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<td>ICP before randomization (mm Hg)</td>
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<td>core temperature before randomization (°C)</td>
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* There were no statistical differences between the two groups. Means are expressed ± standard deviations; percentages are given in parentheses. ICP = intracranial pressure.
† Surgical mass = cases with mass lesions surgically evacuated before the study.

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**FIG. 1.** Graph showing the Glasgow Coma Scale scores on admission in the group with induced mild hypothermia (16 patients) and the control group (17 patients). There were no statistical differences between the groups.
Mild hypothermia for severe head injury

The CBF was measured at the bedside according to the modified Gotoh's method \(^{10,14}\) by recording the appearance and clearance of hydrogen (H\(_2\)) administered by inhalation. Traditionally, the CBF is measured using isotopes such as \(^{133}\)Xe;\(^6\) however, it proved difficult to use isotopes in the intensive care unit so we employed the hydrogen clearance method. A recording electrode was inserted into the internal jugular vein of the intact hemisphere. This recording electrode was made from platinum wire (0.5 mm in diameter). The wire was insulated with Teflon, except for an exposed 1-mm tip which was covered with platinum black to improve its recording properties. This electrode tip reached the base of the skull through a catheter, which was introduced percutaneously into the internal jugular vein. Placement of the radiopaque catheter tip at the base of the skull was verified by x-ray examination. An indifferent electrode was placed on the neck. The potential changes proportional to the concentration of H\(_2\) at the electrode tip were amplified and recorded.

For CBF measurement, H\(_2\) was added to the inspired gas until the H\(_2\) concentration curve on the recorder achieved a plateau. The inhalation of H\(_2\) was then abruptly discontinued and its clearance curve recorded. The CBF was computed from the rate of decrease in the area under the clearance curve. Measurement of the CBF was obtained three times in each patient under normothermic and hypothermic conditions, and the mean value was used as the CBF.

Measurement of AVDO\(_2\) and CMRO\(_2\)

Just before each CBF measurement, samples of arterial and jugular venous blood were collected simultaneously from the catheters described above. The systemic arterial and venous oxygen content were calculated according to the formula: 

\[
\text{O}_2\text{ content (vol\%) = (1.34 x Hb x SO}_2\text{) + (0.003 x pO}_2\text{),}
\]

where Hb is hemoglobin (mg/dl), SO\(_2\) oxygen saturation (%), and pO\(_2\) partial pressure for oxygen (mm Hg).

The AVDO\(_2\) was derived as the difference in O\(_2\) content between arterial and jugular vein samples. The CMRO\(_2\) was estimated from the product of AVDO\(_2\) and the mean CBF.

**Outcome**

The outcome of all patients was assessed 6 months after injury according to the Glasgow Outcome Scale.\(^{15}\) Each survivor received a personal follow-up interview.

**Statistical Analysis**

All values are expressed as the mean ± standard deviation. The physiological measurements within groups were analyzed by Student's t-test for paired data. Intergroup comparison was evaluated by the t-test for unpaired data. Outcome and complications were assessed by the chi-squared test. Significance was assigned when p was less than 0.05.

**Results**

**Cerebral Perfusion Pressure and ICP**

In the control group, 12 of the 17 patients showed progressive elevation of ICP despite conventional ICP reduction therapies. These 12 patients were classified as neurologically dead due to uncontrollable ICP within 48 hours in eight and within 9 days in four. In the other five patients in the control group, intracranial hypertension (ICP > 20 mm Hg) persisted for 4 to 7 days, and then decreased slowly with time.

Figure 3 illustrates the changes in ICP and CPP before and after mild hypothermia (34°C) in the 16 patients in the hypothermia group. To evaluate the ICP baseline values at normothermic conditions (36.5° to 37.5°C), 10 of 16 patients were cooled because their initial temperature was above 37.5°C. The ICP and MABP were evaluated when the patients' condition had stabilized after the intended temperature was reached; this temperature level was constantly maintained during the study. Compared to the normothermic conditions, the ICP declined and CPP rose with mild hypothermia in 12 of the 16 patients. However, the other four patients showed little change in ICP and CPP levels in response to mild hypothermia.

Mild hypothermia reduced the ICP by a mean of 10.4 mm Hg (p < 0.01) and increased the CPP by a

![Graph showing changes in intracranial pressure (ICP) and cerebral perfusion pressure (CPP) during normothermia (37°C) and mild hypothermia (34°C) in 16 patients. Each pair of circles represents measurements in one patient. In 12 patients (open circles), ICP declined and CPP rose with mild hypothermia; four patients (closed circles) showed no ICP or CPP response to mild hypothermia.](https://example.com/graph.png)
mean of 14.0 mm Hg (p < 0.01). Four patients who did not respond to hypothermia were determined to be neurologically dead due to uncontrollable ICP (within 48 hours in three patients and on the 6th hospital day in one patient).

Cerebral Blood Flow and AVDO₂

Figure 4 illustrates the differences in CBF, AVDO₂, and CMRO₂ levels at normothermia (37°C) and mild hypothermia (34°C) in five patients in the hypothermia group; these five patients showed a significant decrease in ICP due to hypothermia. Mild hypothermia resulted in a mean decrease of 15.4 ml/100 gm/min in CBF (p < 0.01) and 1.0 vol% in AVDO₂ (p < 0.01). Consequently, the calculated CMRO₂ level exhibited a mean decrease of 1.1 ml/100 gm/min during hypothermia (p < 0.01). Errors of the mean of three CBF measurements under normothermia and hypothermia were within 10%.

Complications

Complications during the clinical course in the two groups are shown in Table 2. The most frequent complication in both groups was pneumonia. Infection of the central nervous system, arrhythmia, and multiple organ failure were also encountered frequently. A comparison of complications between the two groups showed no statistically significant differences. Complications occurred during rewarming in two patients. One patient with preserved response to hypothermia died of uncontrollable ICP on the 5th hospital day; her temperature rose to 37°C accidentally during cerebral angiography. The other patient sustained hypovolemic shock during rewarming on the 4th hospital day and recovered after administration of catecholamines.

Clinical Outcome

The clinical outcome of the patients is shown in Table 3. Five of 16 patients in the hypothermia group and only one of 17 patients in the control group returned to their previous occupation (good recovery). Fifty percent (eight patients) in the hypothermia group and only 18% (three) in the control group survived (p < 0.05). Uncontrollable ICP was the cause of death in 31% (five) of the patients in the hypothermia group and in 71% in the control group (p < 0.05). In three patients in the hypothermia group and two in the control group, death was not related to ICP level.

Discussion

In several investigations reviewing ICP levels in patients with severe head injury, it has been argued that an increase in ICP is closely correlated to a poor outcome.13,20,22 Miller, et al.,20 demonstrated that elevation of ICP over 20 mm Hg after head injury was an unfavorable prognostic sign. Thus, reduction of ICP to less than 20 mm Hg would be one of the major goals when treating severely head-injured patients.9,20 Based on clinical studies, many investigators have demonstrated that prolonged hyperventilation and high-dose barbiturate treatment offer therapeutic benefits in reducing ICP.24 However, we often failed to control the ICP below 20 mm Hg after head injury despite various combinations of conventional ICP reduction therapies, such as fluid restriction, prolonged hyperventilation, and high-dose barbiturates.
Mild hypothermia for severe head injury

We studied the effect of mild hypothermia (34°C) on uncontrollable intracranial hypertension after head injury because mild hypothermia was reported to have a marked protective effect on ischemic neuronal injury in experimental models and showed promise in controlling brain swelling in children with Reye's syndrome. The present study demonstrated that mild hypothermia combined with conventional therapies was effective in controlling persistent intracranial hypertension in patients in whom conventional therapies were insufficient.

Conventional hypothermia (body temperature < 30°C) has been known to reduce brain metabolic requirements, which may lessen cerebral edema and neuropathological damage. Therefore, conventional hypothermia was used in combination with barbiturate therapy to treat brain swelling and intracranial hypertension. The aggressive use of conventional hypothermia, however, has been abandoned during the last decade because: 1) it was difficult to keep the core temperature at 30°C for several days; 2) clinical outcome proved unfavorable despite the beneficial biochemical effects; and 3) cardiovascular instability often occurred during conventional hypothermia.

Several recent experimental studies have suggested a protective effect of mild hypothermia on the brain during anoxia, hypoxia, and following head injury. Berntman, et al., demonstrated that a decrease in body temperature of 1° to 3°C can minimize or prevent brain energy failure during hypoxia. Similar observations have led some clinicians to employ mild hypothermia in the treatment of brain swelling and intracranial hypertension. In our study, mild hypothermia combined with hyperventilation and high-dose barbiturate therapy exhibited mean decreases of 15.4 ml/100 gm/min in CBF and 1.1 ml/100 gm/min in CMRO2. These results were consistent with those reported for hypothermia protection in experimental models.

Prolonged hyperventilation has been known to be effective in reducing ICP and CBF in acute head injury. It has recently been suggested, however, that in some patients prolonged hyperventilation may produce excessive vasconstriction that could result in an increase in AVDO2. In other words, blood flow is decreased relative to cerebral metabolic requirements during prolonged hyperventilation. In contrast, mild hypothermia resulted in a mean decrease of 1.0 vol% in AVDO2 in the present study (p < 0.01). Therefore, from the viewpoint of the oxygen supply-demand relationship, mild hypothermia may have a greater therapeutic benefit than hyperventilation in some patients with severe head injury.

The most frequent complications in our investigation were pneumonia and arrhythmia. Bohn, et al., argued that hypothermia (body temperature 30° to 33°C) combined with high-dose barbiturate therapy may be associated with bacterial infection after near-drowning in children. In our study, however, patients in both groups had an equally high incidence of pneumonia. Further study is needed to determine whether mild hypothermia increases the incidence of bacterial infection. Premature ventricular contractions occurred in two patients in the control group and in six patients in the hypothermia group. The incidence was somewhat higher in the hypothermia group, although not statistically significant. Arrhythmia did not cause a problem clinically and was resolved easily by the administration of lidocaine.

In the hypothermia group, troublesome complications of hypovolemic shock and abrupt ICP elevation occurred during rewarming. Of the 16 patients in this group, one developed hypovolemic shock during rewarming; this may be the so-called "rewarming shock," as it is generally believed that vasodilation can often lead to a low arterial pressure during the rewarming phase. Another hypothermia group patient showed an unexpected elevation of ICP when she was abruptly rewarmed to 37°C unintentionally. Further prospective study is indicated to confirm the necessity for an adequate period of rewarming.

As shown in Table 3, of the 16 patients receiving mild hypothermia, eight (50%) died; however, judging from the difference in mortality rates between the groups (50% vs. 82%), mild hypothermia may increase the survival rate and decrease morbidity in severely head-injured patients. Of the subjects in our study, five of 16 hypothermic patients and only one of 17 control patients have returned to a productive life. This tendency for a better quality of survival in hypothermic patients indicates the therapeutic benefit of mild hypothermia on neurological improvement. In this study, five of the 16 patients treated with mild hypothermia did not respond to mild hypothermia and subsequently died of uncontrollable ICP. This indicated that an impaired response to mild hypothermia is an unfavorable prognostic sign.

Our study demonstrates that the addition of mild hypothermia (34°C) to conventional ICP reduction therapies significantly reduces ICP, CBF, and CMRO2 in severely head-injured patients. Mild hypothermia may increase the survival rate and improve the neurological recovery in these patients, and may be an important method for managing patients with severe head injury. Further study of this modality is indicated.

References


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