Diverse Effects of Hypothermia Therapy in Patients with Severe Traumatic Brain Injury Based on the Computed Tomography Classification of the Traumatic Coma Data Bank

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Abstract

A multicenter randomized controlled trial of patients with severe traumatic brain injury who received therapeutic hypothermia or fever control was performed from 2002 to 2008 in Japan (BHYPO). There was no difference in the therapeutic effect on traumatic brain injury between the two groups. The efficacy of hypothermia treatment and the objective of the treatment were reexamined based on a secondary analysis of the BHYPO trial in 135 patients (88 treated with therapeutic hypothermia and 47 with fever control). This analysis was performed to examine clinical outcomes according to the CT classification of the Traumatic Coma Data Bank on admission. Clinical outcomes were evaluated with the Glasgow Outcome Scale and mortality at 6 months after injury. Good recovery and moderate disability were defined as favorable outcomes. Favorable outcomes in young patients (≤ 50 years old) with evacuated mass lesions significantly increased from 33.3% with fever control to 77.8% with therapeutic hypothermia. Patients with diffuse injury III who were treated with therapeutic hypothermia, however, had significantly higher mortality than patients treated with fever control. It was difficult to control intracranial pressure with hypothermia for patients with diffuse injury III, but hypothermia was effective for young patients with an evacuated mass lesion.

Key words: CT classification; heterogeneous pathophysiology; hypothermia; multicenter randomized controlled trial; traumatic brain injury; Traumatic Coma Data Bank

Introduction

THE PROTECTIVE EFFECTS OF HYPOTHERMIA were demonstrated in animal models of traumatic brain injury (TBI) in the 1990s.^{1–3} Similar effects of hypothermia therapy for severe TBI have been shown in small clinical trials,^{4–6} but not in a large trial.⁷ As a result, use of hypothermia has ceased worldwide as a therapy for patients with TBI. Aspects of hypothermia therapy, including induction time, duration, and depth of hypothermia, and the rate of rewarming differ among institutions, and the protective effects of hypothermia therapy for patients with TBI are likely to change relative to these factors. Some clinical trials using early induction or prolonged hypothermia have not shown clear results.^{8,9}

It is difficult to show efficacy for TBI in clinical trials because of the heterogeneous pathophysiology of this condition. TBI can be classified into patients with contusion, acute subdural hema-

toma, acute epidural hematoma, diffuse axonal injury, and combinations of these features. Because their pathophysiologies differ, strategies for therapy should also differ. Patients with TBI have been grouped together in previous clinical trials of hypothermia, which has caused difficulty with the trial design and resulted in findings showing that hypothermia therapy is ineffective for those with TBI.

A multicenter randomized controlled trial (BHYPO) of patients with severe TBI who received either therapeutic hypothermia or fever control was performed from 2002 to 2008 in Japan.¹⁰ The absence of a difference in efficacy for TBI between the two groups may be because of the design of the BHYPO trial.¹⁰ Therefore, we reexamined the design and objectives of the trial. Yamamoto and associates¹¹ also reported an age limit of 50 years for hypothermia therapy for TBI to be effective. Therefore, we compared the outcomes of patients based on age and using the CT classification of

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the Traumatic Coma Data Bank (TCDB)¹² to examine the effects of differences in pathophysiology.

Methods

The effects of hypothermia therapy for patients with severe TBI based on the TCDB CT classification were examined using the results of a hypothermia study conducted from December 2002 to September 2008 in Japan.¹⁰ The study was designed as a multicenter randomized controlled trial with prospective analyses and blinded assessment of neurological outcomes. The protocol was approved by the Institutional Review Board of each participating hospital, and the trial was registered at the University Hospital Medical Information Network site (UMIN-CTR, No. C000000231) in Japan, and at the National Institutes of Health site (Clinical Trials. Gov, Identifier NCT00134472) in the United States. A randomization list was automatically generated by the UMIN computer system to allocate patients in a 2:1 ratio to receive therapeutic hypothermia (32.0°C – 34.0°C) or fever control (35.5°C–37.0°C). The temperature of the control group was set to 35.5°C–37.0°C for an ethical reason because mild therapeutic hypothermia was reported to be effective in adult cardiac arrest/resuscitated patients at the time the trial was designed.^{13,14}

Inclusion criteria were age 15–69 years for both sexes, Glasgow Coma Scale (GCS) score of 4–8, and initiation of cooling within 2 h after onset of TBI. After written informed consent was obtained from the patient's legally authorized representative, the patient was allocated to therapeutic hypothermia or fever control based on the randomization list. An internet-based enrollment system managed by UMIN enabled instant randomization on admission at each participating site. Private information on the patient was secured. If informed consent could not be obtained within 2 h of admission, the consent policy was waived.

In this trial, 150 patients with severe TBI received therapeutic hypothermia or fever control after written informed consent was obtained from legally authorized representatives. After enrollment, informed consent could not be obtained for two patients, seven patients had unstable vital signs before temperature management, and neurological outcomes could not be assessed at 6 months in six patients. Therefore, per-protocol analyses were performed in 135 patients (88 treated with therapeutic hypothermia and 47 with fever control).

Core body temperature was measured by a thermistor coupled to an internal jugular venous catheter. If the catheter could not be inserted, body temperature was measured at another site selected in the following order: pulmonary artery, bladder, rectum, and tympanic

membrane. An arterial catheter and an intracranial pressure (ICP) monitoring probe were inserted to maintain hemodynamic status and ICP at the following levels: mean arterial pressure (MAP) >80 mm Hg, ICP <20 mm Hg, and cerebral perfusion pressure (CPP) >60 mm Hg.¹⁵ The partial pressures of arterial oxygen (PaO₂) and carbon dioxide (PaCO₂) were maintained at >100 mm Hg and 30–40 mm Hg, respectively. If ICP was >20 mm Hg, any treatment recommended by the Japanese guidelines was applied, including hyperventilation (>30 mm Hg), decompressive craniectomy, mannitol/glycerol, and/or a bolus infusion of barbiturates.¹⁵

Cooling was initiated within 2 h after onset of TBI. Cooling blankets, rapid cold fluid infusion (up to 1000 mL saline, human plasma products, or dextrose-free plasma expanders), and/or cold gastric lavage were used during the induction phase in both groups. The goal in each group was to achieve the target temperature within 6 h after onset of TBI and maintain this temperature for at least 72 h, mainly using surface cooling blankets. The patient was rewarmed at a rate of <1°C/day. After rewarming, core body temperature was kept at <38.0°C until day 7 after onset of TBI. The sedation protocol used either midazolam (0.2 mg/kg/h) and nonnarcotic analgesics, or neuroleptanalgesia (droperidol 25 µg/kg/h and fentanyl 1 µg/kg/h). Vecuronium (0.05 mg/kg/h) or pancuronium (0.05 mg/kg/h) was also used during the body temperature-control phase, as needed.

All patients were treated based on the guidelines for management of severe TBI of the Japan Society of Neurotraumatology.¹⁵ All data, except CT data, were transmitted to the UMIN center via an internet-based system. CT on admission was classified based on the TCDB classification.¹² Hemodynamic data were recorded on days 0, 1, and 3, and 1 day after rewarming (defined as the day on which the core body temperature reached 36°C). The primary outcome was the Glasgow Outcome Scale at 6 months after injury. Good recovery and moderate disability were designated as favorable outcomes.

Hemodynamic parameters, ICP, CPP, favorable outcome rate, and mortality were compared between the two groups according to CT classification. The primary outcome in young patients (≤50 years) was also examined. Continuous variables were analyzed by the Student *t* test and Mann-Whitney *U* test, as appropriate. Categorical variables were analyzed by the chi-square test. A *p* value of ≤0.05 was deemed significant in all analyses.

Results

The characteristics of the patients are shown in Table 1. There was no significant difference in age, sex, GCS on admission, unreactive pupil(s), blood pressure, or heart rate between the two

TABLE 1. PATIENT CHARACTERISTICS

Variable	All cases			Diffuse injury II			Diffuse injury III			Evacuated mass lesion		
	Therapeutic hypothermia n=88	Fever control n=47	p value	Therapeutic hypothermia n=24	Fever control n=16	p value	Therapeutic hypothermia n=13	Fever control n=9	p value	Therapeutic hypothermia n=43	Fever control n=19	p value
Age (years)	41 ± 18	38 ± 18	0.493	34 ± 17	31 ± 17	0.580	37 ± 17	37 ± 18	0.924	47 ± 19	43 ± 18	0.528
Male (%)	59 (67)	31 (66)	0.898	20 (83)	11 (69)	0.279	9 (69)	6 (67)	0.899	24 (56)	12 (63)	0.589
GCS	5.7 ± 1.4	5.9 ± 1.3	0.434	6.3 ± 1.3	6.4 ± 1.0	0.709	5.8 ± 1.2	6.1 ± 1.3	0.535	5.4 ± 1.4	5.4 ± 1.4	0.945
Unreactive pupil(s)	43 (49)	23 (49)	0.994	9 (38)	6 (38)	1.000	4 (31)	2 (22)	0.658	28 (65)	14 (74)	0.506
Systolic BP (mm Hg)	145 ± 35	150 ± 39	0.486	137 ± 27	149 ± 42	0.313	127 ± 24	151 ± 45	0.131	156 ± 39	151 ± 32	0.599
Diastolic BP (mm Hg)	82 ± 20	83 ± 20	0.810	78 ± 16	83 ± 27	0.574	80 ± 13	84 ± 21	0.630	87 ± 23	84 ± 15	0.580
HR (beats/min)	89 ± 26	88 ± 25	0.804	94 ± 23	96 ± 23	0.719	92 ± 27	101 ± 25	0.452	84 ± 24	74 ± 21	0.140

Values are *n* (%) or mean ± standard deviation.

GCS, Glasgow Coma Scale; BP, blood pressure; HR, heart rate.

TABLE 2. HEMODYNAMIC PARAMETERS

	Day 0			Day 1			Day 3			1 day after rewarming		
	Therapeutic hypothermia	Fever control	p value	Therapeutic hypothermia	Fever control	p value	Therapeutic hypothermia	Fever control	p value	Therapeutic hypothermia	Fever control	p value
All cases												
Temp (°C)	35.2±1.6	36.1±0.9	0.001	33.3±0.7	35.7±1.0	0.000	33.6±1.0	35.6±1.0	0.000	36.5±0.7	36.7±0.8	0.179
MAP (mm Hg)	90±18	94±23	0.208	89±15	89±16	0.913	91±15	94±18	0.250	98±15	98±14	0.901
ICP (mm Hg)	19±20	21±19	0.614	23±25	22±17	0.889	24±25	20±15	0.398	19±15	23±16	0.256
CPP (mm Hg)	76±29	78±28	0.727	67±27	67±28	0.933	68±33	75±29	0.240	81±23	79±23	0.581
Diffuse injury II												
Temp (°C)	35.1±1.6	36.6±1.0	0.003	33.3±0.9	35.6±1.2	0.000	33.2±0.7	35.6±1.0	0.000	36.4±1.0	37.0±0.6	0.054
MAP (mm Hg)	91±16	101±24	0.139	90±14	89±14	0.823	90±12	101±20	0.040	103±14	103±15	0.878
ICP (mm Hg)	16±13	22±17	0.246	11±7	22±17	0.016	13±10	18±8	0.183	14±6	18±7	0.088
CPP (mm Hg)	80±18	86±23	0.361	80±15	66±32	0.109	78±15	81±28	0.753	90±15	91±16	0.980
Diffuse injury III												
Temp (°C)	34.7±1.8	35.8±1.0	0.085	33.0±0.5	35.5±1.3	0.000	33.7±1.0	35.5±1.3	0.003	36.9±0.6	37.0±1.1	0.809
MAP (mm Hg)	85±18	79±28	0.535	84±15	86±22	0.819	88±19	90±15	0.745	94±22	97±15	0.713
ICP (mm Hg)	21±26	18±9	0.786	25±23	17±9	0.321	33±32	14±7	0.060	25±19	20±9	0.555
CPP (mm Hg)	69±33	60±33	0.560	59±36	69±29	0.492	54±44	78±20	0.114	69±30	77±16	0.524
Evacuated mass lesion												
Temp (°C)	35.4±1.5	35.9±0.7	0.129	33.5±0.7	35.7±0.8	0.000	33.6±0.8	35.5±1.1	0.000	36.5±0.6	36.2±0.6	0.158
MAP (mm Hg)	92±20	98±16	0.308	90±17	89±13	0.960	93±16	91±18	0.653	97±13	95±12	0.564
ICP (mm Hg)	22±24	22±25	0.967	27±29	25±20	0.786	25±27	26±19	0.894	20±18	27±22	0.257
CPP (mm Hg)	77±33	81±27	0.721	64±28	64±26	0.951	69±35	68±32	0.915	80±23	68±28	0.110

Values are mean ± standard deviation. Temp, core temperature; MAP, mean arterial pressure; ICP, intracranial pressure; CPP, cerebral perfusion pressure.

TABLE 3. OUTCOMES AND MORTALITY RATES ACCORDING TO COMPUTED TOMOGRAPHY CLASSIFICATION OF TRAUMATIC COMA DATA BANK IN ALL PATIENTS

CT classification (TCDB classification)	Total no.	Favorable outcome		p value	Mortality		p value
		Therapeutic hypothermia (88)	Fever control (47)		Therapeutic hypothermia (88)	Fever control (47)	
Diffuse injury I	2	1/1 (100)	1/1 (100)	-	0/1 (0)	0/1 (0)	-
Diffuse injury II	40	13/24 (54.2)	11/16 (68.8)	0.356	3/24 (12.5)	3/16 (18.8)	0.588
Diffuse injury III	22	5/13 (38.5)	6/9 (66.7)	0.193	7/13 (53.8)	1/9 (11.1)	0.041
Diffuse injury IV	4	1/2 (50.0)	0/2 (0)	-	1/2 (50.0)	0/2 (0)	-
Evacuated mass lesion	62	19/43 (44.2)	6/19 (31.6)	0.351	16/43 (37.2)	6/19 (31.6)	0.669
Nonevacuated mass lesion	3	1/3 (33.3)	0/0 (0)	-	2/3 (66.7)	0/0 (0)	-
Unknown	2	0/2 (0)	0/0 (0)	-	2/2 (100)	0/0 (0)	-

CT, computed tomography; TCDB, Traumatic Coma Data Bank.
Values are no. (%).

treatment groups. Hemodynamic parameters measured on days 0, 1, and 3 of treatment, and 1 day after rewarming are shown in Table 2. These indicate that the hemodynamic status was well controlled, and none of these parameters differed between the two groups in all cases on any measurement day. In diffuse injury II cases, ICP in the fever control group on day 1 and MAP in the fever control group on day 3 were significantly higher than the respective values in the therapeutic hypothermia group ($p=0.016$, 0.040 , respectively). ICP in the therapeutic hypothermia group in diffuse injury III cases also increased during the hypothermic period. In contrast, ICP during the acute phase in evacuated mass lesions did not differ significantly between the two groups (Table 2).

The neurologic outcomes of all patients are shown in Table 3. The favorable outcome rate was not significantly different between the two treatment groups for any classification (Table 3). Mortality in the hypothermia group, however, was significantly higher than that in the fever control group for diffuse injury III cases (53.8% vs. 11.1%, $p=0.041$) (Table 3).

The neurological outcomes of young patients (≤ 50 years) are shown in Table 4. The favorable outcome rate in the therapeutic hypothermia group was significantly higher than that in the fever control group for evacuated mass lesions (77.8% vs. 33.3%, $p=0.015$). The mortality in the therapeutic hypothermia group was also significantly higher than that in the fever control group for diffuse injury III cases (50.0% vs. 0%, $p=0.037$).

Types of evacuated mass lesion are shown in Table 5. About 50% of cases were subdural hematoma (SDH), about 25% had a

pathophysiology of merged brain contusion with SDH, and a few cases had epidural hematoma. The frequency of the type of evacuated mass lesion did not differ significantly between the two treatment groups (Table 5).

A comparison of results from previous studies and this study is shown in Table 6. The results of the three studies were largely similar. In diffuse injury cases, the favorable outcome rate was higher in the normothermia group compared with the hypothermia group, and mortality was higher in the hypothermia group. These differences were particularly significant in our study. In cases with evacuated mass lesions, the favorable outcome rate in the hypothermia group was significantly higher than that in the normothermia group in all three studies.

Discussion

Many clinical trials of hypothermia therapy for patients with TBI have been conducted, but there is no consensus on hypothermic effects for severe TBI because multicenter randomized controlled trials have yet to show protective effects of hypothermia therapy for those with severe TBI.^{7,8} In a recent multicenter randomized controlled trial in Japan, we were again unable to show protective effects of hypothermia therapy for patients with severe TBI.¹⁰

One cause of these poor results may be the heterogeneity of the population. In the current secondary analysis of the BHYPOT trial, we compared the outcome of patients based on their TCDB CT classification. Young patients with an evacuated mass lesion were

TABLE 4. OUTCOMES AND MORTALITY RATES ACCORDING TO COMPUTED TOMOGRAPHY CLASSIFICATION OF TRAUMATIC COMA DATA BANK IN YOUNG PATIENTS (≤ 50 YEARS)

CT classification (TCDB classification)	Total no.	Favorable outcome		p value	Mortality		p value
		Therapeutic hypothermia (52)	Fever control (31)		Therapeutic hypothermia (52)	Fever control (31)	
Diffuse injury I	2	1/1 (100)	1/1 (100)	-	0/1 (0)	0/1 (0)	-
Diffuse injury II	29	9/17 (52.3)	10/12 (83.3)	0.090	3/17 (17.6)	1/12 (8.3)	0.474
Diffuse injury III	16	4/10 (40.0)	5/6 (83.3)	0.193	5/10 (50.0)	0/6 (0)	0.037
Diffuse injury IV	2	1/2 (50.0)	0/0 (0)	-	1/2 (50.0)	0/0 (0)	-
evacuated mass lesion	30	14/18 (77.8)	4/12 (33.3)	0.015	2/18 (11.1)	3/12 (25.0)	0.317
nonevacuated mass lesion	2	1/2 (50.0)	0/0 (0)	-	1/2 (50.0)	0/0 (0)	-
unknown	1	0/1 (0)	0/1 (0)	-	1/1 (100)	0/1 (0)	-

CT, computed tomography; TCDB, Traumatic Coma Data Bank.
Values are no. (%).

TABLE 5. TYPE OF EVACUATED MASS LESION

Type of mass lesions	Therapeutic hypothermia n = 43	Fever control n = 19	p value
SDH	24 (55.8)	12 (63.2)	0.589
cont	1 (2.3)	1 (5.3)	0.546
SDH + cont	11 (25.6)	5 (26.3)	0.951
SDH + cont + EDH	5 (11.6)	0 (0)	0.121
cont + EDH	2 (4.7)	1 (5.3)	0.918

SDH, subdural hematoma; cont, brain contusion; EDH, epidural hematoma.

Values are n (%).

found to benefit from hypothermia therapy, but this therapy increased mortality in those with diffuse injury III. The results for evacuated mass lesions are in good agreement with the National Acute Brain Injury Study: Hypothermia II (NABIS:H II) clinical trial in China and the neurotrauma data bank in Japan.^{8,16,17} Thus, young patients with an evacuated mass lesion are likely to be good candidates for hypothermia therapy.

The protective mechanism of hypothermia for evacuated mass lesions is unclear. In an experimental model, brain compression by acute SDH causes ischemia and removal of the hematoma induces reperfusion.¹⁸ An ischemia/reperfusion insult induces production of free radicals and secondary brain damage in the form of a stroke or TBI.^{19,20}

Hypothermia has commonly been thought to reduce secondary neuronal damage in TBI by suppression of glutamate release, blood-brain barrier disruption, and free radical production.^{20,21} Burger and colleagues²² showed that intras ischemic hypothermia followed by hematoma removal is associated with improved outcome. Hypothermia therapy before removal of the hematoma may thus suppress free radical production at surgery and induce a better outcome in patients with an evacuated mass lesion. Further, Qiu and associates¹⁶ reported significantly elevated superoxide dismutase serum levels at 3 and 7 days after craniotomy in patients with severe TBI who underwent hypothermia therapy. These protective effects of hypothermia on neurotoxicity induced by free radicals in patients with evacuated mass lesions may be associated with improved outcome.

These mechanisms suggest that early induction of hypothermia is important for an evacuated mass lesion. In a secondary analysis of two randomized clinical trials, early induction of hypothermia for an evacuated mass lesion was associated with a reduction in poor

outcome.²³ This led to the suggestion that a body temperature of $\leq 35^{\circ}\text{C}$ should be reached before hematoma evacuation.²³ In our study, patients with evacuated mass lesions took 2.7 ± 5.5 h after the start of surgery to reach 35.5°C and 7.3 ± 7.4 h to reach 34°C . Of the 41 hypothermia-treated patients with evacuated mass lesions, 22 had a temperature of 35.5°C within 1.5 h after the start of surgery, and 20 had a temperature of 34°C within 5.5 h after the start of surgery.

These results show that induction of hypothermia for patients with an evacuated mass lesion in our study was slower than those in the NABIS:H I and NABIS:H II studies.²³ This slow induction of hypothermia may have reduced favorable neurologic outcomes in patients with evacuated mass lesions in our study compared with the NABIS:H I and NABIS:H II studies. This further emphasizes the importance of early hypothermic induction before hematoma evacuation.

In this study, we showed that hypothermia therapy increases mortality in patients with diffuse injury III. Shiozaki and coworkers²⁴ also found that hypothermia therapy is ineffective for preventing elevation of ICP in patients with diffuse injury with ICP > 40 mm Hg, but effective for patients with focal injury. In experimental models, hypothermia has been shown to be effective for diffuse axonal injury,² which is associated with inhibition of secondary axonal/cytoskeletal damage.²⁵ This protective effect, however, is not associated with diffuse brain swelling, which is induced by direct injury to the whole brain.

Hypothermia therapy is unable to prevent this cascade induced by initial or direct traumatic damage. Further, ICP in patients treated with therapeutic hypothermia increased from day to day during the hypothermic phase in cases with diffuse injury III, whereas ICP was stable in patients treated with fever control.

These findings show that hypothermic therapy has adverse effects in cases with diffuse injury III. A critical fall of CPP did not occur along with the rise of ICP, and thus blood pressure was maintained. The mechanisms of the adverse effects are unclear based only on the data collected in this study. Improved understanding will need further investigation of respiratory and circulation states, and brain metabolism in hypothermia for patients with diffuse injury.

Conclusions

We conclude that hypothermia therapy is effective for patients with evacuated mass lesions who are 50 years old or younger. Increased mortality, however, was found in patients in the hypothermia group with diffuse injury III based on the CT classification of the TCDB. Therefore, selection of hypothermic treatment suitable for each pathophysiology of TBI is important.

TABLE 6. RESULTS OF PREVIOUS STUDIES AND THIS STUDY: FAVORABLE OUTCOME AND MORTALITY

Subgroup/study	Type of study	Favorable outcome				Mortality			
		Hypo	vs.	Normo (%)	p value	Hypo	vs.	Normo (%)	p value
Diffuse injury									
Clifton et al. (2011) ⁸	Randomized study	30.0	vs.	50.0	0.09	27.0	vs.	9.0	0.08
Suehiro et al. (2014) ¹⁷	Observational study	38.1	vs.	38.8	0.96	42.9	vs.	24.5	0.12
Our study (≤50 y.o.)	Randomized study	50.0	vs.	84.2	0.02	30.0	vs.	5.3	0.04
Evacuated mass lesion									
Clifton et al. (2011) ⁸	Randomized study	67.0	vs.	31.0	0.02	13.0	vs.	39.0	0.16
Suehiro et al. (2014) ¹⁷	Observational study	52.4	vs.	26.9	0.04	19.0	vs.	23.1	0.71
Our study (≤50 y.o.)	Randomized study	77.8	vs.	33.3	0.02	11.1	vs.	25.0	0.32

Hypo, hypothermia; Normo, normothermia; y.o., years old.

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