Fever Control Management Is Preferable to Mild Therapeutic Hypothermia in Traumatic Brain Injury Patients with Abbreviated Injury Scale 3–4: A Multi-Center, Randomized Controlled Trial

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Abstract

In our prospective, multi-center, randomized controlled trial (RCT)—the Brain Hypothermia (B-HYPO) study—we could not show any difference on neurological outcomes in patients probably because of the heterogeneity in the severity of their traumatic condition. We therefore aimed to clarify and compare the effectiveness of the two therapeutic temperature management regimens in severe (Abbreviated Injury Scale [AIS] 3–4) or critical trauma patients (AIS 5). In the present post hoc B-HYPO study, we re-evaluated data based on the severity of trauma as AIS 3–4 or AIS 5 and compared Glasgow Outcome Scale score and mortality at 6 months by per-protocol analyses. Consequently, 135 patients were enrolled. Finally, 129 patients, that is, 47 and 31 patients with AIS 3–4 and 36 and 15 patients with AIS 5 were allocated to the mild therapeutic hypothermia (MTH) and fever control groups, respectively.

No significant intergroup differences were observed with regard to age, gender, scores on head computed tomography (CT) scans, and surgical operation for traumatic brain injury (TBI), except for Injury Severity Score (ISS) in AIS 5. The fever control group demonstrated a significant reduction of TBI-related mortality compared with the MTH group (9.7% vs. 34.0%, $p = 0.02$) and an increase of favorable neurological outcomes (64.5% vs. 51.1%, $p = 0.26$) in patients with AIS 3–4, although the latter was not statistically significant. There was no difference in mortality or favorable outcome in patients with AIS 5.

Fever control may be considered instead of MTH in patients with TBI (AIS 3–4).

Key words: Abbreviated Injury Scale; heterogeneous pathophysiology; multi-center randomized controlled trial; therapeutic hypothermia; traumatic brain injury

Introduction

TRAUMATIC BRAIN INJURY (TBI) can cause disability and death, which can result due to a combination of primary brain injury (shearing damage to neurons or glial cells at the time of impact) and secondary brain injury (ischemia/hypoxia and reperfusion injury).¹ Hypothermia can be used to treat TBI. The specific effects of hypothermia are to limit secondary brain injury by not only reducing intracranial pressure (ICP) and cerebral metabolic demands but also by decreasing disruption of the blood–brain barrier, inhibiting the inflammatory cytokines, and reducing free radicals related to reperfusion injury.^{2–5}

Although clinical trials have been conducted to investigate the effects of mild therapeutic hypothermia (MTH; at 32°C–34°C) for TBI, they could not demonstrate more favorable outcomes than those obtained by normothermia (at 37°C).^{6–8}

A multi-center, randomized controlled trial (RCT) in patients with severe TBI who received either MTH (32.0°C–34°C) or fever control (35.5°C–37°C) was conducted in Japan by the Brain Hypothermia Study Group (B-HYPO). The protocol was well designed to improve former considerations, such as prolonged MTH (more than 72 h), tight hemodynamic monitoring, and slow rewarming.^{1,6} However, we were unable to show the efficacy of MTH for serious to critical TBI.⁹ One reason for the negative results may

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TABLE 1. PATIENT CHARACTERISTICS

Variable	AIS head 3–4			AIS head 5		
	MTH (32°C–34°C) N=47	Fever control (35.5°C–37°C) N=31	P	MTH (32°C–34°C) N=36	Fever control (35.5°C–37°C) N=15	P
Age (years)	30 (19–48)	42 (20–56)	0.32	39 (21.3–59)	56 (30–65)	0.20
Male	32 (69.6)	20 (66.7)	0.81	24 (66.7)	11 (78.6)	0.51
Systolic blood pressure (mm Hg)	131 (115–168)	144 (123–174)	0.47	134 (109.3–169.5)	170 (145–190)	0.09
Heart rate (beats/min)	86 (72–106)	89 (70–110)	0.72	84 (72.5–103.3)	76 (60–106)	0.48
Glasgow Coma Scale score	6 (5–7)	6 (5–7)	0.40	5 (4–6.8)	6 (4–6)	0.89
4–5	16	8		21	7	
6–8	31	23		15	8	
Unreactive pupil or pupils	20 (42.3)	13 (41.9)	1.00	18 (50)	8 (53.3)	1.00
Platelet counts ($\times 10^4/\text{mm}^3$)	20.9 (17–26)	22.9 (17.4–27.3)	0.13	22.1 (17.3–26.2)	22.4 (17.9–29.6)	0.36
FDP ($\mu\text{g/mL}$)	64.1 (24.4–92.5)	44.2 (24.5–86.2)	0.63	36.9 (18.8–114.2)	74 (40.4–168)	0.07
TCDB classification			0.34			0.87
Diffuse injury grade I	0 (0)	1 (3.3)		1 (2.8)	0 (0)	
Diffuse injury grade II	17 (36.2)	12 (40.0)		6 (16.7)	4 (26.7)	
Diffuse injury grade III	8 (17.0)	7 (23.3)		5 (13.9)	2 (13.3)	
Diffuse injury grade IV	0 (0.0)	1 (3.3)		2 (5.6)	1 (6.7)	
Evacuated mass	20 (42.6)	9 (30.0)		20 (55.6)	8 (53.3)	
Non-evacuated mass	2 (4.3)	0 (0.0)		2 (5.6)	0 (0)	
Surgical operation for TBI	15 (48.4)	24 (51.1)	1.00	27 (77.1)	12 (80)	1.00
Injury Severity Score	18 (16–29)	18 (16–27)	0.82	32 (25–35)	25 (25–29)	0.03
AIS score for head: 3	11 (23.4)	7 (22.6)	1.00			
AIS score for head: 4	36 (76.6)	24 (77.4)				
AIS score >4 for other organs	5 (10.6)	3 (9.7)	1.00	3 (8.3)	0 (0)	0.54

Values are presented as medians (interquartile ranges, IQR).

AIS, Abbreviated Injury Score; CT, computed tomography; FDP, fibrin degradation products; MTH, mild therapeutic hypothermia; TBI, traumatic brain injury; TCDB, Traumatic Coma Data Bank.

have been the heterogeneity of the population, particularly in the Injury Severity Score (ISS; 27 ± 9 vs. 24 ± 7 , $p < 0.037$) in the MTH and fever control groups, respectively.⁹

The Abbreviated Injury Scale (AIS) is an anatomical, consensus derived, global severity scoring system that classifies each injury by body region according to its relative importance on a 6-point ordinal scale (1=minor, 2=moderate, 3=serious, 4=severe, 5=critical, and 6=maximum [currently untreatable]).¹⁰ The head AIS measures and describes TBI severity based on a combination of symptoms, such as loss of consciousness, physical and neurological examination findings, mechanism (blunt or penetrating),

and radiographic findings (computed tomography [CT] findings).^{11,12} AIS is the basis for the ISS calculation of the patient with multiple injuries. Therefore, we considered that analysis on adjusting the AIS head score can reduce the heterogeneity caused by ISS in the B-HYPO study.

AIS on initial CT scan provides useful prognostic information in patients with severe TBI.^{13,14} An AIS head score of 5 indicates critical primary brain injury, which represents an extremely high mortality rate of 31.4% during the first 2 weeks following injury (AIS 1–4; 4.7%),¹⁵ with a low rate of neurologically favorable outcome (16%) in the 6-month follow-up (AIS 0–4; 65%).¹³

TABLE 2. DURATION RELATED TO ADMISSION, COOLING, AND REWARMING

Variable	AIS head 3–4					AIS head 5				
	MTH (32°C–34°C)		Fever control (35.5°C–37°C)		P	MTH (32°C–34°C)		Fever control (35.5°C–37°C)		P
	N	Median (IQR)	N	Median (IQR)		N	Median (IQR)	N	Median (IQR)	
Duration from the onset of TBI										
To admission (min)	47	40 (31–61)	31	42 (28–58)	0.79	36	41.5 (30–65)	15	40 (29–54)	0.75
To start of cooling (min)	47	178 (143–250)				36	193 (133–270)			
To 35.5°C	45	270 (210–405)				34	340 (193–504)			
To 34°C	45	480 (300–665)				34	540 (363–725)			
Duration of cooling (h)	36	74 (67–84)				27	81 (27–85)			
Duration of rewarming (h)	37	72 (61–110)				29	84 (48–121)			

AIS, Abbreviated Injury Score; IQR, interquartile range; MTH, mild therapeutic hypothermia; TBI, traumatic brain injury.

TABLE 3. COMPARISONS OF HEMODYNAMIC PARAMETERS BETWEEN MILD THERAPEUTIC HYPOTHERMIA (32°C–34°C) GROUP AND FEVER CONTROL (35.5°C–37°C) GROUP

	Day 0			Day 1			Day 3			1 day after rewarming		
	MTH	Fever control	P	MTH	Fever control	P	MTH	Fever control	P	MTH	Fever control	P
AIS head 3–4												
Temp (°C)	34.1 (33.1–35.8)	35.6 (32.9–36.4)	0.61	33.2 (32.6–33.9)	35.6 (35.5–36.2)	<0.01	33.5 (33–33.8)	35.8 (35.5–36.3)	<0.01	36.7 (36.3–37.0)	36.8 (36.1–37.4)	0.93
MAP (mm Hg)	89 (81–100)	94 (83–101)	0.54	89 (76–100)	88 (79–99)	0.72	86 (76–104)	96 (85.8–106.5)	0.10	100 (89–113)	98 (86–106)	0.31
ICP (mm Hg)	11 (8–16)	21 (8–30)	0.28	13 (9–18)	17 (11–23)	0.06	14 (9–20)	16 (12–22)	0.32	13 (10–17)	16 (14–29)	0.02
CPP (mm Hg)	78 (64–87)	70 (65–86)	0.65	71 (60–86)	73 (60–83)	0.76	76 (60–92)	81 (64–97)	0.44	90 (75–103)	80 (67–88)	0.04
CI (L/min/m ²)	3 (2.6–4)	3.1 (2.7–4.1)	0.98	3 (2.5–3.4)	3.6 (3–4.4)	<0.01	3.5 (3.2–4.6)	3.9 (3.5–4.6)	0.12	3.8 (3.3–4.7)	3.8 (3.3–4.7)	0.98
SVRI (dynes/sec/cm ⁵)	649 (542–936)	657 (538–854)	0.90	764 (625–974)	579 (482–694)	<0.01	558 (480–802)	554 (419–738)	0.29	629 (505–779)	589 (373–773)	0.25
AIS head 5												
Temp (°C)	35.5 (34.1–37)	35.5 (35.2–35.5)	0.86	33.2 (33–33.7)	35.3 (35–36.4)	<0.01	33.3 (33–34)	35.5 (34.4–36.3)	<0.01	36.6 (36.1–36.8)	35.4 (36.2–37.1)	0.98
MAP (mm Hg)	88 (80–106)	95.5 (82–102.3)	0.55	88 (76–96)	92 (80–103)	0.77	94 (80.8–101.5)	95 (77.5–107)	0.94	99.5 (84.8–106)	105.5 (99–107.8)	0.07
ICP (mm Hg)	11 (7.5–37.5)	30 (9.8–56)	0.33	19 (11–36.3)	23 (11.8–47.5)	0.55	16.5 (8.5–33.3)	22 (15–27)	0.37	19 (9.3–33.3)	18 (11.5–33)	0.99
CPP (mm Hg)	83 (63–100)	83 (34.3–101.5)	0.82	60 (51–84)	69 (16–83)	0.75	77.5 (44.8–91)	80 (61–96.5)	0.63	85 (62.3–89)	86 (77.8–97.8)	0.42
CI (L/min/m ²)	3.1 (2.3–4)	2.7 (2.1–5.5)	0.96	3 (2.4–3.5)	3.1 (2.5–4)	0.50	3.3 (2.8–3.9)	3.2 (2.8–3.9)	0.73	4.2 (3.7–5)	4.1 (2.7–4.5)	0.12
SVRI (dynes/sec/cm ⁵)	721 (553–919)	485 (388–1899)	0.59	737 (637–990)	729 (551–957)	0.76	711 (511–969)	628 (540–1033)	0.79	613 (455–704)	616 (441–971)	0.65

Values are presented as medians (interquartile ranges, IQR).

AIS, Abbreviated Injury Score; CI, Cardiac Index; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; MTH, mild therapeutic hypothermia; Temp, core temperature; SVRI, Systemic Vascular Resistance Index.

Because the specific effects of hypothermia are known to prevent secondary brain injury, we assumed that the efficacy of hypothermia can be accurately evaluated excluding the critical primary brain injury. Therefore, we hypothesized that the efficacy of the management of targeted temperature cooling (MTH and fever control) would be different between those with AIS head scores of 3–4 and AIS head score of 5 (critical primary brain injury).

Methods

Patients, randomization, and blinding

The B-HYPO study was conducted as a prospective, multi-center RCT between December 2002 and September 2008. 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.⁵ Briefly, inclusion criteria were age 15–69 years for both sexes and Glasgow Coma Scale (GCS) score of 4–8. Written informed consent was obtained from the patient's legally authorized representative prior to inclusion. If informed consent could not be obtained within 2 h of admission, the consent policy was waived. One hundred fifty patients were randomly assigned (2:1 allocation ratio) to either the MTH group (32°C–34°C) or the fever control group (35.5°C–37°C) and intention-to-treat analyses were performed.⁹ After enrollment, informed consent could not be obtained for 2 patients, 7 patients had unstable vital signs before temperature management, and neurological outcomes could not be assessed at 6 months in 6 patients. Therefore, per-protocol analyses were performed in 135 patients (88 treated with MTH and 47 with fever control).

In the present post hoc study, we re-evaluated our data based on the severity of brain trauma itself, which was classified as either AIS brain 3–4 or AIS 5.

Consequently, 135 patients were enrolled, whereas 6 patients were excluded because AIS was not recorded. Forty-seven patients with AIS 3–4 were allocated to the MTH group and 31 patients to the fever control group, respectively. Thirty-six patients with AIS 5 were allocated to the MTH group and 15 patients to the fever control group, respectively. The Glasgow Outcome Scale (GOS) evaluated by physicians, who had been blinded to the treatment allocation, and mortality had been compared at 6 months between the two groups.

Treatment

Core body temperature was measured by a thermistor coupled to an internal jugular venous catheter. If the catheter could not be inserted at the jugular vein, temperature was measured at another site selected in the following order: pulmonary artery, bladder, rectum, and tympanic membrane. All patients were treated based on the guidelines for management of severe TBI of the Japan Society of Neurotraumatology.¹⁶ Treatment was performed as described in our original article.⁹ Briefly, 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 targeted temperature within 6 h after onset of TBI and maintain this temperature for at least 72 h, mainly using surface cooling blankets. After 72 h temperature was kept <38°C for 7 days after the onset of the TBI.

Data collection and study outcomes

All data, except for CT data, were transmitted to the UMIN-CTR via an Internet-based system. CT on admission was classified based on the Traumatic Coma Data Bank (TCDB) classification.¹⁷

TABLE 4A. COMPARISON OF MORTALITY BETWEEN MTH (32°C–34°C) GROUP AND FEVER CONTROL (35.5°C–37°C) GROUP

AIS classification	Mortality			
	MTH (32°C–34°C) n (%)	Fever control (35.5°C–37°C) n (%)	Relative risk (95% CI)	P
AIS head 3–4	16 (34.0)	3 (9.7)	4.82 (1.27–18.3)	0.02
AIS head 5	13 (36.1)	7 (46.7)	0.65 (0.19–2.19)	0.54

AIS, Abbreviated Injury Score; CI, confidence interval; MTH, mild therapeutic hypothermia.

TABLE 4B. COMPARISON OF FAVORABLE NEUROLOGICAL OUTCOMES BETWEEN MTH (32°C–34°C) GROUP AND FEVER CONTROL (35.5°C–37°C) GROUP

AIS classification	Favorable outcomes			
	MTH (32°C–34°C) n (%)	Fever control (35.5°C–37°C) n (%)	Relative risk (95% CI)	P
AIS head 3–4	24 (51.1)	20 (64.5)	0.57 (0.22–1.46)	0.26
AIS head 5	13 (36.1)	3 (21.4)	2.07 (0.49–8.80)	0.50

AIS, Abbreviated Injury Score; CI, confidence interval; MTH, mild therapeutic hypothermia.

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 rates of mortality and favorable neurological outcome in the AIS 3–4 and AIS 5 patients were compared between the MTH and fever control groups at 6 months, and complications during and after the treatments were also evaluated. Good recovery and moderate disability in the GOS at 6 months after injury were designated as favorable outcomes.

Statistical analyses

Hemodynamic parameters, ICP, cerebral perfusion pressure (CPP), favorable outcome rate, and mortality were compared between the two groups. Continuous variables were analysed by Mann–Whitney U test, as appropriate, and categorical variables by χ^2 test. The results are presented as medians (interquartile ranges, IQR). A *p* value of ≤ 0.05 was deemed significant.

Results

Comparison of baseline characteristics between MTH (32°C–34°C) group and fever control (35.5°C–37°C) group

No significant differences were observed in the patients' characteristics, except for ISS in AIS 5, between the two groups. The ISS was significantly higher in the MTH group than in the fever control group (Table 1).

Times to the targeted temperature and durations of cooling or rewarming are shown in Table 2. Their systemic and cerebral hemodynamic status was well controlled and none of these parameters differed between the two groups during the first 3 days, except for Cardiac Index (CI); $p < 0.01$ and Systemic Vascular Resistance Index ($p < 0.01$) on day 1, and ICP ($p = 0.02$) and CPP (0.04) on 1 day after rewarming in AIS 3–4 (Table 3). ICP in the fever control group 1 day after rewarming was significantly higher than that in the MTH group, whereas CPP was maintained at >80 mm Hg in AIS 3–4 patients (Table 3).

Comparison of mortality and neurological outcomes between the MTH group and the fever control group

Fever control management was associated with a significant reduction of mortality (AIS 3–4: 9.7% vs. 34%, $p = 0.02$) and an

increase of favorable neurological outcome (AIS3–4: 64.5% vs. 51.1%, $p = 0.26$), which were compared with MTH in the present study (Table 4), although the latter was not statistically significant. There was no significant difference between the two groups in the AIS 5 patients.

Details of complications

In AIS 3–4, there was no significant difference in the rate of complication (10.6% vs. 3.2%, $p = 0.39$, Table 5) between the MTH and fever control groups. In AIS 5, there was no significant difference between the two groups.

Alterations of platelet counts

There was no significant difference in platelet counts between the two groups on admission (Fig. 1); however, the counts decreased in the MTH group compared with those in the fever control group in the patients with AIS 3–4.

There was no significant difference in platelet counts between the two groups on admission; however, the counts decreased significantly in the MTH group compared with those in the fever

TABLE 5. DETAILS OF COMPLICATIONS

Variable	MTH (32°C–34°C)	Fever control (35.5°C–37°C)	P
AIS head 3–4			0.20
Thrombocytopenia	2	0	
Severe pneumonia	0	1	
Sepsis	1	0	
DIC	1	0	
Others	1	0	
AIS head 5			0.94
Thrombocytopenia	5	0	
Severe pneumonia	3	0	
Sepsis	2	0	
Arrhythmia	1	0	
Others	1	0	

AIS, Abbreviated Injury Score; DIC, disseminated intravascular coagulation; MTH, mild therapeutic hypothermia.

FIG. 1. Alterations of platelet counts between MTH (32°C–34°C) and fever control group (35.5°C–37°C) in AIS 3–4 and 5. (A) Comparisons of platelet counts between MTH and fever control group in AIS 3–4. (B) Comparisons of platelet counts between MTH and fever control group in AIS 5. Patients who received MTH at 32°C–34°C are indicated in gray, and those who received fever control at 35.5°C–37°C are indicated in white. The boxes are the 25th to 75th percentile and the whiskers are the 5th to 95th percentiles. * $p < 0.05$ compared with data between MTH group and fever control group. AIS, Abbreviated Injury Scale; MTH, mild therapeutic hypothermia.

control group both on day 1 and day 3 in the patients with AIS 5 ($p = 0.03$ on day 1, $p < 0.01$ on day 3).

Causes of death

Degeneration in intracerebral lesion was the leading cause of death in both groups (Table 6). In the MTH group, sepsis and arrhythmia were observed in one patient each in AIS 3–4 patients. In AIS 5 patients, degeneration in intracerebral lesion was the dominant cause of death.

Period from admission to death

In AIS 3–4 patients who died from degeneration in intracerebral lesion, the period from admission to death was significantly shorter in the MTH group than in the fever control group (medians [IQR]: 10 [6–13] vs. 17 [13–25], $p < 0.05$).

Discussion

In the present post hoc study, fever control management was significantly associated with reduction of mortality (9.7% vs. 34%)

compared with MTH in patients with AIS head 3–4. In both groups, we actively controlled core body temperature at 35.5°C–37°C or 32°C–34°C for more than 72 h and prevented hyperpyrexia (<38°C) for 4 days after rewarming. Consequently, these strict temperature managements were performed for at least 7 days. Additionally, hemodynamics such as CI and CPP were always higher in the fever control group than those in the MTH group on day 1 and 3. These two major results might be associated with a high rate of favorable outcome.

A recent RCT showed no difference in neurological outcomes between the MTH group and the fever control group in patients with cardiac arrest.¹⁸ A Cochrane review was unable to find any RCTs that evaluated the benefit of modest cooling (35°C–37°C) for TBI.¹⁹ At this juncture, it is unclear whether achieving hypothermia or merely preventing hyperthermia is more effective in patients with severe, acute brain insults. Using historical controls, Tokutomi and colleagues compared targeted temperature management at 35°C with 33°C in patients with severe TBI and observed no statistically significant difference in neurological outcome or mortality.²⁰ They compared targeted temperature management at 35°C with 33°C in patients with severe TBI, and demonstrated relatively lower mortality in the 35°C hypothermia group (27% vs. 48%, $p = 0.08$). In their study, C-reactive protein levels remained significantly higher after rewarming in the 33°C group than in the 35°C group. If a higher level of C-reactive protein in blood is related to the ongoing inflammatory responses in the brain itself, the neurological outcome might be worse in the MTH group than that in the fever control group. Because C-reactive protein production is enhanced in the liver by inflammatory cytokine, interleukin-6, and it is significantly elevated more than 40 times in blood and 2000 times in cerebrospinal fluid in post-cardiac arrest patients compared with that in normal control volunteers,²¹ Additionally, ongoing inflammation may cause organ failure and may be related to neurological outcomes.²²

Whole-body hypothermia influences all organ systems, and any potential benefit should be balanced against possible side effects.²³ Several studies demonstrated that the rate of complications significantly increased during prolonged MTH in patients with severe TBI.^{6–8,24} The managements of patients between post-cardiac arrest and severe TBI might be different

TABLE 6. CAUSES OF DEATH AND THE NUMBER IN BOTH GROUPS

Variable	MTH (32°C–34°C)	Fever control (35.5°C–37°C)	P
AIS head 3–4			0.74
Degeneration in intracerebral lesion	11	3	
Sepsis	1	0	
Arrhythmia	1	0	
Others	3	0	
AIS head 5			0.56
Degeneration in intracerebral lesion	9	7	
DIC	1	0	
Pneumonia	1	0	
Ruptured aortic aneurysm	1	0	

AIS, Abbreviated Injury Score; DIC, disseminated intravascular coagulation; MTH, mild therapeutic hypothermia.

at temperatures below 35°C because of their multiple trauma associated with increased mortality.²⁵ This might contribute to coagulopathy, which usually occurs and persists for the first 24–48 h.²⁶ Therefore, fever control should be better than MTH in terms of coagulopathy, which is specific for trauma patients. After the initiation of hypothermia in the present study, platelet counts decreased in the MTH group compared with that in the fever control group. We suspected that the coagulopathy contributed to further degeneration in intracerebral lesion, which was the major cause of death. Indeed, in the current study, in AIS 3–4 patients who died from degeneration in intracerebral lesion, the period from admission to death was significantly shorter in the MTH group than in the fever control group.

There are limitations in the present study. First, the original study was stopped before the accomplishment for futility at half of its full sample size. The sample size for this secondary analysis was further reduced from 150 patients to 129 patients. It would be very difficult to demonstrate the ability of the effectiveness of MTH or fever control. Second, classification of AIS is mainly used in trauma; therefore, it is not a common classification such as the TCDB for TBI, which is frequently used in neurocritical care. Third, our study was a sub-analysis and there may have been selection bias.

Conclusions

Fever control management may be preferable to MTH in patients with TBI (AIS 3–4). However, further studies are required to confirm the effectiveness of fever control management in these patients.

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