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Effect of Early Sustained Prophylactic Hypothermia on Neurologic Outcomes Among Patients With Severe Traumatic Brain Injury

The POLAR Randomized Clinical Trial

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IMPORTANCE After severe traumatic brain injury, induction of prophylactic hypothermia has been suggested to be neuroprotective and improve long-term neurologic outcomes.

OBJECTIVE To determine the effectiveness of early prophylactic hypothermia compared with normothermic management of patients after severe traumatic brain injury.

DESIGN, SETTING, AND PARTICIPANTS The Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury–Randomized Clinical Trial (POLAR-RCT) was a multicenter randomized trial in 6 countries that recruited 511 patients both out-of-hospital and in emergency departments after severe traumatic brain injury. The first patient was enrolled on December 5, 2010, and the last on November 10, 2017. The final date of follow-up was May 15, 2018.

INTERVENTIONS There were 266 patients randomized to the prophylactic hypothermia group and 245 to normothermic management. Prophylactic hypothermia targeted the early induction of hypothermia (33°C–35°C) for at least 72 hours and up to 7 days if intracranial pressures were elevated, followed by gradual rewarming. Normothermia targeted 37°C, using surface-cooling wraps when required. Temperature was managed in both groups for 7 days. All other care was at the discretion of the treating physician.

MAIN OUTCOMES AND MEASURES The primary outcome was favorable neurologic outcomes or independent living (Glasgow Outcome Scale–Extended score, 5–8 [scale range, 1–8]) obtained by blinded assessors 6 months after injury.

RESULTS Among 511 patients who were randomized, 500 provided ongoing consent (mean age, 34.5 years [SD, 13.4]; 402 men [80.2%]) and 466 completed the primary outcome evaluation. Hypothermia was initiated rapidly after injury (median, 1.8 hours [IQR, 1.0–2.7 hours]) and rewarming occurred slowly (median, 22.5 hours [IQR, 16–27 hours]). Favorable outcomes (Glasgow Outcome Scale–Extended score, 5–8) at 6 months occurred in 117 patients (48.8%) in the hypothermia group and 111 (49.1%) in the normothermia group (risk difference, 0.4% [95% CI, –9.4% to 8.7%]; relative risk with hypothermia, 0.99 [95% CI, 0.82–1.19]; $P = .94$). In the hypothermia and normothermia groups, the rates of pneumonia were 55.0% vs 51.3%, respectively, and rates of increased intracranial bleeding were 18.1% vs 15.4%, respectively.

CONCLUSIONS AND RELEVANCE Among patients with severe traumatic brain injury, early prophylactic hypothermia compared with normothermia did not improve neurologic outcomes at 6 months. These findings do not support the use of early prophylactic hypothermia for patients with severe traumatic brain injury.

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Severe traumatic brain injury is a leading cause of neurologic disability, and approximately 50% of patients have long-term outcomes of death or severe disability.¹⁻³ The economic and social costs of severe traumatic brain injury are high.⁴

Acute management of patients after traumatic brain injury targets physiologic parameters to minimize secondary brain injury.^{5,6} Rapid decreasing of body temperature as early as possible after injury, or prophylactic hypothermia, may improve outcomes compared with normothermic traumatic brain injury management.⁷⁻⁹ Prophylactic hypothermia can attenuate cerebral inflammatory and biochemical cascades, which are activated early after traumatic brain injury,⁶ thereby limiting secondary brain injury.^{9,10} This is distinct from late-rescue hypothermia for elevated intracranial pressures, which in the Eurotherm3235 trial¹¹ was associated with harm. However, prophylactic hypothermia may contribute to coagulopathy, immunosuppression, bleeding, infection, and dysrhythmias after trauma.^{9,12}

A 2007 meta-analysis suggested that decreased mortality and long-term neurologic benefit were associated with prophylactic hypothermia after severe traumatic brain injury and provided a low-grade recommendation for clinical use.⁷ The only large randomized trial ($n = 392$) included showed no benefit with prophylactic hypothermia¹³ but had methodological limitations, including delayed induction and limited duration of hypothermia, as well as rewarming triggered by a time irrespective of an individual's intracranial pressure. Two subsequent trials stopped prematurely ($\leq 50\%$ planned recruitment) and reported no effect.^{14,15} A 2018 meta-analysis reported decreased risk of death with prophylactic hypothermia.⁸ These authors found that hypothermia between 33°C and 35°C, cooling in excess of 48 hours, and slow rewarming ($<0.25^\circ\text{C}/\text{h}$) were most strongly associated with improved survival.⁸ Substantial clinical uncertainty in regard to early prophylactic hypothermia remains.

A multinational randomized trial of early prophylactic hypothermia (33°C-35°C) sustained for at least 72 hours, followed by slow rewarming (in the absence of elevated intracranial pressure), compared with normothermia after severe traumatic brain injury was conducted.

Methods

Trial Design and Oversight

The Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury-Randomized Clinical Trial (POLAR-RCT) was a multicenter randomized trial in Australia, New Zealand, France, Switzerland, Saudi Arabia, and Qatar, which planned to recruit 510 patients after severe traumatic brain injury. The first patient was enrolled on December 5, 2010, and the last on November 10, 2017. The last patient's outcome was completed on May 15, 2018.

Ethical approval was obtained from Monash University and local ethics committees for participating sites and ambulance services. Approval was given for a deferred

Key Points

Question Does early prophylactic hypothermia improve long-term neurologic outcomes in patients with severe traumatic brain injury?

Findings In this randomized clinical trial that included 511 adults, the proportion of patients with favorable neurologic outcomes at 6 months was 48.8% after hypothermia vs 49.1% after normothermia, a difference that was not statistically significant.

Meaning These findings do not support the use of early prophylactic hypothermia in patients with severe traumatic brain injury.

model of consent, and written informed consent was then sought from each enrolled patient's nearest relative or designated person as soon as possible, and subsequently from the patient if he or she regained capacity. The trial protocol and statistical analysis plan (Supplement 1) were developed by the management committee and published.¹⁶ Data were collected by investigators and research coordinators at the trial sites (collaborators). The management committee and the independent data and safety monitoring committee conducted planned, blinded interim analyses assessing conduct, progress, and safety after 125 and then 250 participants had been recruited (Supplement 1). After publication of the Eurotherm3235 trial,¹¹ the data and safety monitoring committee recommended the conduct of additional interim analyses for safety at recruitment of 300, 350, 400, and 450 participants.

Participants

Five out-of-hospital or paramedic agencies and 14 emergency departments (EDs) screened for patients with traumatic brain injury. Eligible patients with head injuries were estimated to be aged 18 to 60 years, had a Glasgow Coma Scale score of less than 9, and had actual or imminent endotracheal intubation. Out-of-hospital exclusion criteria included significant bleeding suggested by systolic hypotension (<90 mm Hg) or sustained tachycardia ($>120/\text{min}$), suspected pregnancy, possible uncontrolled bleeding, Glasgow Coma Scale score of 3 and unreactive pupils, or destination hospital not a study site. Patients not enrolled out-of-hospital who fulfilled entry criteria remained eligible for enrollment in the ED (for additional ED exclusion criteria, see eTable 1 in Supplement 2) for up to 3 hours after injury.

Data Collection

Randomized patients were followed up to death or to 6 months after randomization. Online case report forms were used. These included baseline demographic and processes-of-care data, including temperature and intracranial pressure measurements hourly for the first 96 hours.

Randomization and Study Treatment

Participants were randomly assigned 1:1 to prophylactic hypothermia (hypothermia group) or to controlled

normothermia (normothermia group) through the use of sealed opaque envelopes and permuted variable block sizes (2 and 4). Randomization was stratified by out-of-hospital vs ED enrollment and by ambulance service and geographic regions. Treating clinicians were not blinded to trial group assignment. Scoring of the primary outcome was performed by blinded independent assessors using structured telephone questionnaires.

Induction of Hypothermia

In the hypothermia group, in both the out-of-hospital and ED settings hypothermia was induced by patient exposure, a bolus of up to 2000 mL intravenous ice-cold (4°C) 0.9% saline, and surface-cooling wraps once the patient was in the ED targeting an initial core temperature of 35°C. Patients were then assessed in the ED for significant clinical risk of bleeding (positive abdominal ultrasonographic or computed tomographic result, persistent hypotension, or life-threatening injury requiring immediate surgery in any body area except the head). Once these significant risk factors for bleeding were excluded, a core temperature of 33°C was targeted.

Maintenance of Hypothermia

Hypothermia was maintained at 33°C (or 35°C if bleeding concerns persisted) with a Gaymar Meditherm 3 console with surface-cooling wraps for at least 72 hours after randomization. Patients who were randomized to the hypothermia group and subsequently developed hemodynamic instability presumed to be caused by bleeding could be rewarmed to 35°C or to normothermia if their condition was considered life threatening. Target temperature for all other hypothermia patients was 33°C ± 0.5°C.

Rewarming

Intracranial pressure monitors were inserted according to usual site practice. Seventy-two hours after randomization, intracranial pressure was assessed in the hypothermia group. If the intracranial pressure was less than 20 mm Hg, gradual controlled rewarming was commenced at a target rate up to 0.25°C/h. If there was a sustained increase in intracranial pressure greater than 20 mm Hg during rewarming, the patient was recooled and then reassessed regularly for suitability for rewarming. The maximum period of hypothermia was 7 days postrandomization. Once rewarming had reached 37°C, patients were maintained normothermic with automated surface-cooling wraps, if required, for up to 7 days postrandomization.

Normothermia

Patients in the normothermia group were transported to the hospital without exposure or cold fluids and warmed if required to normothermia according to usual practice. In the intensive care unit, the temperature target was 37°C ± 0.5°C. Surface-cooling wraps could be used to manage pyrexia or refractory intracranial hypertension.

Patients in both groups could receive other treatments for elevated intracranial pressure as clinically indicated,

and in both study groups care was recommended to be managed according to international traumatic brain injury guidelines.^{5,7}

Outcomes

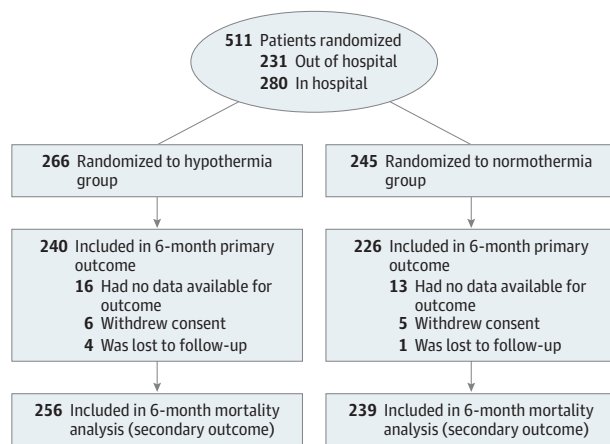
The primary outcome measure was based on the Glasgow Outcome Scale-Extended (GOS-E) score¹⁷ at 6 months after injury. A GOS-E score of 1 indicates death, 2 indicates vegetative state, 3 to 4 indicates severe disability, 5 to 6 indicates moderate disability, and 7 to 8 indicates good recovery. The primary outcome was the percentage of favorable outcomes (GOS-E score, 5 to 8).¹⁸ Secondary outcomes were GOS-E score as an ordinal variable, mortality at hospital discharge and at 6 months, and proportion of patients with adverse events (including intracranial bleeding, extracranial bleeding, pneumonia, bloodstream infections, and other infections) within 10 days of randomization. Duration of mechanical ventilation and intensive care unit and hospital length of stay was also reported. Secondary outcomes of neurologic function assessed by the sliding dichotomy method, complier average causal effect of hypothermia, quality of life, and cost-effectiveness are not reported here.

Statistical Analysis

We published a statistical analysis plan before completion of the study¹⁹ and an update (Supplement 1) before data lock and unblinding. The planned sample size of 500 patients allowed for withdrawals because of dropouts, loss of consent, and crossover from hypothermia therapy to normothermia (ie, significant bleeding or clinician decision that traumatic brain injury was likely not severe), and also allowed interim analyses. A total of 364 evaluable patients enabled detection of an absolute difference of 15% in favorable outcome from an estimated baseline rate of 50%,^{1,16,19} with 82% power and a 2-sided $P = .05$. This hypothesized absolute 15% increase in favorable neurologic outcomes was based on a 46% improvement of favorable outcomes (relative risk, 1.46; 95% CI, 1.12-1.92; $P = .006$) with hypothermia in a 2007 meta-analysis⁷ and on a 50% increase ($P = .02$) in favorable outcomes in a subgroup of patients with severe traumatic brain injury who were younger than 45 years and were hypothermic on arrival in the hospital and subsequently randomized to hypothermia vs normothermia (ie, received early hypothermia).¹³ The final trial size was marginally increased to 510 during 2017 after blinded review of the combined proportion of patients with consent withdrawn or lost to follow-up.

All a priori-defined analyses were performed with patients according to randomized group, excluding those who withdrew consent unless otherwise indicated, with no imputation of missing data. The primary outcome of favorable GOS-E score at 6 months and secondary outcomes (mortality and adverse events) were compared with unadjusted χ^2 test for equal proportions, with results reported as frequency (percentage) per treatment group with a relative risk and risk difference, both accompanied by 95% CIs. We conducted sensitivity analyses with hierarchic multivariable log-binomial regression, adjusting for extended

Figure 1. Patients Included in the Primary Analysis



Patients were screened by ambulance officers, paramedics, and emergency department staff at many out-of-hospital and intrahospital locations, and the numbers of screened patients were not recorded.

International Mission for Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury (IMPACT-TBI) score²⁰ treating randomization strata (location and site) as random effects, with results reported as relative risks (95% CI). The extended IMPACT-TBI score estimates probability of an unfavorable patient outcome, using the key risk factors of age, motor component of the Glasgow Coma Scale, pupil reactivity, brain computed tomography Marshall score, and the secondary insults hypotension and hypoxia. We analyzed GOS-E score as an ordinal variable, using ordinal logistic regression with the proportional odds assumption justified with a score test and results reported as odds ratios (95% CI). Patient survival was assessed with Cox proportional hazards regression censored at 6 months or last known point of contact, with results presented as Kaplan-Meier survival curves with corresponding log-rank test. We visually assessed the proportional hazards assumption across treatment groups, using log-cumulative hazard plots.

Prespecified subgroup analyses were performed for patients with surgically evacuated hematomas and those with any significant intracranial hematomas, with heterogeneity between subgroups determined by fitting an interaction between treatment and subgroup with logistic regression. The effect on favorable outcome of time taken for cooled patients to achieve a target temperature of 33°C was compared with unadjusted χ^2 test for equal proportions, with results reported as frequency (percentage).

Planned analyses were conducted in prespecified per-protocol and as-treated populations¹⁹ (Supplement 1), with both analyses excluding all patients who did not satisfy study inclusion and exclusion criteria. Evaluable patients were then examined for cooling compliance (defined as $\leq 35^\circ\text{C}$ for >48 hours within 96 hours of randomization) and either excluded from the analysis (per protocol) or transferred to the opposite treatment group (as treated). Per-protocol and as-treated sensitivity analyses were per-

formed, with cooling compliance defined as patients who were cooled for the majority of their first 72 hours instead of 96 hours. Post hoc analyses of missingness in the primary outcome and comparison of evaluable patients who received an adequate dose of cooling compared with controls were also performed, with detailed description of per-protocol, as-treated, and post hoc analyses shown in Supplement 1.

All analyses were conducted with SAS version 9.4, and 2-sided $P < .05$ was used to indicate statistical significance. Because no adjustment was made for multiple comparisons, all secondary outcomes should be interpreted as exploratory.

Results

Patient Characteristics

An initial 8 patients had composed a run-in phase without randomization and were not included. A total of 511 patients were enrolled, including 231 patients (45%) who were enrolled out-of-hospital (Figure 1); 266 patients were randomly assigned to the prophylactic hypothermia group and 245 to the normothermia group. Eleven patients (6 hypothermia group and 5 normothermia group) were excluded because of withdrawal of consent (Figure 1), leaving 500 evaluable patients. A total of 293 patients, 132 in the hypothermia group and 161 in the normothermia group, received the full trial protocol (eTable 8 in Supplement 2). A total of 240 patients in the prophylactic hypothermia group and 226 in the normothermia group were evaluated for the primary outcome (Figure 1).

Baseline characteristics of the 2 study groups were similar in all respects (Table 1). The patients were predominantly men, with a mean age of 34.5 years (SD, 13.4) and a median Glasgow Coma Scale score of 6 (interquartile range [IQR], 4 to 7). The majority of patients (70.6%) had diffuse brain injury (brain swelling or hemorrhages, without subdural or extradural brain hematomas), and the median time from injury to randomization was 1.9 hours (IQR, 1.0 to 2.7).

Core temperature was significantly lower in the hypothermia group than in the control group during the first 96 hours after randomization (Figure 2A). Among patients in the hypothermia group who reached target temperatures, for 233 (89.6%) the time from injury to the initial temperature target of 35°C was a median of 2.5 hours (IQR, 0.8 to 5.5), and for 186 patients (71.5%), the time to reach the final temperature target of 33°C was a median of 10.1 hours (IQR, 6.8 to 15.9) (eTable 2 in Supplement 2). A total of 85 evaluable patients (33%) in the hypothermia group received less than 48 hours of hypothermia (33°C-35°C), and 27% of patients in the hypothermia group never reached the final target temperature of 33°C because of complications or physician decisions (eFigures 3 and 4 and eTable 3 in Supplement 2). The median duration of hypothermia until rewarming commenced was 72.2 hours (IQR, 69.8 to 77.3). The median duration of rewarming to normothermia was 22.5 hours (IQR, 16 to 27); 34 patients had rewarming paused because of increased intracranial pressure (eFigure 1 in Supplement 2). Mean daily

intracranial pressure was similar in both groups during induction, maintenance, and rewarming (Figure 2B; eFigure 1 in Supplement 2), as was the elevated intracranial pressure therapy intensity (eTable 4 in Supplement 2).

Primary Outcome

Six months after injury, favorable outcomes occurred for 117 patients (48.8%) in the hypothermia group and 111 (49.1%) in the normothermia group (absolute risk difference, -0.4 percentage points [95% CI, -9.4 to 8.7]; unadjusted relative risk with hypothermia, 0.99 [95% CI, 0.82-1.19]; $P = .94$) (Table 2, Figure 3). This result was similar after adjustment for the IMPACT-TBI extended model prediction²⁰ of unfavorable outcome (Table 2).

Secondary Outcomes

When GOS-E score at 6 months after injury was considered as an ordinal variable, there remained no significant difference between treatments (unadjusted odds ratio for hypothermia vs normothermia, 0.97 [95% CI, 0.71-1.34]; $P = .88$). Mortality occurred at 6 months after injury in 54 of 256 patients (21.1%) in the hypothermia group and 44 of 239 (18.4%) in the normothermia group (absolute risk difference, 2.7 percentage points [95% CI, -4.3 to 9.7]; unadjusted relative risk, 1.15 [95% CI, 0.80-1.64]; $P = .45$) (Table 2). Results were similar for time to death (unadjusted hazard ratio, 1.13 [95% CI, 0.76-1.69]; $P = .54$) (eFigure 2 in Supplement 2).

Additional Outcomes

Results were not significantly different between groups for time to reach target temperature (eTable 7 in Supplement 2), days of mechanical ventilation, intensive care unit and hospital length of stay, mean GOS-E score at 6 months, and unfavorable GOS-E score for survivors (eTable 5 in Supplement 2).

Adverse Events

The proportions of patients with adverse events within 10 days of randomization for new or increased intracranial bleeding were 18.1% in the hypothermia group and 15.4% in the normothermia group; for pneumonia, 55.0% in the hypothermia group and 51.3% in the normothermia group (Table 2; eTable 6 in Supplement 2). Propofol-related infusion syndrome was diagnosed in 3 patients, 2 in the hypothermia group and 1 in the normothermia group; the latter was receiving nonprotocolized late-rescue hypothermia for refractory increased intracranial pressure. One of these patients died.

Per-Protocol and As-Treated Analyses

Some patients in the hypothermia group were rewarmed prematurely because either the clinicians believed that the brain injury was not as severe as initially thought or the patients developed serious bleeding (eTable 3 and eFigures 3 and 6 in Supplement 2). There were, however, no significant baseline differences between groups in either the per-protocol (eTable 8 in Supplement 2) or as-treated (eTable 10 in Supplement 2) analyses. With respect to the primary outcome, favorable outcomes were not different between groups in either the per-protocol or as-treated analyses (eTables 9 and

Table 1. Demographic and Prerandomization Characteristics of the Patients at Baseline (Intent-to-Treat Population)

	No./Total (%)	
	Hypothermia (n = 260)	Normothermia (n = 240)
Men	207 (79.6)	194 (80.8)
Women	53 (20.4)	46 (19.2)
Age, mean (SD), y	35.0 (13.5)	34.1 (13.4)
GCS score, median (IQR)		
Overall score ^a	6 (4-7)	6 (4-7)
Motor score	3 (1-4)	3 (2-5)
One or both pupils reacting ^b	220 (84.6)	202 (84.2)
Hypotension (out-of-hospital or ED) ^c	26/257 (10.1)	27/239 (11.3)
Hypoxia (out-of-hospital or ED) ^d	37/256 (14.5)	39/237 (16.5)
Temperature at the scene, mean (SD), °C ^e	36.0 (1.2)	35.9 (1.0)
CT Marshall classification ^f		
Diffuse injury I (normal findings)	18 (6.9)	17 (7.1)
Diffuse injury II	152 (58.5)	128 (53.3)
Diffuse injury III or IV	18 (6.9)	20 (8.3)
Evacuated mass lesion V	69 (26.5)	72 (30.0)
Nonevacuated mass lesion VI	3 (1.2)	3 (1.3)
Probability of unfavorable outcome at 6 mo: IMPACT-TBI (core + CT), mean (SD) ^g	0.46 (0.24)	0.46 (0.23)
Injury Severity Score, median (IQR) ^h	26.0 (18.0-34.0)	20.0 (20.5-35.0)
Cause of injury		
Motor vehicle	84 (32.3)	89 (37.1)
Motorcycle	29 (11.2)	18 (7.5)
Bicycle	20 (7.7)	20 (8.3)
Pedestrian	28 (10.8)	37 (15.4)
Hit by object	24 (9.2)	16 (6.7)
Fall/jump	60 (23.1)	54 (22.5)
Other	15 (5.8)	6 (2.5)
Positive blood ethanol level	92/208 (44.2)	89/193 (46.1)
Blood ethanol >51 mg/dL	74/208 (35.6)	69/193 (35.8)
Time from injury to randomization, median (IQR), h	1.8 (1.0-2.7)	2.0 (1.1-2.8)

Abbreviations: CT, computed tomography; ED, emergency department; GCS, Glasgow Coma Scale; IMPACT-TBI, International Mission for Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury; IQR, interquartile range.

^a The highest reliable score before randomization is reported; overall scores on the GCS range from 3 to 15, with lower scores indicating a lower level of consciousness. A patient with a GCS score of 6 is unconscious.

^b Some patients had a GCS score greater than 3, with small unreactive pupils.

^c Hypotension was defined as a systolic blood pressure less than 90 mm Hg.

^d Hypoxia was defined as SpO₂ less than 90%.

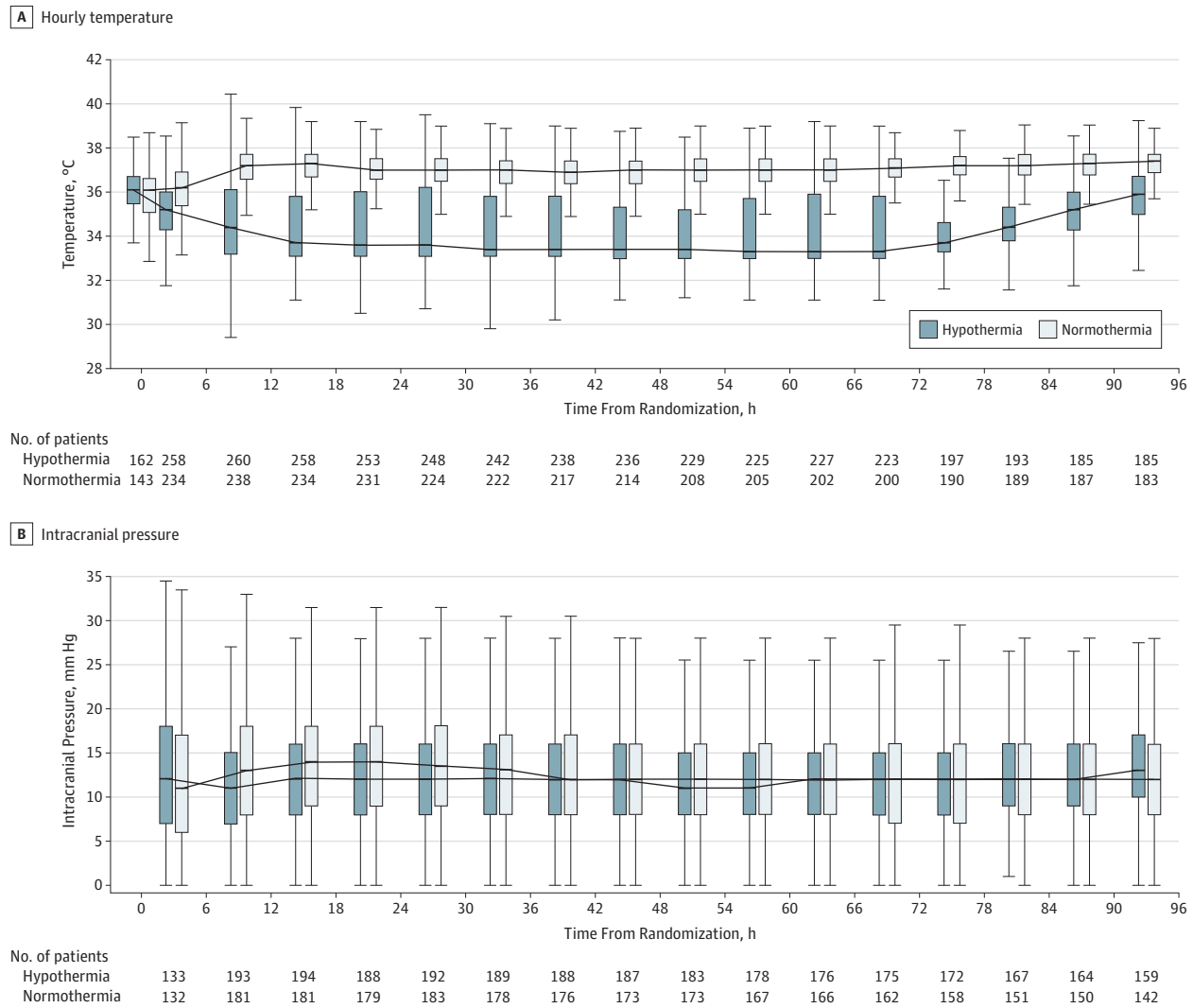
^e Temperature at the scene was available for 162 patients in the hypothermia group and 143 in the normothermia group.

^f The Marshall classification of CT abnormalities in brain trauma ranges from I to VI: a score of I indicates normal findings, II diffuse injury, III or IV radiologic signs of increased intracranial pressure, and V or VI an intracranial mass lesion. The first CT scan was categorized for each patient. Patients who had surgery to evacuate a hematoma <24 hours after injury but whose first CT was conducted before surgery were classified as having Marshall score V.

^g IMPACT-TBI score is validated to predict the outcome of patients with a head injury and a GCS score less than 13. It provides the predicted probability of a 6-month poor outcome (Glasgow Outcome Scale-Extended score of ≤4) ranging from 0.0 to 1.0, in which 1.0 represents 100% and considers age, motor score, pupil response, hypoxia, hypotension, and CT classification.

^h The Injury Severity Score ranges from 0 to 75. Higher scores indicate greater severity of injury; a score of 27 = severe injury and multitrauma.

Figure 2. Hourly Temperature and Intracranial Pressure for the First 4 Days (96 hours) Postrandomization (N = 500)



A and B, Box plots are of the observed data (no imputation). The box shows the interquartile range (IQR), with the bottom and top indicating the 25th and 75th percentiles. The line inside the box indicates the median. The upper whisker extends from the top of the box to the largest value no farther than 1.5 times the IQR, and the bottom whisker extends from the bottom of the box to the smallest value no farther than 1.5 times the IQR. The trajectory line connects the median at each 6-hour block. Box plots have been offset to avoid superimposition.

Box plots and numbers of patients in each interval include the hour of the right-hand tick mark. For example, the box plots between tick marks 0 and 6 represent the data for the interval 1 to 6 hours, between 6 and 12 is the interval 7 to 12 hours, etc. For temperature, there are additional box plots at 0 hours.

The "number of patients" shown in the figures is the number of unique patients contributing to each interval. Each patient can contribute up to 6 hourly measurements in each interval. The median for the number of observations per patient is temperature, 6 (IQR, 5-6), and intracranial pressure, 6 (IQR, 6-6).

11 in Supplement 2). Pneumonia was increased in the hypothermia group in the per-protocol analysis (70.5% in the hypothermia group and 57.1% in the normothermia group; absolute risk difference, 13.3% [95% CI, 2.4%-24.2%]; unadjusted relative risk, 1.23 [95% CI, 1.04-1.47]; $P = .02$) and the as-treated analysis (70.7% in the hypothermia group and 54.6% in the normothermia group; absolute risk difference, 16.1% [95% CI, 5.7%-26.5%]; unadjusted relative risk, 1.29 [95% CI, 1.09-1.53]; $P = .003$) (eTables 9 and 11 in Supplement 2). These results remained consistent in per-protocol and as-treated sensitivity analyses (eFigures 5 and 7 in Supplement 2).

Subgroup Analyses

With respect to the primary outcome, there were no significant interactions between treatment group and either of the prespecified subgroups: presence of surgically evacuated cranial hematomas and any intracranial hematoma (surgically evacuated or not) (Table 2).

Post hoc Analyses

There were no significant differences between groups in post hoc analyses of scenarios for missingness in the primary outcome (eTable 12 in Supplement 2). There were also

Table 2. Primary and Secondary Outcomes, Adverse Events, and Subgroups^a

	No./Total No. (%)		Absolute Difference (95% CI)	Relative Risk (95% CI)	P Value
	Hypothermia	Normothermia			
Primary Outcome					
Favorable outcome (GOS-E score 5-8)	117/240 (48.8)	111/226 (49.1)	-0.4 (-9.4 to 8.7)	0.99 (0.82-1.19)	.94
Severity-adjusted relative risk for favorable outcome (using IMPACT-TBI) ^b				0.98 (0.87-1.11)	.75
Secondary Outcomes					
Death in the hospital	52/260 (20.0)	43/239 (18.0)	2.0 (-4.9 to 8.9)	1.11 (0.77-1.60)	.57
Death at 6 mo	54/256 (21.1)	44/239 (18.4)	2.7 (-4.3 to 9.7)	1.15 (0.80-1.64)	.45
Infections					
Pneumonia	143/260 (55.0)	123/240 (51.3)	3.8 (-5.0 to 12.5)	1.07 (0.91-1.27)	.40
Bacteremia	19/260 (7.3)	12/240 (5.0)	2.3 (-1.9 to 6.5)	1.46 (0.72-2.95)	.29
Other infection	36/260 (13.8)	38/240 (15.8)	-2.0 (-8.2 to 4.3)	0.87 (0.57-1.33)	.53
Bleeding					
New or increased intracranial bleeding	47/260 (18.1)	37/240 (15.4)	2.7 (-3.9 to 9.2)	1.23 (0.43-3.5)	.70
New significant extracranial bleeding	8/260 (3.1)	6/240 (2.5)	0.6 (-2.3 to 3.5)	1.17 (0.79-1.74)	.43
Subgroups, Favorable Outcome (GOS-E Score 5-8)					
Surgically removed hematomas^c					
Yes	22/66 (33.3)	27/68 (39.7)	-6.4 (-22.6 to 9.9)	0.84 (0.54-1.32)	.44
No	95/174 (54.6)	84/158 (53.2)	1.4 (-9.3 to 12.2)	1.03 (0.84-1.25)	.79
Any intracranial mass lesion (Marshall classification V + VI)^d					
Yes	22/69 (31.9)	28/71 (39.4)	-7.6 (-23.4 to 8.3)	0.81 (0.52-1.27)	.35
No	95/171 (55.6)	83/155 (53.5)	2.0 (-8.8 to 12.8)	1.04 (0.85-1.27)	.72

Abbreviations: GOS-E, Glasgow Outcome Scale-Extended; IMPACT-TBI, International Mission for Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury.

Data are presented as n/N (%) unless otherwise indicated and are presented for the intention-to-treat population.

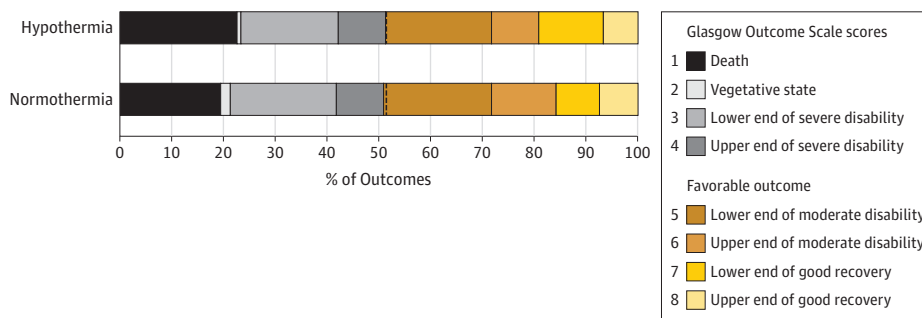
^a Intention-to-treat analysis.

^b IMPACT-TBI score is validated to predict the outcome of patients with a head injury and a Glasgow Coma Scale score less than 13. It provides the predicted probability of a 6-month poor outcome (GOS-E score ≤4) ranging from 0.0 to 1.0, in which 1.0 represents 100% and considers age, motor score, pupil response, hypoxia, hypotension, and computed tomography classification.

^c P value for interaction = .43.

^d P value for interaction = .33.

Figure 3. Distribution of Glasgow Outcome Scale-Extended Scores at 6 Months After Randomization



Each cell corresponds to a score on the scale; the width of each cell represents the proportion of patients with equivalent scores. The vertical hyphenated line indicates the midpoint Glasgow Outcome Scale-Extended score dichotomization.

no significant differences in the proportion of patients with a favorable outcome in a comparison of evaluable patients who received an adequate dose of cooling compared with controls (eTable 13 in Supplement 2).

Discussion

In this international randomized trial, prophylactic hypothermia (early sustained hypothermia followed by slow rewarming) compared with normothermia after severe traumatic brain injury did not increase favorable neurologic outcomes. There

was no benefit from prophylactic hypothermia in any of the secondary outcomes, including mortality, or in predefined subgroups, per-protocol analyses, or as-treated analyses.

Multiple studies and meta-analyses have reported benefit for prophylactic hypothermia as a potential neuroprotectant after traumatic brain injury.^{7,8,21-31} Three higher-quality multicenter randomized trials of prophylactic hypothermia demonstrated no benefit, but these had methodological limitations and 2 stopped prematurely (≤50% projected sample size).¹³⁻¹⁵ The most recent meta-analysis of prophylactic hypothermia after severe traumatic brain injury⁸ suggested that early prophylactic hypothermia may be most beneficial when

it targets hypothermia of 35°C to 33°C, longer cooling (>48 hours), and slower rewarming (<0.25°C/h). Although the Eurotherm3235 trial of late-rescue hypothermia for adult patients with traumatic brain injury with intracranial hypertension reported harm,¹¹ it did not address the effect of prophylactic hypothermia after severe traumatic brain injury. A large high-quality trial addressing the limitations of prophylactic hypothermia trials was required to inform clinical practice and resolve clinician uncertainty.

To our knowledge, this study is the largest trial of prophylactic hypothermia after traumatic brain injury to date. The study design accounted for limitations of previous trials of prophylactic hypothermia.^{7,8,16,32} The protocol included early induction and maintenance of hypothermia for at least 72 hours, followed by individually titrated rewarming. The time from injury to initiating hypothermia was short (median, 1.8 hours). The median time to reach 33°C was greater than 10 hours, reflecting a clinical reality that hypothermia therapy below 35°C in trauma patients requires time for exclusion of undiagnosed injuries. This time also implies that laboratory trials of hypothermia may not translate to trauma patients. Most patients in the hypothermia group remained hypothermic in excess of 48 hours.⁸ The findings of the as-treated analyses demonstrated that crossover of patients who were rewarmed prematurely between groups did not obscure a beneficial effect of hypothermia. Most patients were rewarmed slowly (median, 22.5 hours), without significant elevation in intracranial pressure, whereas 34 patients had rewarming paused because of increased intracranial pressure (eFigure 1 in Supplement 2). Furthermore, there was no effect of hypothermia on intracranial pressure or on elevated intracranial pressure therapy intensity. This trial suggested that prophylactic hypothermia is not neuroprotective after severe traumatic brain injury.

Prolonged hypothermia has been suggested to be immunosuppressive,¹² and the per-protocol analyses found increased risk of pneumonia in the hypothermia group. There were also 3 episodes of propofol-related infusion syndrome. This often fatal syndrome may be more likely during hypothermia because of reduced hepatic metabolism of propofol.³³

Limitations

This trial has several limitations. First, a significant number of patients in the hypothermia group never reached the target temperature of 33°C (19% had hypothermia withdrawn early and a further 13% did not reach 33°C). This reflects the enrollment of patients without severe traumatic brain injury in the out-of-hospital setting before full evaluation, palliation of unsurvivable injuries, or neurosurgical concerns about hypothermia in injuries with significant risk of further intracranial bleeding. Second, clinicians and patients' families were not blinded to the intervention. Although this may have introduced bias, the use of trained blinded outcomes assessors minimized this potential. Third, bedside clinicians had the option not to enroll patients if they believed it was not in the patients' best interests. Although this may have introduced bias, it is an essential part of the ethical conduct of trials in the critically ill.

Conclusions

Among patients with severe traumatic brain injury, early prophylactic hypothermia compared with normothermia did not improve neurologic outcomes at 6 months. These findings do not support the use of early prophylactic hypothermia for patients with severe traumatic brain injury.

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