Comparison of hypothermia and normothermia after severe traumatic brain injury in children (Cool Kids): a phase 3, randomised controlled trial

P David Adelson, Stephen R Wisniewski, John Beca, S Danielle Brown, Michael Bell, J Paul Muizelaar, Pamela Okada, Sue R Beers, Goundappa K Balasubramani, Deborah Hirtz, for the Paediatric Traumatic Brain Injury Consortium

Lancet Neurol 2013; 12: 546–53
Published Online May 8, 2013
http://dx.doi.org/10.1016/S1474-4422(13)70077-2
See Comment page 527

Barrow Neurological Institute at Phoenix Children's Hospital, Phoenix, AZ, USA (Prof P D Adelson MD, S D Brown MS); **University of Pittsburgh School of Medicine, Pittsburgh, and Children's Hospital of Pittsburgh of UPMC, PA, USA** (Prof S R Wisniewski PhD, M Bell MD, S R Beers PhD), **Starship Children's Hospital, Auckland, New Zealand** (J Beca MD); **University of California, Davis, CA, USA** (Prof J P Muizelaar); **University of Texas, Southwestern, Dallas Children's Hospital, TX, USA** (P Okada MD); **Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA** (G K Balasubramani PhD); **and National Institute of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, MD, USA** (D Hirtz MD)

Correspondence to: Prof P David Adelson, Barrow Neurological Institute at Phoenix Children's Hospital, Building B, 4th Floor, 1919 East Thomas Road, Phoenix, AZ 85016, USA **dadelson@phoenixchildrens.com**

Summary

Background On the basis of mixed results from previous trials, we assessed whether therapeutic hypothermia for 48–72 h with slow rewarming improved mortality in children after brain injury.

Methods In this phase 3, multicenter, multinational, randomised controlled trial, we included patients with severe traumatic brain injury who were younger than 18 years and could be enrolled within 6 h of injury. We used a computer-generated randomisation sequence to randomly allocate patients (1:1; stratified by site and age [<6 years, 6–15 years, 16–17 years]) to either hypothermia (rapidly cooled to 32–33°C for 48–72 h, then rewarmed by 0·5–1·0°C every 12–24 h) or normothermia (maintained at 36·5–37·5°C). The primary outcome was mortality at 3 months, assessed by intention-to-treat analysis; secondary outcomes were global function at 3 months after injury using the Glasgow outcome scale (GOS) and the GOS-extended pediatrics, and the occurrence of serious adverse events. Investigators assessing outcomes were masked to treatment. This trial is registered with ClinicalTrials.gov, number NCT00222742.

Findings The study was terminated early for futility after an interim data analysis on data for 77 patients (enrolled between Nov 1, 2007, and Feb 28, 2011): 39 in the hypothermia group and 38 in the normothermia group. We detected no between-group difference in mortality 3 months after injury (6 [15%] of 39 patients in the hypothermia group *vs* two [5%] of 38 patients in the normothermia group; p=0·15). Poor outcomes did not differ between groups (in the hypothermia group, 16 [42%] patients had a poor outcome by GOS and 18 [47%] had a poor outcome by GOS-extended paediatrics; in the normothermia group, 16 [42%] patients had a poor outcome by GOS and 19 [51%] of 37 patients had a poor outcome by GOS-extended paediatrics). We recorded no between-group differences in the occurrence of adverse events or serious adverse events.

Interpretation Hypothermia for 48 h with slow rewarming does not reduce mortality of improve global functional outcome after paediatric severe traumatic brain injury.

Funding National Institute of Neurological Disorders and Stroke and National Institutes of Health.

Introduction

Despite preventive measures, severe traumatic brain injury remains a leading cause of paediatric deaths and permanent disability around the world.[1–3] Therapeutic regimens for paediatric traumatic brain injury, which are often derived from adult studies, have not been shown to be successful in improving outcome in children.

Therapeutic hypothermia has been shown to prevent or reduce secondary injury in animal experiments through several mechanisms including decreased cerebral metabolic demands, inflammation, lipid peroxidation, excitotoxicity, and cell death, with improved outcomes after experimental traumatic brain injury in mature and immature animals.[4–8] Therapeutic hypothermia for 24–48 h was also successful in phase 2 and 3 clinical studies[9] of adults after traumatic brain injury and in several clinical trials in newborn babies after hypoxic-ischaemic encephalopathy,[10] with improved outcomes,[11] particularly mortality. Thus, the paediatric guidelines[12,13] concluded that further study was needed to establish the effect of temperature regulation and hypothermia in children after severe traumatic brain injury.

Although a multicentre, phase 3, randomised controlled trial of moderate hypothermia in adults was stopped early owing to futility,[14] post-hoc analysis drew attention to the potential for effectiveness in younger patients (aged <18 years). A phase 3, multicentre, international (Canada and Europe) randomised controlled trial of hypothermia (at 32·0–33·0°C) for 24 h initiated within 8 h of severe traumatic brain injury in children and adolescents reported that hypothermia worsened outcomes at 6 months post-injury and possibly increased mortality (21% *vs* 14%; p=0·06).[15] However, issues related to study design raised concerns about the study findings.[4] Questions remained as to whether altering different parameters—ie, early or extended cooling period—would improve outcome.[15,16]

In view of the results of our phase 2 trial showing reduced mortality using hypothermia in children after severe traumatic brain injury,[16] we aimed to assess whether hypothermia improved outcome—particularly

mortality—after injury. Also, on the basis of findings from our preliminary work[16] and issues from the previous randomised controlled trial,[5] our study was designed to ensure early randomisation and initiation of cooling, longer cooling periods, slower rewarming, and strict protocols for management of patients compared with previous paediatric severe traumatic brain injury hypothermia trials.

Methods

Study sites and participants

The Paediatric Traumatic Brain Injury Consortium: Hypothermia (the Cool Kids Trial) was a multinational, multicentre, phase 3 randomised controlled trial assessing the effect on mortality of moderate hypothermia with slow rewarming after paediatric severe traumatic brain injury. Hypothermia was maintained for 48–72 h in conjunction with standardised head injury management and compared with normothermia. Patients were enrolled in the emergency department or intensive care unit at study hospitals within 6 h of injury from 15 sites in the USA, New Zealand, and Australia. Parents or guardians of all participants provided written informed consent before enrolment. In some hospitals, children were enrolled via an emergency waiver of consent.

Patients were eligible for inclusion if they were aged 0–17 years; had non-penetrating brain injury, a Glasgow coma scale score of 3–8, and a motor score on the Glasgow coma scale of less than 6 after resuscitation; and were available for randomisation within 6 h of injury (which required known injury time, to exclude children with non-accidental trauma). Patients were excluded if they had a normal CT, a Glasgow coma scale score of 3, unreactive pupils, hypotension (defined as systolic blood pressure <5th percentile for age) for more than 10 min, uncorrectable coagulopathy (prothrombin time/partial thromboplastin time >16/40 s, international normalised ratio >1·7), hypoxia (defined as oxygen saturation <90% for >30 min after resuscitation), abbreviated injury severity score of 4 or greater for organs other than the brain, suspected pregnancy, or unavailable parent or guardian to consent (at some study sites—those without emergency waiver of consent). The trial protocol was approved by the Institutional Review and Ethics Boards at each participating centre and allowed emergency waiver of consent (at five of the 15 study sites) if a family member was unavailable.

Randomisation and masking

Patients were randomly assigned in a one-to-one ratio, stratified by site and age (<6 years, 6–15 years, 16–17 years), to hypothermia or normothermia using a web-based random assignment algorithm. Randomisation was done by the site study coordinator after screening for eligibility. Investigators who assessed outcome were masked to treatment allocation. Emergency service personnel, study nurses involved in randomisation, and personnel who managed the patients were unmasked to treatment

Panel 1: **Tiered protocol for the management of patients (both hypothermic and normothermic)**

Patients were started on tier-one treatment. If treatment failed, the patient was started on tier-two treatment.

Tier one

- Head in a neutral position at 0–30° elevation.
- Intermittent or continuous ventricular drainage of CSF.
- Systemic neuromuscular paralysis (pancuronium or vecuronium) with sedation (confirmed by non-movement on a twitch monitor) or sedation alone with a continuous infusion of narcotic (fentanyl or morphine).
- Sedation followed by hyperosmolar therapy with either mannitol (initially at 0·25 g/kg every 4–6 h, with escalation to 0·5–1 g/kg until serum osmolality was greater than 320 mOsm per kg) or hypertonic saline (3%) continuous drip (started at 0·1–0·5 mL/kg, up to 1·0 mL/kg, titrated to effect to maintain serum osmolality less than 360 mOsm per kg) as needed for intracranial pressure increases.

Tier two

- Treating clinician's choice of the following:
  - Option one: barbiturates, initially 5 mg/kg every 4–6 h, with escalation to coma with 80–90% burst suppression by continuous electroencephalogram monitoring 10 s epochs (pressors and further volume expansion were used to maintain central venous pressure, cerebral perfusion pressure, and mean arterial pressure, and to avoid hypotension with higher doses of barbiturates or narcotics).
  - Option two: decompressive craniectomy, contusion excision, or both, or temporal lobectomy for failure of medical management.
- Phenytoin was given to all patients at 20 mg/kg followed by maintenance doses (of 5 mg per kg per day in three divided doses) for 7 days.
- Blood gases were not corrected for body temperature.
- Central venous pressures and volume and serum potassium concentrations were monitored and treated with intravenous replacement, except for before and during rewarming. $PaCO_2$ less than 30 mm Hg was avoided through controlled ventilation when possible.

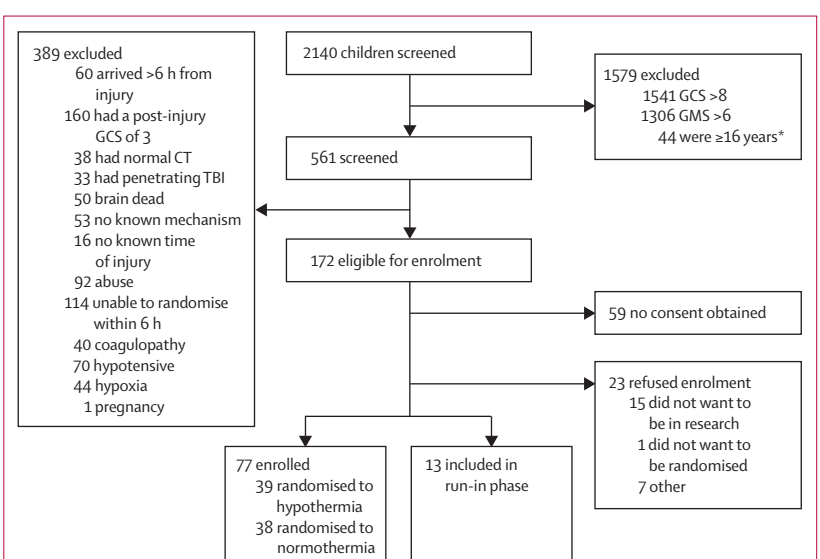

Figure 1: **Trial profile**
Patients could have been excluded for more than one of the listed reasons. GCS=Glasgow coma scale. GMS= Glasgow motor score. TBI=traumatic brain injury. *Before expansion of inclusion criteria to patients older than 16 years but younger than 18 years on Feb 1, 2010.

allocation. Anyone involved in obtaining outcomes and outcome data including, psychologists, neuropsychologists, and or neuropsychology technicians, were masked to treatment. A run-in period was used to ensure patient safety and data quality. Requirements for the study to pass beyond the run-in period included entry of one patient assigned to hypothermia and managed according to protocol, and transfer of all necessary data to the data centre. Data from patients in the run-in phase were not included in the analysis.

Procedures

All emergency treatment procedures and specific guidelines for head injury management were based on paediatric guidelines[12] and other standardised operating protocols agreed to by consensus of all the site investigators. We used a standard servo-controlled cooling and heating blanket unit placed underneath the patient for temperature regulation and to cool or rewarm patients to the target temperature. Children's temperatures were taken with rectal or brain temperature probes.

	Total (N=77)	Therapeutic hypothermia (N=39)	Normothermia (N=38)
Boys	48 (62%)	21 (54%)	27 (71%)
Ethnic origin			
White	58 (75%)	26 (67%)	32 (84%)
Black	12 (16%)	9 (23%)	3 (8%)
Other	7 (9%)	4 (10%)	3 (8%)
Hispanic	16 (21%)	6 (15%)	10 (26%)
Cause			
Fall	13 (17%)	9 (23%)	4 (11%)
Motor vehicle collision	51 (66%)	25 (64%)	26 (68%)
Assault	1 (1%)	0	1 (3%)
Other	12 (16%)	5 (13%)	7 (18%)
Right pupil reaction			
Data not available	1 (1%)	0	1 (3%)
Normal	34 (46%)	16 (44%)	18 (47%)
Sluggish	23 (31%)	12 (33%)	11 (29%)
Fixed	16 (22%)	8 (22%)	8 (21%)
Left pupil reaction			
NA	1 (1%)	0	1 (3%)
Normal	36 (49%)	15 (42%)	21 (55%)
Sluggish	24 (32%)	16 (44%)	8 (21%)
Fixed	13 (18%)	5 (14%)	8 (21%)
Number of fixed pupils			
None	53 (73%)	26 (72%)	27 (73%)
One	11 (15%)	7 (19%)	4 (11%)
Two	9 (12%)	3 (8%)	6 (16%)
Apnoea	6 (9%)	2 (5%)	4 (11%)
Aspiration	12 (17%)	7 (19%)	5 (14%)
Cardiac arrest	2 (3%)	1 (3%)	1 (3%)
Hypotension	6 (8%)	4 (11%)	2 (6%)
Hypoxia	10 (13%)	7 (18%)	3 (8%)
Seizure	12 (16%)	4 (10%)	8 (21%)

Data are number of patients (%). NA=data not available.

Table 1: **Baseline characteristics**

Patients in the hypothermia group were rapidly cooled initially using iced saline (4°C) to 34–35°C and then surface cooled to 32–33°C and maintained for the requisite 48 h period. The patient was then rewarmed by 0·5–1·0°C every 12–24 h as part of a slow rewarming protocol. If at 48 h their intracranial pressure (ICP) was high (>20 mm Hg) a further 24 h of cooling at target (32–33°C) was maintained. At this point, rewarming occurred, irrespective of ICP levels, albeit slowly (<1·0°C every 24 h) to prevent rebound intracranial hypertension. Patients in the normothermia group were maintained at 36·5–37·5°C. Patients with temperatures greater than 38°C were treated with rectal acetaminophen and cooling blankets.

The main goals of therapy in intensive care units and operating rooms were to avoid hypotension, hypoxia, and intracranial hypertension by: maintaining mean arterial pressure (MAP) at within two SD of the mean for their age,[12,13] peripheral oxygen saturation greater than 90%, and ICP less than 18 mm Hg (for children aged <6 years), ICP of 20 mm Hg or lower (≥6 years), and or cerebral perfusion pressure greater than MAP (for their age) plus 20 mm Hg. A two-tiered protocol was followed in a stepwise linear manner with failure of the first-tier treatment dictating escalation to second tier treatments (panel 1). All physiological data, daily fluid volumes, drugs and dosages, neurological and Glasgow coma score, and daily paediatric intensity level of therapy scores were recorded over the first 7 days of admission to hospital.[16,17]

Our primary outcome, assessed by intention-to-treat analysis, was mortality at 3 months after injury.

We hypothesised that induced early cooling (<6 h) with hypothermia (32–33°C) after paediatric severe traumatic brain injury maintained for 48 h would reduce all-cause mortality at 3 months after injury compared with normothermia (36·5–37·5°C). The secondary outcome measures were global function at 3 months after injury using the Glasgow outcome scale (GOS) and Glasgow outcome scale-extended pediatrics (GOS-E Peds) as well as the occurrence of serious adverse events and adverse events. GOS scores were dichotomised into good outcomes for good or moderate functional disability (GOS 1 and 2, respectively) or poor outcomes for those who were severely disabled, were vegetative, or died (GOS 3, 4, or 5, respectively). GOS-E Peds scores were also dichotomised into good outcomes (GOS-E Peds 1–3) and poor outcomes (GOS-E Peds 4–8).

Statistical analysis

On the basis of findings from our previous trial,[16] the planned sample size was 340 patients, which would allow detection of a 10% difference in the percentage of patients who died with 80% power. An interim analysis of outcome and complications was planned at the midpoint of the trial (when 170 people had been enrolled). Interim

	All (N=77)		Hypothermia (N=39)		Normothermia (N=38)	
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Age (years)	77	10·9 (3·4–14·6)	39	9·7 (4·2–14·5)	38	12·5 (3·3–14·8)
Height (cm)	72	136·5 (100·5–165)	37	137 (110–167)	35	135 (94–161)
Weight (Kg)	77	32 (16–60)	39	30 (15·4–62)	38	38 (16–60)
Glasgow coma scale score	77	6 (5–7)	39	6 (5–7)	38	6 (5–7)
Body mass index	72	18·5 (16–21·4)	37	18·8 (16–22)	35	18 (16–21)
Right pupil size (mm)	73	3 (2–4)	35	4 (3–4)	38	3 (2–3)
Left pupil size (mm)	73	3 (2–4)	35	3 (3–4)	38	3 (2–3)
AIS-head	77	4 (4–5)	39	4 (3–5)	38	4 (4–5)
AIS-face	77	1 (0–2)	39	1 (0–2)	38	1 (0–2)
AIS-neck	77	0 (0–0)	39	0 (0–0)	38	0 (0–0)
AIS-thorax	77	0 (0–2)	39	0 (0–2)	38	0 (0–0)
AIS-abdomen	77	0 (0–0)	39	0 (0–0)	38	0 (0–1)
AIS-spine	77	0 (0–0)	39	0 (0–0)	38	0 (0–0)
AIS-upper extremities	77	0 (0–1)	39	0 (0–1)	38	0 (0–0)
AIS-lower extremities	77	0 (0–1)	39	0 (0–1)	38	0 (0–1)
AIS-external	77	0 (0–0)	39	0 (0–1)	38	0 (0–0)

AIS=Abbreviated injury severity.

Table 2: **Clinical characteristics by treatment group**

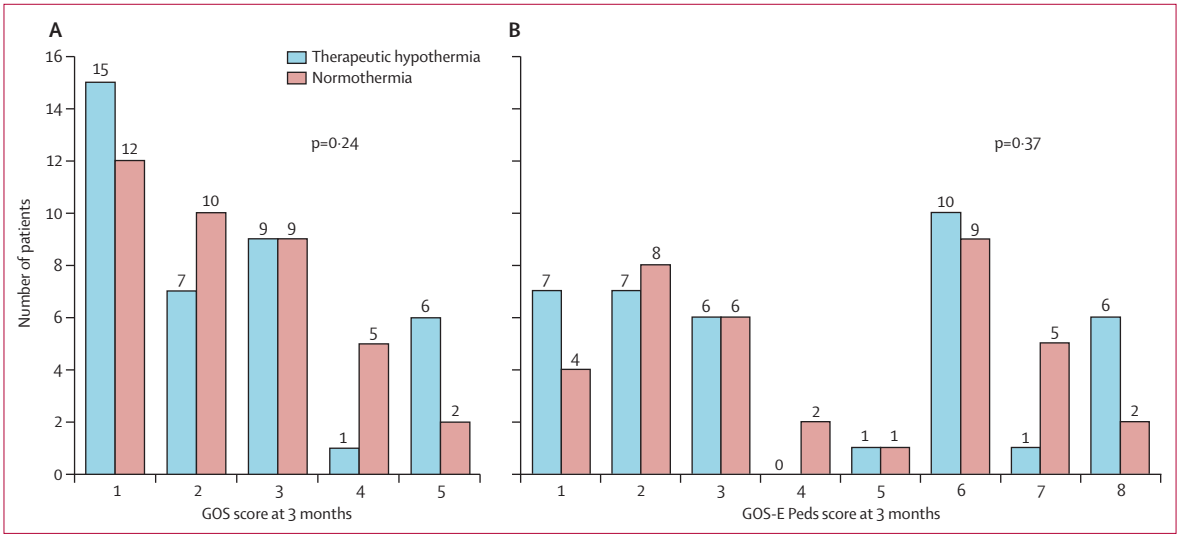

Figure 2: **Outcomes at 3 months after injury**

Outcomes in terms of Glasgow outcome scale (GOS; A) and GOS-extended paediatrics (GOS-E Peds; B). A GOS of 5 and a GOS-E Peds of 8 corresponds to mortality; a score of 1 corresponds to normal functioning for both measures. p values are for comparison between therapeutic hypothermia and normothermia.

analyses were done every 6 months in conjunction with the data safety and monitoring board meeting. A group sequential analytic approach was used to adjust the overall type-1 error for multiple comparisons. Stopping rules stated that the trial should be terminated at the futility or interim analysis if there was less than a 20% chance of confirming the primary hypothesis.

Baseline characteristics by treatment group are reported as means and SDs for continuous variables and percentages for discrete variables. We compared functional outcomes and the occurrence of serious adverse events using a Pearson χ^2 test or a Fisher's exact test. We used a logistic regression model to assess the probability of mortality up to 3 months after injury; we selected this model because we wanted to assess the association of treatment with mortality by a specific timepoint, not to estimate the risk of mortality at any given time. We used SAS (version 9.2) for statistical analyses, which included only patients randomly allocated to the one of the two treatment groups only (ie, no run-in patients).

This trial is registered with ClinicalTrials.gov, number NCT00222742.

	Total	Hypothermia	Normothermia
Glasgow outcome scale*			
Good outcome (scores 1–2)	44/76 (59%)	22/38 (58%)	22/38 (58%)
Poor outcome (scores 3–5)	32/76 (41%)	16/38 (42%)	16/38 (42%)
Glasgow outcome scale-extended pediatrics†			
Good outcome (scores 1–4)	38/75 (51%)	20/38 (53%)	18/37 (49%)
Poor outcome (scores 5–8)	37/75 (49%)	18/38 (47%)	19/37 (51%)

Data are number of patients (%). *Between-group difference (p value=0·90). †Between-group difference (p value=0·73). Despite random assignment, there were missing data for two patients: one patient was lost to follow-up at 3 months, and Glasgow outcome scale-extended pediatrics data were missing for one patient in the normothermia group.

Table 3: **Secondary outcomes at 3 months after injury**

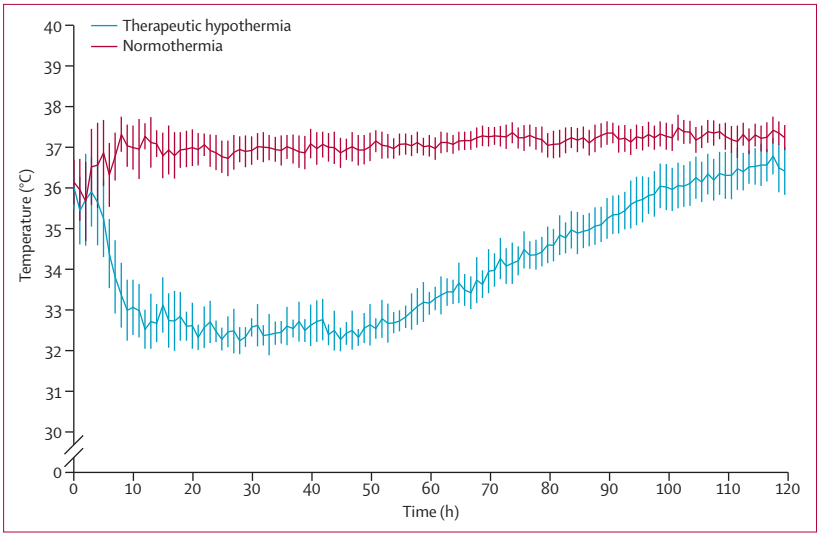

Figure 3: **Temperatures of patients during the first 5 days after randomisation**
Error bars are SDs.

Role of the funding source

The sponsor had no role in data collection, analysis, or interpretation, or in writing the report, but was involved in study design and chose the timing of the futility analysis. The corresponding author had full access to all the data at the completion of the study and had final responsibility for the decision to submit for publication.

Results

Because of slow accrual and concerns from the data safety and monitoring board about safety data from another randomised controlled trial[15] in children with severe traumatic brain injury treated with hypothermia for 24 h (p=0·14), a futility analysis was done and the trial was stopped in Feb 28, 2011.

We had randomly allocated 77 patients to treatment: 39 to hypothermia and 38 to normothermia (written consent was given for 74 patients, the other three had an emergency waiver of consent; figure 1).

Three hypothermia-treated patients were later found to meet exclusion criteria: one child had an unknown time of injury related to assault, one child had a complete spinal cord injury and physiological decapitation (both children later died), and one child improved after resuscitation to a Glasgow coma scale score greater than 8. No patients in the normothermia group later met exclusion criteria. Three sites enrolled 75% of the randomised patients: Children's Hospital of Pittsburgh, PA, USA (23 patients), University of California, Davis, CA, USA (12 patients), and University of Texas, Southwestern, TX, USA (ten patients). Follow-up for primary and secondary outcome measures continued until May 28, 2011.

Baseline characteristics were much the same between the two groups apart from the median size of the right pupil, which was larger in the hypothermia group than it was in the normothermia group (tables 1 and 2).

The primary outcome of mortality within 3 months of injury, available for all 77 patients, did not differ between hypothermia-treated patients (6 [15%] of 39 patients) and normothermia-treated patients (2 [5%] of 38 patients; p=0·15) when the trial was stopped. Secondary outcome data were missing for two patients: one (in the hypothermia group) was lost to follow-up at 3 months for global function, and one (in the normothermia group) had missing data for GOS-E Peds. We detected no significant difference between the interventions in categorical GOS and GOS-E Peds scores (figure 2) or in the dichotomised (good or poor) GOS and GOS-E Peds scores at 3 months (table 3).

37 (95%) of 39 patients assigned to hypothermia were cooled for at least 48 h before rewarming; one progressed rapidly to brain death before cooling and the other improved substantially and was rewarmed before completing 48 h of cooling. Of the remaining 37 cooled patients, mean time to randomisation and initiation of cooling was 5 h 8 min (SD 55 min) after injury, although three patients who were allocated to the hypothermia group before 6 h after injury began cooling at more than 6 h after injury. All patients in the hypothermia group reached target temperature (32–33°C) with mean time to target from injury of 9 h 0 min (3 h 10 min; range 4 h 31 min to 22 h 18 min). Seven (18%) of 38 patients reached target within 2 h of initiation of cooling (range 0 h 0 min to 1 h 58 min).

Mean temperature for the 48 h period of hypothermia was 32·9°C (SD 0·8) and for the concurrent 48 h period in the normothermia group was 36·9°C (SD 0·7; p<0·0001 for between-group difference). No patient assigned to normothermia was cooled lower than 36·5°C. Normothermic temperature (36·5–37·5°C) was maintained for 48 h in 12 (32%) of 38 patients in the normothermia group. Rewarming for hypothermia patients occurred with a mean temperature of 32·8°C (SD 0·5) with mean time of rewarming to 36°C of 60 h 5 min (SD 26 h 26 min; figure 3).

We recorded no differences in medical management, mean arterial pressure, or cumulative fluid balances between the treatment groups, but a higher proportion of

patients in the normothermia group underwent decompressive craniectomy treatment than in the hypothermia group (17 [45%] of 38 patients *vs* 7 [18%] 39 patients; p=0·0220). During the first 120 h, the number of interventions for intracranial hypertension, as indicated by mean paediatric intensity level of therapy scores (modified by excluding the score for induced hypothermia) were 5·6 (SD 2·4) with hypothermia and 6·4 [2·7] with normothermia (p=0·079). We recorded no differences in the laboratory data between treatment groups for blood chemistries, coagulation parameters, or arterial blood gas values for partial pressure of arterial oxygen concentrations lower than 100 mm Hg or carbon dioxide concentrations lower than 30 mm Hg.

We recorded no differences between treatment groups in the percentage of any individual complication or group of complications, whether critical or non-critical (table 4). We recorded no difference in the number of serious adverse events per person, the number of adverse events per person, the percentage of patients with any serious adverse event, or the percentage of patients with any adverse events (table 4).

Discussion

This trial was stopped due to futility because hypothermia, initiated early, used globally for 48–72 h, and with a slow rewarming period, did not improve mortality or global function 3 months after injury compared with normothermia. Although many therapeutic interventions for severe traumatic brain injury have been used and tested in clinical trials, no new treatment regimens—for adults or children—have been shown to be effective.[5,18,19] Hypothermia has alleviated secondary brain injury after acute brain injury in both adult and immature animal models of injury, including traumatic brain injury.[7,8,20–24] This trial expanded on the few previous, limited, and small-scale, hypothermia clinical studies in paediatric severe traumatic brain injury and on the only three randomised controlled trials (panel 2). Findings from an international phase 3 multicentre randomised controlled trial of hypothermia[15] in 225 children with severe traumatic brain injury indicated that delayed initiation of cooling, cooling for up to 24 h, rapid rewarming, and hypotension in the acute period after injury should be avoided. Thus, in the present study, we attempted to build on the available evidence by starting cooling earlier, for a longer duration (48 h), and with slow rewarming while maintaining perfusion by avoiding hypotension with fluids and pressors. We saw no difference in mortality or 3 month global function, as was the case in the other randomised controlled trials of hypothermia in adults[9,14] and in children,[15] but by contrast with our previous phase 2 trial in which hypothermia improved mortality.[16]

There are several limitations and potentially confounding variables (ie, age-related changes in brain development, similar aged children at different levels of maturity) in clinical trials for traumatic brain injury, especially in trials done with children. Other design approaches can be considered that would increase the necessary sample size. Although the Glasgow coma score has been the mainstay for initial assessment of severity of brain injury and then inclusion in clinical trials, the types and variability of pathology seen on imaging despite similar Glasgow coma score emphasise the need for improved initial assessment for stratification into clinical studies. For example, hypothermia might have selective efficacy in particular types of pathology—eg, surgically evacuated haematomas versus diffuse injury—which could be used as the selection criteria rather than Glasgow coma score.[29]

Despite consensus of site investigators to a step-wise clinical pathway for management of intracranial pressure, application of that algorithm varied both within and between sites, with variations in treatment potentially confounding results and contributing to futility. In

	Total (N=77)	Therapeutic hypothermia (N=39)	Normothermia (N=38)	p value
Serious adverse events				
Total	78	34	44	..
Death	8 (10%)	6 (18%)	2 (5%)	..
Uncontrollable intracranial hypertension	7	5	2	..
Occipital-atlantial dislocation	1	1	0	..
Infection	7 (9%)	2 (6%)	5 (12%)	..
Hypotension	4 (5%)	3 (9%)	1 (2%)	..
Haemorrhage	5 (6%)	3 (9%)	2 (5%)	..
Pulmonary	7 (9%)	5 (15%)	2 (5%)	..
Arrhythmias	1 (1%)	1 (3%)	0	..
Other	46 (59%)	14 (41%)	32 (73%)	..
Adverse events				
Total	216	123	93	..
Acute (<120 h after injury) non-serious infection	128	79	49	..
Pneumonia	16 (13%)	7 (9%)	9 (19%)	..
Other infections	58 (45%)	43 (54%)	15 (30%)	..
Coagulopathy	53 (41%)	29 (37%)	24 (49%)	..
Post-traumatic seizures	1 (1%)	0	1 (2%)	..
Late (>120 h after injury) non-serious infection	88	44	44	..
Ventriculitis	1 (1%)	0	1 (2%)	..
Pneumonia	11 (13%)	6 (14%)	5 (11%)	..
Other infections	49 (56%)	23 (52%)	26 (59%)	..
Deep vein thrombosis requiring treatment	5 (6%)	3 (7%)	2 (5%)	..
Coagulopathy	18 (20%)	9 (20%)	9 (20%)	..
Post-traumatic seizures	4 (5%)	3 (7%)	1 (2%)	..
Serious adverse events per person	2·0 (1·2)	1·6 (0·9)	2·3 (1·3)	0·0622
Any serious adverse events	40/77 (52%)	21/39 (54%)	19/38 (50%)	0·7356
Adverse event per person	7·3 (6·4)	8·2 (6·5)	6·3 (6·2)	0·2362
Any adverse event	69/77 (90%)	36/39 (92%)	33/38 (87%)	0·4320

Data are n (%), mean (SD), or n/N (%).

Table 4: **Adverse events**

Panel 2: Research in context

Systematic review

We searched Medline (from Jan 1, 1950, to Feb 1, 2013) and the Cochrane Central Register of Controlled Trials (The Cochrane Library issue 1, 2013) for human studies with the following MeSH search terms: "brain injuries"[MeSH terms] OR ("brain"[all fields] AND "injuries"[all fields]) OR "brain injuries"[all fields] OR ("traumatic"[all fields] AND "brain"[all fields] AND "injury"[all fields]) OR "traumatic brain injury"[all fields] (TBI) AND outcome [all fields]; AND (Clinical Trial[ptyp]). We repeated the search adding the terms, "children" and "paediatric". All types of trial design with at least three patients were reviewed and considered. All included clinical trials were assessed for methodological quality—in terms of the randomisation generation, double blinding, and proportion of patients lost to follow-up.

Interpretation

We identified only three randomised controlled clinical trials[15,16,25] that tested therapeutic hypothermia after severe traumatic brain injury in children. Biswas and colleagues' trial[25] was a small study underpowered for outcome and its findings were inconclusive with respect to mortality, although it did show that hypothermia lowered intracranial pressure. We previously reported a phase 2 randomised controlled trial in which moderate hypothermia (32–33°C) for 48 h did improve outcome (Glasgow outcome scale) with decreased mortality.[17] Since our previous study, phase 3 randomised trials were done by Clifton and colleagues[9,14] in adults (moderate hypothermia, early cooling, for 48 h, and then slow rewarming) and Hutchison and colleagues[15] in children (moderate hypothermia for 24 h, then rapid rewarming), all reporting no improvement in mortality or global functional outcome after severe traumatic brain injury. The present study was stopped early owing to futility, showing that moderate hypothermia (32–33°C) for 48–72 h with slow rewarming after severe paediatric traumatic brain injury did not improve outcome with regard to mortality or global function at 3 months after injury. These few studies have not shown beneficial effects of therapeutic hypothermia in the clinical setting after paediatric brain injury. Further research might be beneficial to assess whether there is the potential efficacy of therapeutic hypothermia in severe traumatic brain injury in children under other circumstances. Such studies could include investigation of cooling temperature, timing, and injury type, as well as long term follow-up with alternative measures.

particular, decompressive craniectomy was used for intracranial pressure control in more patients in the normothermia group than in the hypothermia group. Further prospective studies of a large number of patients, across multiple centres, are needed to assess the comparative effectiveness of this variability in the management of these children and their intracranial hypertension.

Similarly, outcome assessment after injury is not easily defined. On the basis of our previous findings,[16] we used mortality as our primary outcome measure for the present study because its measurement gave the largest difference in our paediatric patients, and we used it to calculate the sample size. During the accrual period for this study, mortality of children after brain injury in the USA decreased overall, lessening the power of the study. Furthermore, during the accrual period, the incidence of non-accidental trauma as the mechanism of injury seemed to increase. Because this type of injury was an exclusion criteria (because of difficulty in determining the exact time of injury), many children with severe non-accidental injuries were excluded, further reducing power.

In children, traumatic brain injury affects not only a wide range of functional abilities, but also normal development,[30] and global outcome measures (GOS and GOS-E Peds) that depend heavily on parent or caregiver report of signs and symptoms might have little usefulness in the assessment of functional outcome after paediatric brain injury.

Finally, consent could not be obtained for many potentially eligible patients for the following reasons: distance to paediatric study centres (parents or guardians were often not available for consent within the requisite time for randomisation and initiation of cooling); inability to obtain emergency waiver of consent at most of the sites (present day regulations and compliance for emergency waiver requirements—eg, community education—cannot be budgeted into the cost of the study and are often prohibitively expensive in large studies); and a higher rate of refusal of consent from parents and guardians than in the previous study. The reasons for the higher rate of refusals are unclear, but this finding does cause concern for future studies of acute therapeutic intervention if accessibility to paediatric patients becomes difficult.

Further clinical trials will need improved stratification by injury and alternative outcome measures if they are to be able to establish the potential of hypothermia to treat children with severe traumatic brain injury.

Contributors

PDA contributed to the literature search, figures, study design, data collection, data analysis, data interpretation, and writing. SRW contributed to the literature search, figures, study design, data analysis, data interpretation, and writing. JB contributed to the data collection, data analysis, data interpretation, and writing. SDB contributed to the literature search, figures, study design, data collection, data analysis, data interpretation, and writing, MB contributed to the data collection, data analysis, data interpretation, and writing. JPM and PO contributed to the data collection. SRB contributed to the literature search, figures, study design, data collection, data analysis, data interpretation, and writing. DH contributed to the figures, study design, data collection, data analysis, data interpretation, and writing. GKB contributed to the data analysis and interpretation.

Conflicts of interest

SRW has received grant support from Eli Lilly and has done consulting for Cyberonics Inc, lmaRx Therapeutics Inc, Bristol-Myers Squibb Company, Organon, Case-Western University, Singapore Clinical Research Institute, Dey Pharmaceuticals, and Venebio. All other authors declare that they have no conflicts of interest.

Acknowledgments

We thank the National Institute of Neurological Disorders and Stroke and the National Institutes of Health (NIHU01NS052478) for funding this project, and all the members of the Paediatric Traumatic Brain Injury Consortium for their support and willingness to participate in this study. Additionally, we would like to thank the Data and Safety Monitoring Board for their oversight and counsel during the course of this trial. We would also like to thank Christina Casanova for administrative assistance in the preparation of this paper.

References

1 Luerssen TG, Klauber MR, Marshall LF. Outcome from head injury related to patient's age. A longitudinal prospective study of adult and pediatric head injury. *J Neurosurg* 1988; **68:** 409–16.

2 Frankowski RF, Annegers JF, Whitman S. Epidemiological and descriptive studies. Part 1: the descriptive epidemiology of head trauma in the United States. Bethesda: National Institute of Health, NINCDS, 1985.

3 Kraus JF. Epidemiological features of brain injury in children: occurrence, children at risk, causes and manner of injury, severity, and outcomes. In: Broman SH, Michel ME, eds. Traumatic Head Injury in Children. New York: Oxford University Press, 1995: 22–39.

4 Adelson PD. Hypothermia in pediatric traumatic brain injury. *J Neurotrauma* 2009; **26:** 429–36.

5 Adelson PD, Dixon CE, Robichaud P, Kochanek PM. Motor and cognitive functional deficits following diffuse traumatic brain injury in the immature rat. *J Neurotrauma* 1997; **14:** 99–108.

6 Clark RS, Kochanek PM, Marion DW, et al. Mild posttraumatic hypothermia reduces mortality after severe controlled cortical impact in rats. *J Cereb Blood Flow Metab* 1996; **16:** 253–61.

7 Adelson PD. Animal models of traumatic brain injury in the immature: a review. *Exp Toxicol Pathol* 1999; **51:** 130–36.

8 Mansfield RT, Schiding JK, Hamilton RL, Kochanek PM. Effects of hypothermia on traumatic brain injury in immature rats. *J Cereb Blood Flow Metab* 1996; **16:** 244–52.

9 Clifton GL, Allen S, Barrodale P, et al. A phase II study of moderate hypothermia in severe brain injury. *J Neurotrauma* 1993; **10:** 263–71.

10 Gunn AJ. Cerebral hypothermia for prevention of brain injury following perinatal asphyxia. *Current Opin Pediatr* 2000; **12:** 111–15.

11 Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med* 2005; **353:** 1574–84.

12 Adelson PD, Bratton SL, Carney NA, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. *Pediatr Crit Care Med* 2003; **4:** S1–75.

13 Kochanek PM, Carney N, Adelson PD, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents—second edition. *Pediatr Crit Care Med* 2012; **13** (suppl 1)**:** S1–82.

14 Clifton GL, Miller ER, Choi SC, et al. Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med* 2001; **344:** 556–63.

15 Hutchison JS, Ward RE, Lacroix J, et al. Hypothermia therapy after traumatic brain injury in children. *N Engl J Med* 2008; **358:** 2447–56.

16 Adelson PD, Ragheb J, Kanev P, et al. Phase 2 clinical trial of moderate hypothermia after severe traumatic brain injury in children. *Neurosurgery* 2005; **56:** 740–54.

17 Shore P, Adelson PD, Kochanek PM, et al, Reliability and validity of the Pediatric Intensity Level of Therapy (PILOT) Scale: A measure of the use of intracranial pressure-directed therapies. *Crit Care Med* 2006; **34:** 1981–87.

18 Adelson PD. Evidence-based recommendations: time, implementation, and strength of evidence. *Pediatr Crit Care Med* 2008; **9:** 230–31.

19 Bullock MR, Chesnut R, Ghajar J, et al. Guidelines for the surgical management of traumatic brain injury. *Neurosurgery* 2006; **58** (suppl 3)**:** S2-iv.

20 Colbourne F, Corbett D. Delayed and prolonged post-ischemic hypothermia is neuroprotective in the gerbil. *Brain Res* 1994; **654:** 265–72.

21 Leonov Y, Sterz F, Safar P, et al. Mild cerebral hypothermia during and after cardiac arrest improves neurologic outcome in dogs. *J Cereb Blood Flow Metab* 1990; **10:** 57–70.

22 Moyer DJ, Welsh FA, Zager EL. Spontaneous cerebral hypothermia diminishes focal infarction in rat brain. *Stroke* 1992; **23:** 1812–16.

23 Pomeranz S, Safar P, Radovsky A, Tisherman SA, Alexander H, Stezoski W. The effect of resuscitative moderate hypothermia following epidural brain compression on cerebral damage in a canine outcome model. *J Neurosurg* 1993; **79:** 241–51.

24 Taft WC, Yang K, Dixon CE, Clifton GL, Hayes RL. Hypothermia attenuates the loss of hippocampal microtubule-associated protein 2 (MAP2) following traumatic brain injury. *J Cereb Blood Flow Metab* 1993; **13:** 796–802.

25 Biswas AK, Bruce DA, Sklar FH, Bokovoy JL, Sommerauer JF. Treatment of acute traumatic brain injury in children with moderate hypothermia improves intracranial hypertension. *Crit Care Med* 2002; **30:** 2742–51.

26 Grinkeviciute D, Kevalas R. Induced mild hypothermia in children after brain injury. *Rev Neurosci* 2009; **20:** 261–66.

27 Gruszkiewicz J, Doron Y, Peyser E. Recovery from severe craniocerebral injury with brain stem lesions in childhood. *Surg Neurol* 1973; **1:** 197–201.

28 Li H, Lu G, Shi W, Zheng S. Protective effect of moderate hypothermia on severe traumatic brain injury in children. *J Neurotrauma* 2009; **26:** 1905–09.

29 Clifton GL, Valadka A, Zygun D, et al. Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial. *Lancet Neurol* 2011; **10:** 131–39.

30 Beers SR, Wisniewski SR, Garcia-Filion P, et al. Validity of a pediatric version of the Glasgow Outcome Scale-Extended. *J Neurotrauma* 2012; **29:** 1126–39.

For a **list of all members of the Paediatric Traumatic Brain Injury Consortium** see http://www.phoenixchildrens.com/medical-specialties/barrow-neurological-institute/Clinical-Protocol-v3-2-January-2011.pdf