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CLINICAL RESEARCH ARTICLE

Differences in patient characteristics and care practices between two trials of therapeutic hypothermia

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BACKGROUND: The Induced Hypothermia (IH) and Optimizing Cooling (OC) trials for hypoxic–ischemic encephalopathy (HIE) had similar inclusion criteria. The rate of death/moderate–severe disability differed for the subgroups treated with therapeutic hypothermia (TH) at 33.5 °C for 72 h (44% vs. 29%, unadjusted $p = 0.03$). We aimed to evaluate differences in patient characteristics and care practices between the trials.
METHODS: We compared pre/post-randomization characteristics and care practices between IH and OC.
RESULTS: There were 208 patients in the IH trial, 102 cooled, and 364 in the OC trial, 95 cooled to 33.5 °C for 72 h. In OC, neonates were less ill, fewer had severe HIE, and the majority were cooled prior to randomization. Differences between IH and OC were observed in the adjusted difference in the lowest PCO_2 (+3.08 mmHg, $p = 0.005$) and highest PO_2 (−82.7 mmHg, $p < 0.001$). In OC, compared to IH, the adjusted relative risk (RR) of exposure to anticonvulsant prior to randomization was decreased (RR 0.58, (0.40–0.85), $p = 0.005$) and there was increased risk of exposure during cooling to sedatives/analgesia (RR 1.86 (1.21–2.86), $p = 0.005$).
CONCLUSION: Despite similar inclusion criteria, there were differences in patient characteristics and care practices between trials. Change in care practices over time should be considered when planning future neuroprotective trials.

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INTRODUCTION

Therapeutic hypothermia (TH) has been widely adopted into clinical practice for treatment of moderate to severe neonatal encephalopathy secondary to presumed perinatal asphyxia. The five large randomized trials of TH demonstrated a significant reduction in the risk of death and disability compared to non-treated neonates; however, there remain a large proportion of neonates who die or develop disability despite treatment.[1] Following animal studies that suggested further benefit of deeper TH or longer duration of treatment, the NICHD Neonatal Research Network (NRN) performed the Optimizing Cooling (OC) trial. The OC trial randomized newborns with moderate or severe encephalopathy to four hypothermia regimens: 33.5 °C for 72 h (usual treatment); 33.5 °C for 120 h; 32 °C for 72 h; and 32 °C for 120 h. However, this trial was stopped early for safety and futility and later animal studies question the potential benefit and possible harm of deeper or longer cooling.[2,3] A lower death rate was observed in the usual treatment arm compared to the longer and/or deeper cooling arms. When comparing outcomes from the OC trial to the initial NRN Induced Hypothermia (IH) trial, patients in the usual care arm of OC had lower unadjusted rates of in-hospital death and death or neurodevelopmental disability (7% vs. 19%, $p = 0.02$) and (29% vs. 44%, $p = 0.03$), respectively.[4,5] Enrollment criteria and study procedures in the OC trial were similar to the original IH trial, except that clinical cooling could be initiated prior to randomization. Neonates were excluded if they had a temperature recorded of <32 °C for 2 h.

It is important to understand possible reasons for the lower rate of death or disability in the "standard of care" arm of the OC trial as other trials of adjunctive treatment to hypothermia are currently ongoing or in development. Changes in clinical care may contribute to the observed differences in morbidity and mortality rates. Secondary analyses of TH trials reported on the associations between blood gas tensions of carbon dioxide,[6] oxygen,[7] and blood glucose levels[8] and outcome. The use of sedation and analgesia may have also changed between trials; however, its association with outcome is controversial.[9,10] Changes in the approach to the identification, diagnosis, and treatment of seizures have been cited in the literature with potential impact on outcome.[11–14] Intensive care by a team now experienced in the provision of TH may have differentially impacted the clinical outcome of patients in the OC trial. Finally, as the OC trial was initiated, TH was recognized as a safe and effective treatment likely resulting in increased focus on the recognition and enrollment of eligible patients, particularly those with moderate encephalopathy, and shorter time to initiation of TH. However, therapeutic drift is also occurring with treatment being applied to neonates who may not have met all of the criteria outlined by the trials. Registry data in the United Kingdom confirm an increase in the use of TH after the TOBY trial with concern for therapeutic drift between 2007 and 2011, indicating that patients with less severe hypoxic–ischemic encephalopathy (HIE) are now being treated.[15] Further systematic analysis of patient characteristics and clinical care practices among infants enrolled in the two trials of TH may provide

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helpful information for planning future trials and determining sample size. Our objective was to perform an analysis of differences in patient characteristics and care practices between the IH and OC trials.

METHODS

Enrollment into the IH and OC trials occurred 2000–2003 and 2010–2013, respectively, at NICHD NRN centers (15 centers in IH and 18 centers in OC). The institutional review board at each NRN center approved the trial protocols. Inclusion criteria for both trials were similar and as follows: neonates born at a gestational age of at least 36 weeks and admitted to an NRN center within 6 h of birth, the presence of physiologic criteria, and seizures (clinical or electrographic) or moderate to severe encephalopathy identified by a certified examiner using a standardized modified Sarnat examination.[4,16,17] A training session for research personnel was held to standardize the neurologic examination and each site principal investigator certified additional neonatologists to perform the neurologic examinations. Encephalopathy was defined as the presence of moderate or severe signs in three out of the following six categories: level of consciousness, spontaneous activity, posture, tone, primitive reflexes, and autonomic nervous system. The number of moderate or severe signs determined the severity of encephalopathy at enrollment, and if the number of signs were equally distributed, then the determination was based on the level of consciousness. There were definitional differences in the OC trial in the categories of tone and one sub-category of neonatal reflexes, suck. In the OC trial, both hypotonia and hypertonia were defined as moderate abnormalities wherein IH-only hypotonia was included. In the severe category for tone, a neonate could be described as flaccid or rigid wherein IH-only flaccid was used. For moderate abnormalities in suck reflex, the presence of a "bite" was added to the description of a "weak" suck used in IH. Exclusion criteria for both trials were similar, except for the addition of a core temperature of <32.5 °C for at least 2 h prior to randomization for the OC trial. Passive or active cooling was allowed prior to randomization in the OC trial.

For all neonates enrolled in the IH trial ($N = 208$) and all enrolled in the OC trial ($N = 364$), we compared maternal and baseline neonatal characteristics, and variables reflecting resuscitative measures at birth. To evaluate subtle differences in the severity of encephalopathy between the two trials, we compared the distribution of the severity of findings in the pre-randomization modified Sarnat exam categories in neonates determined to have moderate HIE and those with severe HIE between the two trials. In the subgroup of IH infants ($n = 102$) randomized to therapeutic hypothermia (33.5 °C for 72 h) and OC infants ($n = 95$) randomized to usual cooling (33.5 °C for 72 h), we also compared baseline maternal and neonatal characteristics.

Specific clinical care practices prior to and during the 72 h of treatment were compared between the two groups treated with cooling at 33.5 °C for 72 h in IH and in OC. The following variables were analyzed: lowest PCO_2 and highest PO_2 levels; lowest and highest blood glucose levels; proportion of neonates who were intubated and mechanically ventilated, fraction of inspired oxygen (FiO_2), use of anticonvulsant medication, analgesics and sedatives, inotropic agents prior to baseline, at baseline (defined as time esophageal probe was placed and initiation of study treatment), and at 24, 48, and 72 h of treatment. Differences in the use of electroencephalogram (EEG) and short-term outcomes, including electrographic seizures, length of stay, need for gastrostomy tube or gavage feeds at discharge, discharge on anticonvulsant medications, and in-hospital death were evaluated. The primary outcome of each trial, death or moderate or severe disability at 18–22 months was compared. The definition of moderate or severe disability was similar in both trials.[4,5] To assess cognitive development, in the IH trial, the Bayley II was used, and in the OC trial, the Bayley III, developed in 2006, was used. The cutoffs for moderate or severe cognitive impairments were identical in both studies, each reflecting either 1 or 2 SD (±15) below the population mean of 100, respectively. A mental developmental index (MDI) on the Bayley II or a cognitive score in the Bayley III of 70–84 was used as part of the definition for moderate and an MDI or cognitive score of <70 was used as part of the definition of severe disability.

Statistical analyses

χ^2 Tests (or Fisher's exact test) for categorical variables, and t tests for continuous variables were used to evaluate differences in maternal and neonatal baseline characteristics, care practices, and outcome measures. Logistic and linear regression analysis were used to evaluate differences in care practices and outcome between the subgroups in IH treated with TH and those in the usual care arm of OC with adjustment for severity of HIE and center (as a random effect) to evaluate differences in the primary outcome of death or disability between the IH and OC trials. Tests for interaction between severity of encephalopathy and trial (IH or OC) were performed.

RESULTS

Maternal and neonatal characteristics

Maternal and baseline neonatal characteristics of all subjects enrolled in the IH and OC trials, as well as those randomized to the cooling arm of the IH trial (33.5 °C for 72 h) and the usual care arm of the OC trial (33.5 °C for 72 h), are shown in Table 1. In the OC trial, maternal thyroid disease, hypertension, and hemorrhage were more common than in the IH trial, while uterine rupture occurred more frequently in IH than OC. Fewer neonates in OC were delivered by emergent cesarean section. Compared to OC, neonates enrolled in IH had more frequent: Apgar score <5 at 10 min after birth, lower pH and greater base deficits, intubation at delivery, delayed onset of spontaneous respirations, severe encephalopathy, and clinical seizures prior to randomization. In contrast, neonates enrolled in OC compared to IH were born at slightly younger gestational ages and more were outborn and thus transferred to an NRN center.

Use of pre-randomization cooling, initiation of cooling, and temperature at baseline

The majority of subjects (69%) in OC were either passively or actively cooled prior to randomization. In the usual cooling arm in OC, 70 of 95 (74%) were cooled prior to randomization, 52 were clinically cooled (placed on a cooling device), 17 were cooled passively, and 1 was cooled with ice/gel packs. Despite randomization occurring at a later age in OC compared to IH (5.1 ± 1.0 vs. 4.3 ± 1.3 h), subjects clinically cooled prior to randomization in OC had cooling initiated earlier (3.8 ± 1.3 vs. 5.0 ± 1.2 h, $p < 0.0001$). Overall mean age at initiation of cooling occurred earlier in OC, 4.2 ± 1.4 h, compared to, 5.0 ± 1.2 h, that in IH, $p < 0.0001$.

Continuous temperature data prior to randomization was not available and after baseline core temperature was measured every 15 min for the first 4 h of intervention. At the time of randomization, 54% of those in OC and only 4% of subjects in IH had a temperature within one degree of goal temperature (32.5−34.5 °C), p value <0.0001. The age at which a core temperature of <34 °C was first documented occurred earlier in OC 5.27 ± 1.66 h compared to IH 5.83 ± 1.23h, $p = 0.008$ (t test). Those who were cooled prior to randomization in OC ($n = 70$) had a temperature of 33.8 ± 1.4 °C at randomization. Overall, neonates in OC had significantly lower mean temperatures at baseline (initiation of study intervention) compared to IH (34.6 ± 1.8 vs. 36.9 ± 1.0 °C, $p < 0.0001$).

Table 1. Maternal and neonatal characteristics across all randomized patients and subgroups of TH-treated IH trial and OC usual cooling arm

	IH trial (all patients)	OC trial (all patients)	*P* value	IH trial (33.5 × 72 h)	OC trial (33.5 × 72 h)	*P* value
N	208	364	N/A	102	95	N/A
Maternal characteristics						
Maternal race			0.52			0.99
Black	72 (35%)	114 (32%)		32 (31%)	29 (31%)	
White	126 (61%)	219 (61%)		64 (63%)	60 (63%)	
Other	10 (5%)	25 (7%)		6 (6%)	6 (6%)	
Maternal age (years)	27.3 ± 6.1	27.9 ± 6.8	0.29	27.4 ± 5.6	27.8 ± 6.0	0.58
	28 (22–32)	28 (22–33)		27 (24–31)	29 (23–32)	
Gravida	2 (1–3)	2 (1–3)	0.57*	2 (1–4)	2 (1–3)	0.76*
Parity	2 (1–3)	1 (1–3)	0.07*	2 (1–3)	1 (1–3)	0.34*
Complications of pregnancy						
Hypertension	26 (13%)	73 (20%)	0.02	12 (12%)	16 (17%)	0.31
Antepartum hemorrhage	30 (14%)	40 (11%)	0.24	10 (10%)	12 (13%)	0.51
Thyroid disease	2 (1%)	14 (4%)	0.04	1 (1%)	4 (4%)	0.20
Diabetes	17 (8%)	46 (13%)	0.09	8 (8%)	9 (9%)	0.68
Intrapartum complications						
FHR decelerations	153 (74%)	282 (78%)	0.23	74 (73%)	74 (79%)	0.32
Cord prolapse	37 (18%)	49 (13%)	0.16	23 (23%)	16 (17%)	0.32
Uterine rupture	29 (14%)	22 (6%)	0.001	16 (16%)	3 (3%)	0.003
Maternal pyrexia	21 (10%)	41 (11%)	0.64	12 (12%)	9 (9%)	0.60
Antibiotics for suspected maternal infection	38 (18%)	85 (25%)	0.08	22 (22%)	22 (24%)	0.76
Shoulder dystocia	20 (10%)	29 (8%)	0.49	11 (11%)	6 (6%)	0.26
Placental problem	52 (25%)	80 (22%)	0.41	22 (22%)	23 (24%)	0.66
Maternal hemorrhage	14 (7%)	55 (15%)	0.003	6 (6%)	13 (14%)	0.06
Maternal trauma	1 (0%)	2 (1%)	1.0	0 (0%)	0 (0%)	N/A
Maternal cardio-respiratory arrest	2 (1%)	4 (1%)	1.0	0 (0%)	1 (1%)	0.48
Maternal seizures	1 (0%)	5 (1%)	0.42	0 (0%)	1 (1%)	0.48
Rupture of membranes						
None	0 (0%)	97 (28%)		0 (0%)	28 (30%)	
≤18 h	173 (92%)	216 (62%)		82 (91%)	56 (61%)	
>18 h	15 (8%)	38 (11%)	0.29**	8 (9%)	8 (9%)	0.96**
Emergency C-section	152 (73%)	231 (63%)	0.02	72 (71%)	61 (64%)	0.34
Neonatal characteristics						
Gestational age (weeks)	38.9 ± 1.60	38.6 ± 1.46	0.06	39.0 ± 1.55	38.5 ± 1.45	0.03
Male	117 (56%)	212 (58%)	0.64	51 (50%)	52 (55%)	0.51
Birthweight	3377 ± 630	3359 ± 599	0.73	3385 ± 617	3230 ± 528	0.06
Length	50.8 ± 3.1	50.7 ± 3.0	0.61	50.6 ± 3.0	50.6 ± 2.8	0.98
Head circumference	34.1 ± 1.9	34.1 ± 1.8	0.93	34.4 ± 1.5	34.1 ± 1.5	0.16
Outborn	93 (45%)	234 (64%)	<0.0001	48 (47%)	59 (62%)	0.03
Apgar score ≤5						
At 5 min	189 (91%)	306 (85%)	0.03	92 (91%)	79 (83%)	0.10
At 10 min	154 (81%)	223 (69%)	0.004	80 (84%)	54 (69%)	0.02
Cord blood gas						
ph	6.86 ± 0.21	6.95 ± 0.19	<0.0001	6.87 ± 0.19	6.94 ± 0.19	0.02
Base deficit	19.2 ± 7.7	16.0 ± 7.3	0.0001	18.5 ± 6.7	15.7 ± 8.1	0.04
Neonatal blood gas						
pH	7.1 ± 0.2	7.1 ± 0.2	0.89	7.1 ± 0.2	7.1 ± 0.2	0.62
Base deficit	18.0 ± 7.7	17.2 ± 7.2	0.20	17.3 ± 6.9	17.2 ± 7.6	0.96
Intubated at delivery	195 (94%)	286 (79%)	<0.0001	97 (95%)	73 (77%)	0.0002
Continued resuscitation at 10 min (Y/N)	195 (94%)	315 (87%)	0.01	95 (93%)	82 (86%)	0.11
Time to spontaneous respiration			<0.001			0.0002
<5 min	22 (11%)	115 (34%)		12 (12%)	33 (37%)	
5–10 min	35 (18%)	76 (22%)		16 (16%)	15 (17%)	
>10 min	140 (71%)	150 (44%)		69 (71%)	41 (46%)	
Moderate encephalopathy	134 (65%)	280 (77%)	0.002	69 (68%)	74 (78%)	0.13
Severe encephalopathy	73 (35%)	84 (23%)		32 (32%)	21 (22%)	
Seizures at randomization	94 (45%)	105 (29%)	<0.0001	43 (42%)	27 (28%)	0.04

Table 1 continued

	IH trial (all patients)	OC trial (all patients)	*P* value	IH trial (33.5 × 72 h)	OC trial (33.5 × 72 h)	*P* value
[a]Cooled prior to randomization	N/A	252 (69%)	N/A	N/A	70 (74%)	N/A
If yes—clinical cooling	N/A	201 (80%)	N/A	N/A	52 (74%)	N/A
If yes—age cooling initiated (clinical cooling only)	N/A	3.9 ± 1.3	N/A	N/A	3.8 ± 1.3	N/A
Age at randomization	4.3 ± 1.2	4.9 ± 1.2	<0.0001	4.3 ± 1.3	5.1 ± 1.0	<0.0001
Age at baseline (time study intervention initiated)	4.8 ± 1.3	5.1 ± 1.1	0.02	5.0 ± 1.2	5.2 ± 1.1	0.25
Temperature at baseline	36.9 ± 1.0	34.6 ± 1.8	<0.0001	36.6 ± 1.0	34.3 ± 1.7	<0.0001

TH therapeutic hypothermia, *RR* relative risk, *CI* confidence interval, *IH* induced hypothermia, *OC* optimizing cooling, *FHR* fetal heart rate, *N/A* not available, *ROM* reactive oxygen metabolites

P values for categorical variables are from χ^2 tests (or Fisher's exact test for sparse data) and *p* values for continuous variables are from *t* tests, unless otherwise noted

*P values from median two-sample test

**This *p* value compares >18 h vs. no ROM or ≤18 h

[a]Includes use of ice packs, passive cooling, or clinical cooling (use of cooling device)

Modified Sarnat examination

Infants were diagnosed with moderate/severe encephalopathy if they had ≥3 of the six categories that were moderately or severely abnormal. Differences in the distribution of the severity of the modified Sarnat exam components in neonates determined to have moderate HIE at randomization (IH vs. OC) and those determined to have severe HIE (IH vs. OC) at enrollment are shown in Supplemental Table S1. For neonates with moderate HIE, the distribution of severity of abnormalities in the level of consciousness, spontaneous activity, tone, and autonomic nervous system differed between IH and OC. For neonates with severe HIE at randomization, the distribution of severity of findings in the different exam categories was similar, except for the autonomic nervous system, with the difference being in the subcomponent of respiration.

Care practices during therapeutic hypothermia

Blood gas tensions of oxygen and carbon dioxide in the first 72 h after birth differed between IH and OC with lower PCO_2 and higher PO_2 values being observed in IH compared to OC (Table 2). These differences in PCO_2 and PO_2 remained significant after adjustment for severity of encephalopathy and for center. At baseline (start of intervention), 90% of neonates in IH were intubated and on mechanical ventilation compared to 78% of those in OC, adjusted relative risk (RR) 0.85, 95% confidence interval (CI): 0.73–0.99, *P* value 0.04. At 24, 48, and 72 h, fewer subjects were intubated and on mechanical ventilation in OC compared to IH, but these differences were not statistically significant after adjusting for severity of encephalopathy and center. FiO_2 at baseline and at 24, 48, and 72 h is shown in Table 2. Neonates in OC received a lower FiO_2 compared to IH at baseline, 24, and 48 h (*P* value 0.004–0.03). The use of inotropic support was lower at all time points in OC, but not statistically significant after adjusting for severity of encephalopathy and center. The adjusted RR of anticonvulsant exposure prior to randomization was significantly decreased in OC compared to IH, but did not remain significant at ≥24 h. Analgesics and sedating medications were more frequently used in OC compared to IH and was statistically significant after adjustment for severity of encephalopathy and center at 24, 48, and 72 h of treatment. A table describing the types of sedative and analgesic medications used in both studies is available as Supplementary material (Supplemental Table S2).

In-hospital, discharge, and 18–22 month outcomes

The frequency of the diagnosis of clinical or electrographic seizures prior to hospital discharge was similar (62% in IH vs. 55% in OC). EEGs were not required but were performed in 68% of patients in IH and 76% of those in OC; this difference was not statistically significant. Data on EEG confirmation of seizures was not available for IH. In OC usual care arm, 76 patients had an EEG performed and 24% had electrographic seizures identified. The use of anticonvulsants at discharge was decreased in OC, but this difference was not statistically significant after adjusting for severity of HIE and center (Table 3). Length of stay and need for gavage tube or gastrostomy feeds at discharge were similar between the trials. A significant difference in in-hospital death was present between the hypothermia-treated patients in IH and OC (19% vs. 7%, $p = 0.02$) and in primary outcome at 18–22 months (44% vs. 29%, $p = 0.03$). After adjusting for severity of HIE and center, the relative risk of in-hospital death (RR 0.46, 95% CI: 0.17–1.27, $p = 0.13$) and the primary outcome (RR 0.73, 95% CI: 0.47–1.15, $p = 0.17$) in OC compared to IH was not statistically significant. In moderate and severe groups alone, the frequencies of in-hospital death and the primary outcome were lower in OC compared to IH (Table 3), but this difference was not statistically significant. On multivariate analysis, there was no interaction between severity of HIE and trial. Rates of cerebral palsy and distribution of the gross motor function classification system (GMFCS) are also shown in Table 3.

DISCUSSION

Therapeutic hypothermia treatment has emerged rapidly as the standard of care for moderate or severe HIE following completion of the initial clinical trials. There was rapid diffusion of this therapy around the United States and abroad.[15] In 2005, as the IH trial was published, only 6.4% of NICU directors reported utilizing TH and 30% felt it was effective or very effective, but by 2011 this increased to 50% using TH and 85% felt it was an effective or very effective treatment.[18] This increase in the use of TH likely led to the development of expertise in the care of central nervous system (CNS) and non-CNS organ dysfunction observed in this patient population. Multiple publications during this period focused on optimizing the clinical management of these patients.[19] In this analysis, we documented that both patient characteristics and care practices of infants receiving TH changed in OC relative to IH.

There were differences identified in both maternal and neonatal characteristics that may reflect differences in severity of perinatal asphyxia and encephalopathy between the two trials. We did not have obstetric practice data to compare in the two trials, but identified that neonates in OC were born at slightly younger gestational ages and fewer were delivered by emergent cesarean section. In the OC trial, neonates were less critically ill after birth

Table 2. Variables reflecting care practices prior to and during TH

	IH trial (33.5° × 72 h), $N = 102$	OC (33.5° × 72 h), $N = 95$	[a]RR and 95% CI, p values
During first 72 h (baseline–>72 h)			
Lowest PCO_2 (mmHg)	25.2 ± 6.4	28.0 ± 7.5	[b]3.08 (SE 1.09), 0.005
Highest PO_2 (mmHg)	210.3 ± 119.1	142.9 ± 106.4	[b]−82.7 (SE 18.3), <0.0001
Lowest glucose	66.1 ± 39.9	60.5 ± 24.3	[b]−5.69 (SE 4.83), 0.24
Highest glucose	231 ± 124.9	227.5 ± 141.4	[b]4.19 (SE 19.2), 0.83
Prior to baseline			
[c]Intubated	92 (90%)	74 (78%)	0.85 (0.73–0.99), 0.04
[c]FiO_2	0.64 ± 0.30	0.53 ± 0.31	−0.10 (SE 0.05), 0.03
Inotropic agent	32 (32%)	25 (27%)	0.95 (0.68–1.34), 0.79
Anticonvulsants	49 (49%)	25 (27%)	0.58 (0.40–0.85), 0.005
Analgesics/sedatives	12 (12%)	20 (22%)	1.77 (0.95–3.31), 0.07
24 h			
Intubated	66 (67%)	54 (58%)	0.95 (0.74–1.22), 0.69
FiO_2	0.57 ± 0.31	0.42 ± 0.27	−0.15 (SE 0.05), 0.004
Inotropic agent	45 (47%)	31 (34%)	0.70 (0.46–1.05), 0.09
Anticonvulsants	55 (55%)	36 (38%)	0.69 (0.47–1.01), 0.06
Analgesics/sedatives	31 (31%)	52 (55%)	1.86 (1.21–2.86), 0.005
48 h			
Intubated	49 (53%)	44 (47%)	0.95 (0.69–1.31), 0.75
FiO_2	0.53 ± 0.31	0.40 ± 0.25	−0.13 (SE 0.05), 0.01
Inotropic agent	37 (40%)	25 (27%)	0.71 (0.50–1.02), 0.06
Anticonvulsants	45 (47%)	31 (33%)	0.72 (0.50–1.05), 0.08
Analgesics/sedatives	25 (26%)	44 (47%)	1.85 (1.23–2.79), 0.003
72 h			
Intubated	45 (50%)	36 (40%)	0.88 (0.61–1.27), 0.49
FiO_2	0.50 ± 0.32	0.40 ± 0.22	−0.08 (SE 0.06), 0.15
Inotropic agent	27 (31%)	23 (26%)	0.89 (0.53–1.49), 0.65
Anticonvulsants	39 (41%)	25 (27%)	0.74 (0.49–1.14), 0.17
Analgesics/sedatives	18 (19%)	35 (38%)	2.03 (1.24–3.31), 0.005

TH therapeutic hypothermia, *RR* relative risk, *CI* confidence interval, *IH* induced hypothermia, *OC* optimizing cooling, *GEE* generalized estimating equation, *FiO_2* fraction of inspired oxygen

[a]Results are from GEE regression (log-binomial), adjusted for the level of HIE and intracenter correlations. IH-cooled is the reference group

[b]Results are estimated differences in means, from linear regression adjusted for level of HIE and center as a random effect. IH-cooled is the reference group

[c]Reflects intubation (high-frequency ventilation or intermittent mandatory ventilation) and FiO_2 at baseline

with higher pH and lower base deficits and fewer had severe encephalopathy (23% in OC vs. 32% in IH). This difference in the proportion of subjects with severe encephalopathy despite using similar inclusion criteria may reflect unmeasured changes in obstetric practice and acceptance of hypothermia as a safe treatment, as well as improved awareness of its effectiveness in reducing the risk of death or disability for neonates with moderate or severe encephalopathy.[1] Evaluation of the distribution of the severity of modified Sarnat exam components identified differences in several categories in those with moderate HIE between the trials. In contrast, in those with severe HIE the only difference observed between OC and IH was in the distribution of the respiratory subcomponent of the autonomic nervous system. Despite the differences in patient characteristics, there was not a statistically significant difference in the adjusted risk of death or disability in OC compared to IH (RR 0.73, 95% CI: 0.47–1.15, $p = 0.17$).

Our analysis indicates that there were several changes in care practices between the two trials. The relative contribution of each difference in practice is not able to be determined in this study. A potentially important difference was the use of passive or active cooling prior to randomization in OC. Centers were encouraged to not delay initiation of clinical cooling and the majority of neonates in OC were cooled passively or actively before randomization. More than half of the patients in OC had core temperatures that were within one degree of goal temperature at study baseline. Pre-clinical and an observational study indicates that earlier onset of cooling delays the onset of secondary energy failure and that the latent phase duration is inversely related to the severity of the insult.[20–22] Meta-analyses have not been performed evaluating the impact of earlier cooling on outcome; however there has been an educational focus on improving identification of eligible patients and timely initiation of TH.[23] Thoresen et al.[24] retrospectively analyzed a cohort of infants with HIE in which cooling initiation at <3 h after birth was associated with an improved motor outcome.[20] Reasons for the initiation of cooling at <3 and >3 h are not provided. The TOBY trial demonstrated a trend ($p = 0.08$) towards better outcomes in newborns cooled within 4 h of birth.

Blood gas tensions of oxygen and carbon dioxide differed between the IH and OC trials, even after adjusting for severity of encephalopathy. This suggests that practitioners were more aware of the deleterious effects of hypocarbia and hyperoxia and

Table 3. Hospital, discharge, and 18–22 month outcomes

	IH (33.5° × 72 h), *N* = 102	OC (33.5° × 72 h), *N* = 95	Unadjusted RR (95% CI), *p* value	[a]Adjusted RR (95% CI), *p* value
Length of stay (days)	17.1 ± 15.0	20.5 ± 15.6	3.45 (SE 2.18), 0.12	[b]4.25 (SE 2.21), 0.06
Gavage or gastrostomy tube	15/81 (19%)	18/87 (21%)	1.12 (0.60–2.07), 0.72	1.07 (0.55–2.09), 0.83
Discharge on anticonvulsants	31/81 (38%)	21/87 (24%)	0.63 (0.40–1.00, 0.052)	0.71 (0.38–1.31), 0.27
Death in hospital	19 (19%)	7 (7%)	0.40 (0.17–0.90), 0.03	0.46 (0.17–1.27), 0.13
Death by 18 months	24 (24%)	8/93 (9%)	0.37 (0.17–0.77), 0.009	0.38 (0.14–1.05), 0.06
Moderate HIE	9/69 (13%)	4/72 (6%)	0.43 (0.14–1.32), 0.14	0.41 (0.13–1.36), 0.15
Severe HIE	15/32 (47%)	4/21 (19%)	0.41 (0.16–1.06), 0.06	0.43 (0.15–1.24), 0.12
Death or disability	45 (44%)	27/92 (29%)	0.67 (0.45–0.98), 0.04	0.73 (0.47–1.15), 0.17
Moderate HIE	22/69 (32%)	14/71 (20%)	0.62 (0.35–1.11), 0.11	0.62 (0.34–1.14), 0.13
Severe HIE	23/32 (72%)	13/21 (62%)	0.86 (0.58–1.28), 0.46	0.86 (0.56–1.32), 0.49
Cerebral palsy	19/77 (25%)	16/85 (19%)	0.76 (0.42–1.38), 0.37	0.79 (0.50–1.24), 0.31
GMFCS	*N* = 77	*N* = 79	[c]0.35	N/A
Normal	55 (71%)	64 (81%)		
Level 1	6 (8%)	2 (3%)		
Level 2	2 (3%)	2 (3%)		
Level 3	1 (1%)	3 (4%)		
Level 4	5 (6%)	0 (0%)		
Level 5	8 (10%)	8 (10%)		

IH induced hypothermia, *OC* optimizing cooling, *RR* relative risk, *CI* confidence interval, *HIE* hypoxic–ischemic encephalopathy, *GEE* generalized estimating equation, *N/A* not applicable, *GMFCS* gross motor function classification system
[a]Results are from GEE regression (log-binomial) adjusted for the level of HIE and intracenter correlations. IH group is the reference group
[b]Results are estimated differences in means from linear regression adjusted for the level of HIE and center as a random effect
[c]Cochran-Armitage trend test

perhaps reflects changes in management to respiratory care in order to minimize exposure to low carbon dioxide and high oxygen tensions. This may also reflect that infants in OC were less sick and therefore less likely to have hypocarbia and hyperoxia. Free oxygen radicals are thought to mediate the adverse effects of hyperoxia, while hypocarbia is known to decrease cerebral blood flow. Both have been found in a multivariate model to be associated with adverse outcomes, including death, cerebral palsy, and poor developmental outcome.[6,25]

Differences in the use of medications commonly used during cooling, including inotropes, anticonvulsants, and sedatives/analgesics, were documented. Some may be related to differences in severity of illness, although in some cases the difference persisted after adjusting for severity of HIE at enrollment and for center. Changes in the use of anticonvulsants may be related to changes in seizure identification and management practices between the two trials. Neonates with HIE are known to be at high risk for the development of seizures, with a documented frequency ranging from 30 to 60% in recent studies.[13,26–29] The use of EEG was higher in the OC trial and this may reflect the impact of multiple publications highlighting the high incidence of electrographic seizures.[13,29] In 2011 the American Clinical Neurophysiology Society recommended that 24 h of continuous EEG monitoring should be implemented in neonates with HIE.[11] During this same period, there was increased awareness that many seizures are subclinical and that the diagnosis of seizures based on clinical exam is difficult and is known to be inaccurate regardless of the level of experience of the clinician.[30] Seizures also likely impact outcome with prolonged electrographic seizures being independently associated and a risk factor for poor outcome.[31–33] We also identified that fewer infants were discharged home on anticonvulsants in the OC trial compared to the IH trial, although this difference was not statistically significant. Exposure of the immature brain to anti-epileptic drugs is known in animal studies to increase apoptosis and may alter behavior and cognition.[34] In a cohort study of hospital exposure to phenobarbital and/or levetiracetam, increased cumulative phenobarbital and/or levetiracetam exposure were both associated with decreased cognitive and motor scores, although the degree of brain injury on imaging was not controlled for and the study did not address the impact of ongoing outpatient treatment with these medications.[35] Given the limited sample size it is difficult to evaluate the impact that a change in the use of both in-hospital and post-discharge anticonvulsants could have had on the primary outcome.

Finally, we also identified a difference in the use of sedation and analgesia between the trials with increased use in OC compared to IH during TH. Increased use of sedation/analgesia may reflect increased surveillance by practitioners to address patient comfort. The NRN did not prescribe the use of sedation or analgesia to participating centers. Use of analgesia during hypothermia was identified in the Simbruner trial of TH as a possible mechanism for improved efficacy in his trial.[36] The mechanism of action is not well understood, but may be related to a reduction in cold stress and shivering and therefore a decrease in metabolic rate.[9] In a secondary analysis of the IH trial exposure to sedation/analgesia was not associated with the primary outcome.[10]

The risk ratios of death alone and death or disability after adjustment for center and level of encephalopathy suggest that at least part of the difference in mortality and disability between trials is related to patient acuity. Randomized controlled trials would be needed to determine the impact of earlier initiation of treatment, sedation/analgesia, monitoring for seizures, and thresholds to treat seizures on outcomes. It is also important to consider that TH is being applied in clinical practice to neonates with less severe perinatal asphyxia and encephalopathy including some with mild HIE.[37–39] Design of future trials of neuroprotection will need to consider the impact of the severity of perinatal asphyxia, degree of encephalopathy after birth, and common care practices.

Limitations

Given the small number of patients included in this analysis and who experienced the primary outcome, we are not powered to perform a multivariate model to determine the impact of differing care practices between the trials. Data elements collected were not all identical between the two studies and some direct comparisons were difficult. We were not able to determine if there were differences in obstetric practice between the trials that may have contributed to the differences in severity of illness although neonates in OC were born at a slightly younger gestational age and fewer were delivered by emergent cesarean section. There was likely variation in practice across and within centers in blood pressure, seizure management, and use of analgesics and sedatives as standard management guidelines were not part of either study protocol. Use of two different standardized tests, the Bayley II in IH and Bayley III in OC may limit the ability to make direct comparisons in outcome between the trials. Direct comparison between Bayley II (MDI) and Bayley III (Cognitive) scores in both preterm and term HIE populations have been published.[40] In both these populations, Bayley III cognitive scores are thought to underestimate the degree of impairment when compared directly to the Bayley II. In the term HIE population, a Bayley III cognitive score of <85 identified all but 1 patient who had a Bayley II MDI of <70.[40] Thus, the use of Bayley III in the OC trial with a cut-off of <85 for moderate–severe cognitive impairment should identify all neonates with severe impairments as determined by the Bayley II, but may have underestimated the frequency of those with mild–moderate impairments. Finally any differences observed may be related to chance.

CONCLUSIONS

Despite similar inclusion criteria between the two NRN trials of TH there were significant differences in patient characteristics at enrollment. In OC compared to IH, newborns were less critically ill, fewer had severe HIE, they were cooled earlier, anticonvulsant use was lower, there was less hypocarbia and hyperoxia, and use of sedation or analgesia was more prevalent. These demographic and care practice differences may have contributed to the unadjusted differences in survival and disability rates in the usual care arm of the OC trial when compared to the cooled arm of the IH trial, although these differences were no longer significant after adjustment. Severity of perinatal asphyxia, degree of encephalopathy, and care practices need to be considered in the design of future trials.

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AUTHOR CONTRIBUTIONS

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ADDITIONAL INFORMATION

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