Effect of Therapeutic Hypothermia Initiated After 6 Hours of Age on Death or Disability Among Newborns With Hypoxic-Ischemic Encephalopathy
A Randomized Clinical Trial

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IMPORTANCE Hypothermia initiated at less than 6 hours after birth reduces death or disability for infants with hypoxic-ischemic encephalopathy at 36 weeks' or later gestation. To our knowledge, hypothermia trials have not been performed in infants presenting after 6 hours.

OBJECTIVE To estimate the probability that hypothermia initiated at 6 to 24 hours after birth reduces the risk of death or disability at 18 months among infants with hypoxic-ischemic encephalopathy.

DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial was conducted between April 2008 and June 2016 among infants at 36 weeks' or later gestation with moderate or severe hypoxic-ischemic encephalopathy enrolled at 6 to 24 hours after birth. Twenty-one US Neonatal Research Network centers participated. Bayesian analyses were prespecified given the anticipated limited sample size.

INTERVENTIONS Targeted esophageal temperature was used in 168 infants. Eighty-three hypothermic infants were maintained at 33.5°C (acceptable range, 33°C-34°C) for 96 hours and then rewarmed. Eighty-five noncooled infants were maintained at 37.0°C (acceptable range, 36.5°C-37.3°C).

MAIN OUTCOMES AND MEASURES The composite of death or disability (moderate or severe) at 18 to 22 months adjusted for level of encephalopathy and age at randomization.

RESULTS Hypothermic and noncooled infants were term (mean [SD], 39 [2] and 39 [1] weeks' gestation, respectively), and 47 of 83 (57%) and 55 of 85 (65%) were male, respectively. Both groups were acidemic at birth, predominantly transferred to the treating center with moderate encephalopathy, and were randomized at a mean (SD) of 16 (5) and 15 (5) hours for hypothermic and noncooled groups, respectively. The primary outcome occurred in 19 of 78 hypothermic infants (24.4%) and 22 of 79 noncooled infants (27.9%) (absolute difference, 3.5%; 95% CI, −1% to 17%). Bayesian analysis using a neutral prior indicated a 76% posterior probability of reduced death or disability with hypothermia relative to the noncooled group (adjusted posterior risk ratio, 0.86; 95% credible interval, 0.58-1.29). The probability that death or disability in cooled infants was at least 1%, 2%, or 3% less than noncooled infants was 71%, 64%, and 56%, respectively.

CONCLUSIONS AND RELEVANCE Among term infants with hypoxic-ischemic encephalopathy, hypothermia initiated at 6 to 24 hours after birth compared with noncooling resulted in a 76% probability of any reduction in death or disability, and a 64% probability of at least 2% less death or disability at 18 to 22 months. Hypothermia initiated at 6 to 24 hours after birth may have benefit but there is uncertainty in its effectiveness.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00614744

+ Supplemental content

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Hypoxic-ischemic encephalopathy represents a subset of neonatal encephalopathy, occurring in approximately 1.5 per 1000 live births.[1] It is an important etiology of neonatal mortality and serious or devastating lifelong cerebral palsy, neurosensory deficits, and cognitive impairments.[2] Therapeutic hypothermia initiated within 6 hours after birth for moderate or severe hypoxic-ischemic encephalopathy reduced the composite outcome of death or disability at 18 months in multiple randomized clinical trials[3-8] and improved outcomes at 6 to 7 years.[9,10] The American Academy of Pediatrics published a framework to ensure appropriate use of hypothermia.[11]

In all previous neonatal trials, hypothermia was initiated within 6 hours after birth,[3-8] reflecting a 6-hour therapeutic window for hypothermia after brain ischemia in fetal sheep.[12-14] However, only 5 fetal sheep were cooled at 8.5 hours after ischemia,[14] and the results could not exclude the possibility of a longer therapeutic window. Initiating hypothermia before 6 hours after birth can be difficult if infants are born in remote communities and need to be transferred, or if encephalopathy evolves or is recognized after 6 hours. Initiation of hypothermia beyond 6 hours is currently without evidence of benefit.[15] A definitive trial to determine benefit or harm cannot be conducted for this uncommon condition because even large research networks have an insufficient number of patients to achieve high statistical power in a reasonable time. To provide the most feasible estimate of treatment effect, a multicenter, randomized clinical trial was conducted over 8 years among infants with moderate or severe hypoxic-ischemic encephalopathy treated with hypothermia initiated at or after 6 hours but before 24 hours of age compared with noncooled infants. Bayesian analyses were performed to estimate the probability that hypothermia reduced the risk of death or disability at 18 months.

Key Points

Question Does initiation of hypothermia at 6 to 24 hours after birth reduce the risk of death or disability at 18 months among term newborns with hypoxic-ischemic encephalopathy?

Findings In this Bayesian analysis of a randomized clinical trial of 168 newborns with hypoxic-ischemic encephalopathy, treatment with hypothermia initiated at 6 to 24 hours after birth compared with noncooling resulted in a 76% probability of any reduced death or disability, and a 64% probability of at least 2% less death or disability at 18 to 22 months.

Meaning Hypothermia treatment initiated at 6 to 24 hours for newborns with hypoxic-ischemic encephalopathy may reduce death or disability but there is uncertainty in its effectiveness.

Methods

Participants

Trial enrollment occurred between April 2008 and July 2014 and follow-up was completed in June 2016 at 21 centers of the Eunice Kennedy Shriver National Institutes of Child Health and Human Development Neonatal Research Network located across the United States. The full trial protocol is available in Supplement 1. Each center received institutional review board approval and infants were enrolled after written informed parental consent was obtained. Newborns with gestational age 36 weeks or later and postnatal age 6 to 24 hours were screened for eligibility if they were admitted to a participating neonatal intensive care unit with a diagnosis of encephalopathy, perinatal asphyxia, or neurological depression. Enrollment until 24 hours of age was based on the variability in the manifestations of newborn encephalopathy,[16] ongoing injurious processes in the hours to days after hypoxia-ischemia,[17] benefit from hypothermia initiated at 12 hours after ischemia in a preclinical study,[18] and the uncertainty in extrapolating from animal to human newborns.

Inclusion criteria were identical to the prior Neonatal Research Network hypothermia trial[4] except for postnatal age.

Infants who fulfilled biochemical or clinical criteria and were determined to have seizures or moderate or severe encephalopathy on examination by certified examiners were eligible.[4] Infants without moderate or severe encephalopathy by examination but with clinical seizures were classified as having moderate encephalopathy. Exclusion criteria included a core temperature of less than 34°C for more than 1 hour, known anomaly, chromosomal aberration, birth weight less than 1800 g, in extremis condition, and parental or attending physician refusal. Race/ethnicity was obtained by maternal report using fixed categories to ensure group comparability along with other demographic variables.

Randomization

Infants were stratified by postnatal age (≤12 hours or >12 hours) and stage of encephalopathy (moderate or severe), and they were randomly assigned by telephone by the data center to hypothermia or noncooling using a computer-generated permutated block algorithm with block size of 2 and 4 with a 1:1 ratio.

Intervention

Before randomization, temperature control was per center practices. The hypothermia group underwent whole-body cooling similar to the Neonatal Research Network hypothermia trial[4,19] to maintain esophageal temperature at 33.5°C (acceptable range, 33.0°C-34.0°C) using a Hyper-Hypothermia Blanketrol system (Cincinnati Sub-Zero). The duration of hypothermia was lengthened from 72 hours[4] to 96 hours based on preclinical data before 2008 that a longer duration of hypothermia was needed to achieve neuroprotection with increasing delays between hypoxia-ischemia and initiation of cooling.[18,20] At 96 hours, rewarming was conducted at 0.5°C per hour using the Blanketrol system and completed using a radiant warmer to maintain esophageal temperature of 37.0°C over 5 hours. Temperatures were recorded every 15 minutes during the first 3 hours of cooling, every hour until 12 hours, and at 4-hour intervals through the remainder of cooling and rewarming. The noncooled group was treated with an esophageal temperature probe and temperatures maintained at 37.0°C (acceptable range, 36.5°C-37.3°C). Infants were cared for on radiant warmers and the

Figure 1. Flow Diagram of Neonates With Hypoxic-Ischemic Encephalopathy Through a Trial of Hypothermia Initiated at 6 to 24 Hours After Birth
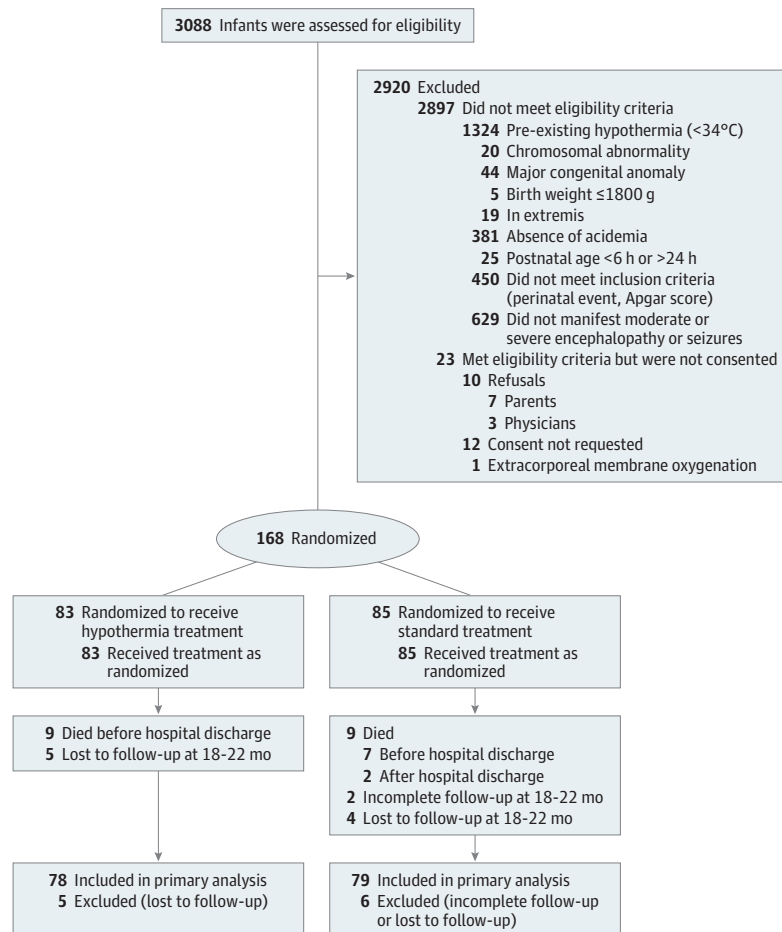
control set point for the skin temperature was adjusted to achieve the desired esophageal temperature. An algorithm was used to correct hyperthermia by ensuring appropriate thermal care if the esophageal temperature exceeded 37.3°C, and a tepid bath and/or cooling blanket if the temperature exceeded 37.5°C. Temperatures were recorded every 4 hours in the noncooled group. At 108 hours, esophageal temperature probes of both groups were removed and temperature control was resumed per local practice.

Outcomes

The primary outcome was death or disability, either moderate or severe, at 18 to 22 months of age. Certified examiners trained to reliability[21] and masked to treatment assignment conducted a neurological examination and psychometric testing, assessed growth, and reviewed vision and hearing with the family. The Bayley Scales of Infant Development III were used to obtain cognitive, language, and motor scores (reported mean [SD] score, 100 [15]; range, 55-145).[22] The Gross Motor Function Classification Score (GMFCS; range, 0 [normal] to 5 [worst]) was used to classify motor findings.[23] Severe disability was defined as any of the following: a cognitive score less

than 70, a GMFCS level of 3 to 5, and blindness or hearing impairment with inability to follow commands despite amplification. Moderate disability was defined as a cognitive score between 70 and 84 and any of the following: a GMFCS level of 2, an active seizure disorder (antiepileptic drugs in use), or a hearing deficit with the ability to follow commands after amplification.[4] Infants who did not meet the primary outcome were categorized as either mild disability or normal. Mild disability was defined by a cognitive score of 70 to 84 alone or a cognitive score of 85 or greater, and any of the following: a GMFCS level of 1 or 2, a seizure disorder (without medication), or a hearing deficit with the ability to follow commands without amplification.

Prespecified secondary outcomes were the frequency of death alone, moderate-severe disability alone, disability (severe, moderate, and mild), disability based on level of encephalopathy, seizures (with or without electroencephalograms), do not resuscitate order (DNR), DNR and support withdrawn, DNR and survival or death, and nonbrain organ dysfunction. The latter 2 are not reported. Outcomes not prespecified were adverse events, in-hospital organ system morbidities, components of disability, normal infants (cognitive

Table 1. Maternal and Neonatal Characteristics[a]

Characteristic	Hypothermia Group (n = 83)	Noncooled Group (n = 85)
Maternal		
Age, mean (SD), y	27 (6)	26 (6)
Married, No. (%)	54 (65)	43 (50.6)
Race/ethnicity, No. (%)		
Black	13 (16.1)	21 (25)
White	61 (75.3)	60 (71.4)
Other[b]	7 (8.6)	3 (3.6)
Gravida, median (IQR)	2 (1-3)	2 (1.3)
Parity, median (IQR)	1 (1-2)	1 (1-2)
Education, No. (%)		
≤ High school	36 (45.6)	34 (42.5)
Any college or beyond	43 (54.4)	46 (57.5)
Pregnancy complications, No. (%)		
Hypertension or pre-eclampsia	13 (15.7)	17 (20.2)
Antepartum hemorrhage	3 (3.6)	7 (8.2)
Thyroid dysfunction	2 (2.4)	3 (3.6)
Diabetes	7 (8.4)	9 (10.7)
Intrapartum complications, No. (%)		
Fetal decelerations	59 (72)	60 (70.6)
Cord mishap (prolapse, rupture)	9 (10.8)	13 (15.3)
Uterine rupture	2 (2.4)	2 (2.4)
Maternal pyrexia (≥37.6°C)	10 (12.1)	9 (10.8)
Placental problems (abruptio, previa)	9 (10.8)	10 (11.8)
Maternal trauma, CPR	2 (2.4)	7 (8.2)
Shoulder dystocia	8 (9.8)	4 (4.7)
Rupture of membranes, median (IQR), h	3.2 (0.02-11.9)	5.5 (0.03-15.5)
Chorioamnionitis, clinical	5 (6.1)	7 (8.5)
Chorioamnionitis, histologic, No./total No. (%)[c]	13/30 (43.3)	8/22 (36.4)
Emergency cesarean delivery	47 (56.6)	52 (61.2)
Infant		
Gestational age, mean (SD), wk	39 (2)	39 (1)
Birth weight, mean (SD), g	3379 (528)	3303 (553)
Length, mean (SD), cm	51 (3)	51 (3)
Head circumference, mean (SD), cm	34 (2)	34 (2)
Male, No. (%)	47 (56.6)	55 (64.7)
Transferred to treating center, No. (%)	71 (85.5)	75 (88.2)
Delivery room, No. (%)		
Intubation	47 (58.0)	45 (52.9)
Chest compressions	19 (23.5)	25 (29.4)
Medication	9 (11.1)	11 (12.9)
Time to spontaneous respirations >10 min	24 (30.0)	34 (41.0)
Apgar score <5, No.		
At 5 min	42 (50.6)	43 (50.6)
At 10 min[d]	18 (28.6)	20 (26.0)

(continued)

Table 1. Maternal and Neonatal Characteristics[a] (continued)

Characteristic	Hypothermia Group (n = 83)	Noncooled Group (n = 85)
Cord blood, mean (SD)		
pH	6.96 (0.16)	6.99 (0.16)
Base deficit	14.8 (5.8)	13.9 (5.3)
At randomization		
Age, mean (SD), h	16 (5)	15 (5)
≥6 to ≤12 h, No. (%)	26 (31.3)	28 (32.9)
>12 to 24 h, No. (%)	57 (68.7)	57 (67.1)
Level of encephalopathy, No. (%)		
Moderate encephalopathy	73 (88.0)	78 (91.8)
Severe encephalopathy	10 (12.1)	7 (8.2)
Clinical seizures at randomization, No. (%)	63 (75.9)	56 (65.9)
Anticonvulsants at randomization, No. (%)	56 (72.7)	48 (67.1)
Inotropic support at randomization, No. (%)	17 (21.0)	16 (18.8)

Abbreviations: CPR, cardiopulmonary resuscitation; IQR, interquartile range.

[a] Percentages are based on the number of mothers and infants for whom data were available. Missing data: maternal education (9 missing), race/ethnicity (3 missing), rupture of membrane (8 missing), hypertension/pre-eclampsia (1 missing), fetal decelerations (1 missing), cord mishap (1 missing), fetal decelerations (2 missing), shoulder dystocia (1 missing), length (2 missing), head circumference (3 missing), intubation (2 missing), chest compression (2 missing), medication (2 missing), time to spontaneous respiration (5 missing), Apgar score at 10 min (79 missing), pH (42 missing), base deficit (65 missing), anticonvulsants at randomization (21 missing), and inotropic support at randomization (3 missing).

[b] Other race/ethnicity includes American Indian or Alaskan Native, Asian, Native Hawaiian or other Pacific Islander, and multiracial.

[c] Percentage based on the number of mothers with placental pathology performed (n = 30 in the hypothermia group and n = 22 in the noncooled group).

[d] The number of infants with an Apgar score at 10 minutes was 63 in the hypothermia group and 77 in the noncooled group.

score of ≥85, a normal GMFCS level, no neurosensory deficits, and no seizures), and growth parameters at follow-up.

Sample Size and Statistical Analyses

The effect size was expected to be smaller than the prior Neonatal Research Network hypothermia trial (risk ratio [RR], 0.72; 95% CI, 0.54-0.95).[4] A sample size of 168 was predefined and represented the largest sample that could be attained in a feasible time interval (6-year enrollment). A Bayesian analysis was prespecified to estimate the probability of treatment benefit based on recommendations for trials of rare conditions with limited sample size and power in frequentist analyses to identify conclusive treatment effects.[24]

In Bayesian analyses, the probability of treatment effect (posterior probability) is estimated after the trial and incorporates the prior probability estimated from the best data from previous studies (clinical trials or pilot trials).[25] Judgment of the prior probability may vary and be neutral, enthusiastic, or skeptical. Therefore, analyses were performed using 3 different prior probabilities: (1) a neutral prior, assuming no treatment effect (RR, 1.0); (2) an enthusiastic prior, assuming a 28% reduction in the risk of death or

Table 2. Neonatal Adverse Events and Hospital Outcomes[a]

Event or Outcome	No. (%) Hypothermia (n = 83)	Noncooled (n = 85)	P Value	Absolute Differences (95% CI)
Adverse Events[b]				
Arrhythmia needing treatment	0	0		
Persistent metabolic acidosis	0	0		
Thrombosis	0	0		
Bleeding	4 (4.8)	1 (1.2)	.21	0.04 (−0.02 to 0.09)
Altered skin integrity	1 (1.2)	0 (0)		0.01 (−0.01 to 0.04)
Death	6 (7.2)	5 (5.9)	.76	0.01 (−0.06 to 0.09)
Other[c]	2 (2.4)	0		0.02 (−0.01 to 0.06)
Neonatal Outcomes in the Hospital				
Meconium aspiration syndrome	23 (27.7)	20 (23.5)	.60	0.04 (−0.09 to 0.17)
Pulmonary artery hypertension	20 (24.1)	13 (15.3)	.18	0.09 (−0.03 to 0.21)
Inhaled nitric oxide use	14 (16.9)	15 (17.7)	>.99	0.01 (−0.11 to 0.12)
ECMO	3 (3.6)	2 (2.4)	.68	0.01 (−0.04 to 0.06)
Ventilation during 96-h intervention	49 (59.0)	44 (51.8)	.34	0.07 (−0.08 to 0.22)
Cardiac ischemia[d]	14 (16.9)	13 (15.5)	.84	0.02 (−0.1 to 0.13)
Hypotension treated with vasopressors	28 (33.7)	24 (28.2)	.51	0.05 (−0.08 to 0.19)
Oliguria	19 (23.0)	18 (21.2)	.85	0.02 (−0.11 to 0.14)
Hepatic dysfunction	19 (22.9)	24 (28.2)	.48	0.05 (−0.08 to 0.19)
Disseminated intravascular coagulation	9 (10.8)	4 (4.7)	.16	0.06 (−0.02 to 0.14)
Bacteremia	2 (2.4)	1 (1.2)	.62	0.01 (−0.03 to 0.05)
Clinical seizures (any time)	64 (77.1)	64 (75.3)	.86	0.02 (−0.11 to 0.15)
EEG recording	69 (83.1)	70 (82.4)	>.99	0.01 (−0.11 to 0.12)
Electrographic seizures[e]	26 (37.7)	25 (34.7)	.86	0.02 (−0.14 to 0.18)
Abnormal EEG background[e]	49 (71.0)	48 (68.6)	.85	0.02 (−0.13 to 0.18)
Glucose concentration <40 mg/dL	5 (6.0)	6 (7.1)	>.99	0.01 (−0.06 to 0.09)
Glucose concentration >150 mg/dL	33 (39.8)	14 (16.7)	.001	0.23 (0.1 to 0.36)
Analgesics during 96-h intervention	41 (50.0)	30 (35.6)	.055	0.15 (0.0 to 0.30)
DNR order	7 (8.4)	8 (9.4)	>.99	0.01 (−0.08 to 0.1)
DNR order and support withdrawn	6 (7.2)	8 (9.4)	.47	0.02 (−0.06 to 0.11)
Gastrostomy tube or gavage feed at discharge	1 (1.4)	1 (1.3)	>.99	0 (−0.03 to 0.03)
Death prior to discharge	9 (10.8)	7 (8.2)	.61	0.04 (−0.09 to 0.17)

Abbreviations: DNR, do not resuscitate; ECMO, extracorporeal membrane oxygenation; EEG, electroencephalogram.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

[a] Percentages are based on the number of infants for whom data were available. Hospital outcomes reflect the number of infants experiencing the outcome. Multiple adverse events occurred in 3 hypothermic infants and 1 control infant.

[b] Adverse events during the 96-h intervention and the interval of rewarming.

[c] Other indicates adverse events not prespecified. This was persistent pulmonary artery hypertension with induction of hypothermia in one infant and during hypothermia in a second infant.

[d] Cardiac ischemia was defined as elevation of cardiac enzymes or troponin or electrocardiographic changes

[e] Denominator is the number of infants who had an EEG recording.

disability as in the earlier Neonatal Research Network trial[4] (RR, 0.72); and (3) a skeptical prior, assuming a 10% increase in the risk of death or disability (RR, 1.10). Whether neutral, enthusiastic, or skeptical, assessments of prior probability involve uncertainty about the minimum and maximum likely treatment effects. To reflect this uncertainty in each analysis, a probability distribution for the treatment effect with the 95% credible intervals that ranged from half to twice the assumed RR (SD, 0.35 in the log scale) was used. For example, the probability distribution for the neutral prior was centered at an RR of 1.0 (mean of 0 in the log scale) with a 50% prior probability of a better outcome, a 50% prior probability of a worse outcome, and a 95% credible interval for the RR of 0.5 to 2.0 (eAppendix in Supplement 2). The RR of 0.5 to 2.0 includes treatment effects for major clinical outcomes of the size observed in almost all large clinical trials.[26] For adequately powered trials, differences between neutral, enthusiastic, and skeptical priors have almost no effect on the posterior probability. However, for smaller trials, Bayes-

ian analyses allow assessment of how much the estimated probability of a treatment effect is affected by differing assessments of the prior evidence.

All analyses followed the intention-to-treat principle. A binomial model was used with a log link to estimate the posterior RR for different binary outcomes for the hypothermia group compared with the noncooled group. The model to obtain the adjusted RR (aRR) included 3 main effects: treatment (hypothermia or noncooling), age at time of randomization (≤12 hours or >12 hours), and level of encephalopathy (moderate or severe). Center was not included because models did not converge with center as a covariate. The original analysis plan specified a logistic model. This represented an oversight as the intent was to present adjusted relative risks to quantify the treatment effect. The decision to use a log binomial model was made prior to the derivation of the primary outcome and all analyses.

Interactions of treatment with age at enrollment, level of encephalopathy at randomization, and sex on the primary

Table 3. Primary and Secondary Outcomes: aRRs and Posterior Probability of Treatment Effect[a]

Outcome	No. (%)		Enthusiastic Prior (RR, 0.72)		Neutral Prior (RR, 1.0)		Skeptical Prior (RR, 1.10)	
	Hypothermia (n = 78)	Noncooled (n = 79)	aRR (95% Credible Interval)	P-TB, %	aRR (95% Credible Interval)	P-TB, %	aRR (95% Credible Interval)	P-TB, %
Primary Outcome								
Death or moderate-severe disability	19 (24.4)	22 (27.9)	0.78 (0.52-1.15)	90	0.86 (0.58-1.29)	76	0.89 (0.60-1.32)	73
Secondary Outcomes								
Death[b]	9 (11.5)	9 (11.4)	0.74 (0.45-1.21)	89	0.86 (0.54-1.44)	73	0.90 (0.56-1.52)	67
Moderate or severe disability[c]	10 (12.8)	13 (16.5)	0.74 (0.44-1.24)	87	0.89 (0.54-1.48)	68	0.93 (0.56-1.55)	61
Severe disability[c]	9 (11.5)	12 (15.2)	0.73 (0.43-1.23)	88	0.88 (0.53-1.50)	68	0.93 (0.55-1.55)	61
Moderate disability[c,d]	1 (1.3)	1 (1.3)						
Mild disability[c]	16 (20.5)	12 (15.2)	1.0 (0.62-1.62)	50	1.18 (0.73-1.91)	25	1.23 (0.76-2.0)	20

Abbreviations: aRR, adjusted risk ratio; P-TB, posterior probability of treatment benefit (risk ratio <1.0); RR, risk ratio.

[a] Reference for the aRR is the noncooled group and the aRR is adjusted for level of encephalopathy (moderate, severe) and age at randomization (≤12 h, >12 h). Variables in the adjusted analyses were outcome, treatment, level of encephalopathy at randomization, and age at randomization.

[b] Causes of death in the hypothermia group were asphyxia brain injury (n = 5), multiorgan failure (n = 1), persistent pulmonary hypertension (n = 1), respiratory failure associated with intractable seizures (n = 1), and intracranial hemorrhage (n = 1). Causes of death in the noncooled group were asphyxia brain injury (n = 5), multiorgan failure (n = 1), and meconium aspiration syndrome (n = 1), and 2 were without an assigned cause (after discharge).

[c] Disability categories were defined as follows: severe included any of the following: a cognitive score less than 70, a Gross Motor Function Classification Score (GMFCS) level of 3 to 5, or blindness or hearing impairment with inability to follow commands despite amplification; moderate included a cognitive score between 70 and 84 and any of the following: a GMFCS level of 2, an active seizure disorder (antiepileptic drugs in use), or a hearing deficit with the ability to follow commands after amplification; and mild included a cognitive score between 70 and 84 or a cognitive score of 85 or greater with any of the following: a GMFCS level of 1 or 2, seizure disorder (without medication), or a hearing deficit with the ability to follow commands without amplification.

[d] Analyses could not be performed with 1 infant in each group.

outcome were assessed with a log-linear model. Bayesian analyses were used to determine probabilities for the absolute risk difference (binomial model) and adjusted cognitive scores (linear regression). *P* values from parallel frequentist analyses are provided for outcomes not prespecified, using 2-sided χ^2, Fisher exact, Wilcoxon, and *t* tests; 1-sided *t* tests were used for absolute differences. A *P* < .05 was considered significant and was not adjusted for multiple comparisons. Statistical software for Bayesian analysis was JAGS version 4.6 and OpenBUGS version 3.2.3., and for frequentist analysis was SAS version 9.3 (SAS Institute). The data safety monitoring committee reviewed safety after every 20 infants and effectiveness at 33%, 50%, and 75% of outcome accrual.
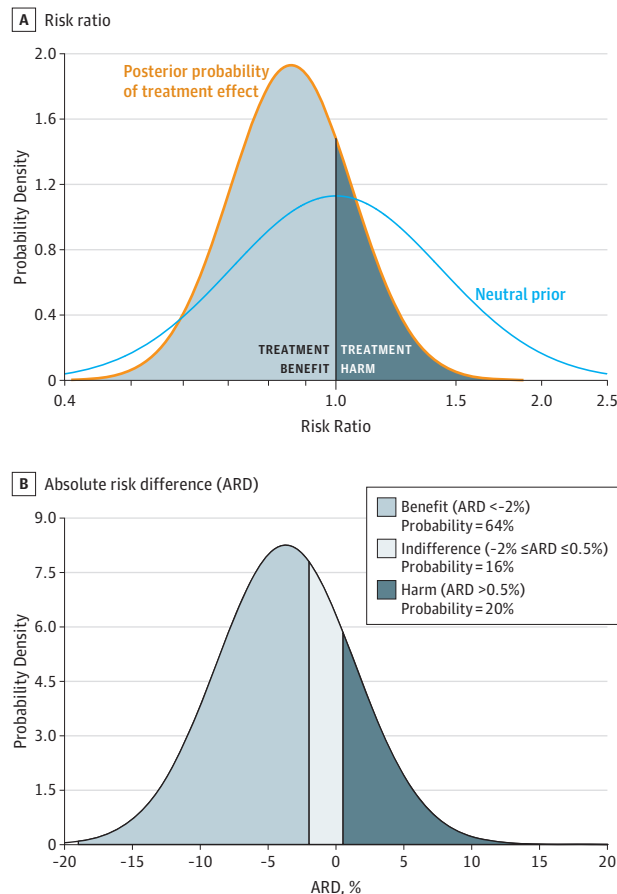
Results

There were 168 participants and 83 were randomly assigned to hypothermia and 85 to noncooling (**Figure 1**). Hypothermic and noncooled infants were term (mean [SD], 39 [2] and 39 [1] weeks' gestation, respectively), and 47 of 83 (57%) and 55 of 85 (65%) were male, respectively. Emergency cesarean delivery was performed for 99 of 168 infants (59%), of whom 146 (87%) were transferred to the treating center (**Table 1**). At birth, intubation was performed in 92 of 168 infants (55%) and chest compressions were performed in 44 of 168 infants (26%). Hypothermic and noncooled infants were randomized at a mean (SD) of 16 (5) and 15 (5) hours, respectively. Enrollment beyond 12 hours after birth

occurred in 114 of 168 infants (68%) and moderate encephalopathy was found in 151 of 168 infants (90%). Ten infants in each group were enrolled based on clinical seizures without moderate or severe encephalopathy. Infants with incomplete or no follow-up (n = 11) were similar to those with a known outcome (eTable 1 in Supplement 2).

Following hypothermia induction, mean (SD) esophageal temperature was maintained at 33.3 (0.3)°C between 3 and 96 hours (eFigure in Supplement 2). The mean (SD) esophageal temperature for the noncooled group during the intervention was 36.8 (0.5)°C. In the noncooled group, the median number of esophageal temperatures per infant below 36.5°C was 1 (interquartile range [IQR], 0-3) and the mean of these values was 36.2°C (IQR, 35.9°C-36.4°C). The median number of esophageal temperatures per infant greater than 37.3°C was 1 (IQR, 0-4) and the mean of these values was 37.5°C (IQR, 37.4°C-37.7°C). Interventions to reduce elevated temperature were performed in 27 of 85 infants (32%) in the noncooled group; 24 infants (28%) received a tepid bath and 7 infants (8%) were treated with a cooling blanket.

During the intervention and rewarming, unmasked observers recorded 13 and 6 adverse events in the hypothermia and noncooled groups, respectively (**Table 2**). One infant (hypothermia) developed subcutaneous fat necrosis and 1 infant (noncooled) developed diabetes insipidus, both remote from the intervention. There were no group differences in organ system morbidities or need for extracorporeal membrane oxygenation. A blood glucose concentration greater than 150 mg/dL occurred more frequently in the

Figure 2. Posterior Probability of Death or Disability With Hypothermia Initiated at 6 to 24 Hours After Birth vs Noncooling

A   Risk ratio

B   Absolute risk difference (ARD)

Legend for B:
- Benefit (ARD <-2%) Probability = 64%
- Indifference (-2% ≤ARD ≤0.5%) Probability = 16%
- Harm (ARD >0.5%) Probability = 20%

A, The probability density describes the frequency distribution of observed values and is unit-less. The curves are scaled so that the total area under the curve is 1, and the area between any 2 values on the x-axis equals the probability of observing a value in that range. The blue line plots a neutral prior distribution centered at a risk ratio of 1.0 and indicates an equal number of infants would be expected to benefit by either temperature management group, hypothermia or noncooled. The posterior probability of treatment effect is derived by combining the prior distribution with the trial results. The distribution is shifted to the left of a risk ratio of 1.0 with a point estimate of 0.86. The area under the curve that is less than a risk ratio of 1.0 (light blue) represents the posterior probability of any reduction in death or disability (76% for this trial). The area under the curve that is greater than a risk ratio of 1.0 (dark blue) represents the posterior probability of an increase in death or disability (24% for this trial). B, The light blue portion indicates a 64% probability that death or disability in infants treated with hypothermia is at least 2% less than noncooled infants (benefit). The pale blue area (near zero) is an arbitrary zone of indifference to illustrate the probability of risk differences where hypothermia and noncooling may be viewed as equivalent. The dark blue indicates the probability of death or disability among infants treated with hypothermia is higher than for noncooled infants (harm). In this example, a 2% absolute risk difference was associated with a 3.2-times (64%/20%) higher probability of reduced compared with increased death or disability risk among hypothermia relative to noncooled infants.

hypothermia than the noncooled group (to convert glucose to millimoles per liter, multiply by 0.0555).

Complete follow-up at a mean (SD) of 21 (3) months was achieved among 69 of 74 (93%) and 72 of 78 (92%) hypothermia and noncooled survivors to discharge, respectively.

There were 9 deaths in each group. There were minimal missing data for the components of disability among survivors, which did not prevent assignment of a primary outcome except for 2 infants with incomplete follow-up evaluations (Figure 1). Death or disability (moderate or severe) at follow-up was known for 157 infants (93.5%) and occurred in 19 of 78 (24.4%) of the hypothermia group and 22 of 79 (27.9%) of the noncooled group (absolute difference, 3.5%; 95% CI, −1% to 17%; Table 3). Bayesian analysis using a neutral prior indicated a 76% posterior probability of reduced death or disability with a posterior aRR of 0.86 (95% credible interval, 0.58-1.29) (Figure 2). The corresponding frequentist aRR was 0.81 (95% CI, 0.44-1.51). Further, 73% and 68% probabilities were identified for reduction in death and in moderate-severe disability, respectively, under the neutral prior. Expressed as an absolute risk difference, the posterior probability that death or disability for hypothermia using a neutral prior was at least 1%, 2%, or 3% less compared with noncooled treatment was 71%, 64%, and 56%, respectively. A 2% absolute risk difference was associated with a 3.2-times (64%/20%) higher probability of reduced compared with increased death or disability among hypothermia relative to noncooled infants, assuming a range of risk differences viewed as equivalent (Figure 2). Using an enthusiastic prior, the posterior probability that death or disability was at least 1%, 2%, or 3% less compared with noncooled increased to 86%, 80%, and 74%, respectively. Death or moderate-severe disability did not differ by age at randomization: 6 of 25 infants (24.0%) and 7 of 26 infants (26.9%) when randomized at 12 hours or less, and 13 of 53 infants (24.5%) and 15 of 53 infants (28.3%) when randomized between 12 and 24 hours in the hypothermia and noncooled groups, respectively. There were no interactions between treatment and age at randomization, level of encephalopathy, or sex for the primary outcome (Bayesian probability of an interaction, 46%, 38%, and 22%, respectively).

Other prespecified and exploratory outcomes did not differ between groups (eTable 2 in Supplement 2). Although Bayley cognitive scores did not differ, they contributed to the extent of disability within each group; a post-hoc Bayesian analysis (neutral prior) indicated a 97% probability of higher scores among hypothermia infants. A post-hoc aRR for survival of infants with a normal outcome was 0.98 (95% credible intervals, 0.76-1.26; neutral prior).

Discussion

Among term infants with hypoxic-ischemic encephalopathy, hypothermia initiated at 6 to 24 hours after birth resulted in a 76% probability of any reduction in death or disability using a Bayesian analysis with a neutral prior. The probability that death or disability was at least 2% less in hypothermia compared with noncooled infants was 64%. Enrolled infants met criteria for hypothermia of the earlier Neonatal Research Network trial.[4] Death or disability (moderate or severe) was known for 93.5% of enrollees and follow-up assessments were performed by examiners blinded to the intervention.

It can be difficult to study therapies for rare diseases or uncommon features of previously studied disease processes. Extrapolation from animal studies has limitations.[27] The therapeutic window during which hypothermia may modify hypoxic-ischemic brain injury may differ between preclinical studies and human newborns owing to species maturation, methods to induce hypoxia-ischemia, and outcomes studied. Randomized clinical trials are unlikely to have sufficient power to identify clinically important treatment effects in traditional frequentist analysis. This is especially pertinent to a trial of hypothermia initiated after 6 hours of age as it addresses a small subset of infants with moderate-severe encephalopathy. Furthermore, based on preclinical studies,[12-14] hypothermia started after 6 hours was anticipated to provide less neuroprotection than hypothermia started before 6 hours, making it even less feasible to achieve high power even in the Neonatal Research Network, with 21 centers serving large delivery cohorts and referral bases throughout the United States. However, the high rates of potentially catastrophic outcomes associated with hypoxic-ischemic encephalopathy, and reports of initiating hypothermia after 6 hours in a subset of infants with moderate-severe encephalopathy without any systematic study, provided justification to undertake this trial.

With the sample size studied, traditional frequentist analysis identified no significant difference for death or disability between the hypothermic and noncooled groups. A frequentist analysis of an underpowered trial would provide little help for clinicians treating infants with encephalopathy who present beyond 6 hours. However, frequentist analyses do not allow calculation of the probability of a specified benefit while Bayesian methods allow for direct assessment of the probability of treatment effect based on the trial results.[24,25,28] A series of absolute risk differences in death or disability were provided to assess effect size. An absolute risk reduction of 1% or 2% in death or moderate-severe disability may be viewed as clinically important given the seriousness of the outcome. Perinatal and adult therapies have been recommended at a similar low absolute risk reduction for major adverse outcomes. A risk reduction of 1.6% for cerebral palsy has been reported among preterm newborns whose mothers were treated with magnesium sulfate,[29] a treatment now widely used in obstetrics.[30] Statins have been recommended in adults with a cardiovascular disease risk of 10% but without cardiovascular disease[31] based on absolute risk reductions of 0.4% and 1.4% for all-cause and composite cardiovascular mortality, respectively.[32]

The reduction in death or disability for hypothermic compared with noncooled infants is suggestive but not conclusive. No evidence of commensurate harm was found. Adverse events, prespecified and those not prespecified, occurred in more hypothermic than noncooled infants but did not differ by frequentist analysis. The number of deaths per group was the same, but the Bayesian analysis indicated the aRR favored hypothermia and the posterior probability of reduced death was 73% under a neutral prior. A decision to use hypothermia at 6 to 24 hours will need to consider the probability of benefit, the frequency of adverse events, and the availability of evidence-based alternative treatments.

In all neonatal trials, hypothermia initiated at less than 6 hours reduced death or disability,[33] and therefore a prior based on an RR between 1.0 (no benefit) and 0.72 (the benefit identified in the previous Neonatal Research Network hypothermia trial[4]) might be considered appropriate. If so, the estimated probabilities for any reduction or a greater than 1% or greater than 2% absolute reduction in death or disability would be somewhat higher and intermediate between the estimates using a neutral prior and those using an enthusiastic prior. Given these considerations, estimated probabilities based on a neutral prior could be considered conservative. Since the initiation of this trial, there is little new information on late hypothermia treatment to provide an estimate of treatment effect. A trial from China randomized 93 newborns within 10 hours of birth to hypothermia or normothermia; only 9 infants received hypothermia between 6 and 10 hours.[34] Single-center and registry data reported initiation of hypothermia after 6 hours but did not provide treatment effect.[15,35]

Hypoxic-ischemic encephalopathy resulting in moderate or severe disability is a devastating outcome. The results of this trial should not change the priority of early identification of infants with hypoxic-ischemic encephalopathy and initiation of hypothermia at less than 6 hours. This trial provides an approach to estimate the treatment effect for uncommon diseases in the largest feasible clinical trial and avoid the biases inherent in observational studies.

Limitations

This study has several limitations. During this trial, the Neonatal Research Network initiated the Optimizing Cooling trial to study longer (120 hours) or deeper (32°C) cooling initiated at less than 6 hours of age.[36,37] The Optimizing Cooling trial was stopped early partly owing to safety concerns for increased in-hospital mortality among infants cooled for 120 rather than 72 hours. Whether the current trial results would differ if the intervention was shortened to 72 hours cannot be answered. Elevated esophageal temperature occurred among noncooled infants and such temperatures have been associated with a greater risk of death or disability in prior trials.[38-40] The algorithm used in noncooled infants largely mitigated the extent and duration of esophageal temperatures greater than 37.3°C compared with the earlier Neonatal Research Network hypothermia trial.[4] Also, the reason for presentation at or beyond 6 hours was not always known.

Conclusions

Among term infants with hypoxic-ischemic encephalopathy, hypothermia initiated at 6 to 24 hours after birth compared with noncooling resulted in a 76% probability of any reduction in death or disability, and a 64% probability of at least 2% less death or disability at 18 to 22 months. Hypothermia initiated at 6 to 24 hours after birth may have benefit but there is uncertainty in its effectiveness.

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Obtained funding: Shankaran, Bell, Ambalavanan, Hensman, Walsh, Faix, Frantz III, Truog, Carlton, Cotten, Sánchez.

Administrative, technical, or material support: Bell, Goldberg, Chaudhary, Hensman, Chalak, Khan, Hamrick, Faix, Devaskar, Chock, Wyckoff, McGowan, Carlton, Hibbs, Higgins.

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