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Whole-Body Hypothermia for Neonatal Encephalopathy in Preterm Infants 33 to 35 Weeks' Gestation
A Randomized Clinical Trial

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IMPORTANCE Hypothermia begun less than 6 hours after birth reduces death or disability in infants with encephalopathy due to hypoxia-ischemia at 36 or more weeks' gestation. Trials of hypothermia for infants younger than 36 weeks' gestation are lacking.

OBJECTIVE To assess the probability that hypothermia at less than 6 hours after birth decreases death or disability in infants 33 to 35 weeks' gestation with moderate or severe hypoxic-ischemic encephalopathy.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial was conducted between July 2015 and December 2022 for infants 33 to 35 weeks' gestation with moderate or severe hypoxic-ischemic encephalopathy at less than 6 hours after birth. Bayesian and intention-to-treat analyses were prespecified. The setting included 19 US Neonatal Research Network centers. Data were analyzed from March 2023 to November 2024.

INTERVENTIONS Infants received unblinded targeted esophageal temperature management. Infants with hypothermia were maintained at 33.5 °C (acceptable 33-34 °C) for 72 hours and then rewarmed. Infants with normothermia were to be maintained at 37 °C (acceptable 36.5-37.3 °C).

MAIN OUTCOMES AND MEASURES Composite of death or disability (moderate or severe) at 18 to 22 months' corrected age adjusted for level of encephalopathy and center.

RESULTS A total of 168 infants with hypothermia and normothermia were preterm (mean [SD] age, 34.0 [0.8] weeks' gestation and 34.1 [0.8] weeks' gestation, respectively), while 46 of 88 (52%) and 45 of 80 (56%) were male, respectively. Randomization occurred at mean (SD) 4.5 (1.2) hours and 4.5 (1.3) hours for the groups with hypothermia and normothermia, respectively. The primary outcome occurred in 29 of 83 infants (35%) with hypothermia and 20 of 69 infants (29%) with normothermia (adjusted relative risk [hypothermic/normothermic], 1.11; 95% credibility interval, 0.74-2.00), and death occurred in 18 of 88 infants (20%) with hypothermia and 9 of 78 infants (12%) with normothermia (adjusted relative risk, 1.38; 95% credibility interval, 0.79-2.85). Bayesian analysis with neutral prior indicated 74% probability of increased death or disability and 87% probability of increased death with hypothermia.

CONCLUSIONS AND RELEVANCE Among infants 33 to 35 weeks' gestation with hypoxic-ischemic encephalopathy, hypothermia at less than 6 hours' age did not reduce death or disability at 18 to 22 months' corrected age.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01793129

Visual Abstract

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The members of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network appear in Supplement 4.

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Perinatal hypoxia-ischemia (HI) is a major cause of brain injury and death at all gestational ages (GAs). The only effective treatment supported by multiple randomized clinical trials (RCTs) is therapeutic hypothermia for infants 36 weeks' GA and older.[1-5] Despite minimal evidence for efficacy and safety at less than 36 weeks, use of hypothermia in such infants has increased.[6,7] Multiple reports describe such experience without randomized controls.[8-11] Infants with GA younger than 36 weeks may be at increased risk for problems that may be triggered or respond adversely to therapeutic hypothermia (eg, intracranial hemorrhage, necrotizing enterocolitis, coagulopathy, shock) as well as death.

We conducted a randomized clinical trial to assess effectiveness and safety of therapeutic hypothermia in infants 33 to 35 weeks' GA. We hypothesized that therapeutic hypothermia (esophageal temperature [Tes] 33.5 °C) for 72 hours will decrease death or moderate/severe disability at 18 to 22 months' corrected age in infants with moderate or severe encephalopathy due to HI at less than 6 hours of age compared with infants treated with targeted normothermia (Tes, 37.0 °C)

Key Points

Question Does hypothermia initiated at less than 6 hours after birth reduce the probability of death or disability at 18 to 22 months' corrected age in infants 33 to 35 weeks' gestation with neonatal encephalopathy due to hypoxia-ischemia?

Findings In this bayesian randomized clinical trial of 168 newborns of 33 to 35 weeks' gestation with hypoxic-ischemic encephalopathy, treatment with hypothermia resulted in a 74% probability of increased death or disability and 87% probability of increased death at 18 to 22 months' corrected age.

Meaning This trial provided no evidence that hypothermia begun at less than 6 hours after birth in infants 33 to 35 weeks' gestation with hypoxic-ischemic encephalopathy decreases death or disability at 18 to 22 months' corrected age.

Methods

Ethics Approval

Study documents and consent forms were reviewed and approved by the institutional review boards at all participating institutions. Written informed consent by a parent or legal guardian was required. The trial protocol and statistical analysis plan are available in Supplement 1 and Supplement 2, respectively. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Inclusion and Exclusion Criteria

Many features of this trial were similar to previous therapeutic hypothermia trials conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN).[2,12,13] All infants admitted to neonatal intensive care units (NICUs) of participating centers at 33-0/7 to 35-6/7 weeks' GA by best obstetrical estimate and less than 6 hours of age with a diagnosis of encephalopathy, perinatal asphyxia, neurologic depression, or similar condition were screened for eligibility. Inclusion criteria required both (1) blood pH (cord or neonatal at <1 hour) of 7.0 or less or base deficit greater than or equal to 16 mEq/L or, if no blood gas or lesser acidosis (pH 7.01-7.15 or base deficit 10.0-15.9 mEq/L), an acute perinatal event with either 10-minute Apgar score of 5 or less or ventilation initiated at birth and continued for 10 minutes or longer and (2) moderate or severe encephalopathy using modified Sarnat score assessed by certified examiners or clinical seizures at less than 6 hours.[2,12,13] Clinical seizures did not require electroencephalography confirmation. Because of concern about changes in Sarnat scoring attributable to prematurity, abnormal level of consciousness (moderate or severe) was required to be present. Similarly, criteria for posture and Moro reflex were modified to account for maturational changes between 33 and 35 weeks' GA.[14] Exclusion criteria included the following: (1) core temperature less than 34.0 °C for greater than 1 hour before screening, (2) receipt of paralytic or sedative agents obscuring Sarnat examination, (3) encephalopathy unlikely due to HI, (4) major anomaly, (5) moribund and not receiving intensive care, (6) birth weight less than 1500 g, and (7) clinician-declined enrollment. Thermal management before randomization was per practice at each center. Passive cooling (ie, withholding external heat) during transport was discouraged. Randomization was performed by telephone with the Research Triangle Institute data center using computer-generated randomized permutated block algorithm with block sizes 2 and 4 in 1:1 ratio and stratified for encephalopathy level (moderate vs severe) and center. Participants belonged to the following parent- or guardian-identified races and ethnicities: Black, Hispanic, White, and other, which included Asian, Native American, Pacific Islander, and unspecified. Race and ethnicity were reported as required for clinical studies funded by the National Institutes of Health.

Materials and Measures

After randomization, all infants underwent placement of a temperature monitoring probe in the distal esophagus. Placement time was considered time 0. By 108 hours, esophageal probes were removed and further thermal management implemented per local practice.

Those randomized to hypothermia underwent whole-body cooling with a Blanketrol Hyper-Hypothermia II or III device (Cincinnati Subzero). This device was used with an US Food and Drug Administration investigational device exemption because of the study population GA. Target Tes was 33.5 °C (range, 33.0-34.0 °C) for 72 hours. Rapid cooling with this device is accompanied by a transient Tes decrease below the target (overshoot) followed by warming to return to target, then maintained. Overshoot occurs most often with cooling initiation. Tes in this group was recorded every 15 minutes for the first 4 hours, every hour for the next 8 hours, and every 2 hours for the remaining intervention period. Rewarming proceeded at 0.5 °C per hour.

Those randomized to normothermia had a target Tes of 37.0 °C. Temperature monitoring was similar except for hourly temperatures during the first 4 hours. Skin temperature associated with Tes 37.0 °C for individual infants was identified

and servo-controlled by radiant warmer or incubator to maintain Tes 36.5 to 37.3 °C. Because of the association of hyperthermia with adverse outcomes, steps were incorporated to minimize hyperthermia in this group.[15-17] If Tes greater than 37.3 °C occurred, standard thermoregulatory management was verified. If Tes was greater than 37.5 °C, a single tepid sponge bath was implemented, and if unsuccessful, active cooling with the Cincinnati Subzero cooling blanket was implemented until the target Tes was attained.

Cranial ultrasound was required within 24 hours of randomization, and brain magnetic resonance imaging (MRI) was required at 7 to 21 days postnatal age in survivors. MRI results will be reported separately. Laboratory and imaging studies were obtained per standard care. Infants were not fed during the intervention. Other aspects of management such as sedation/analgesia, respiratory support, and anticonvulsant therapy were managed by local standards.

Primary Outcome

The primary outcome was death or disability (severe or moderate) at 18 to 22 months' corrected age. Certified examiners trained to reliability perform assessments at follow-up were blinded to group assignment, including postdischarge history, growth, neurologic examination, Bayley Scales of Infant Development third edition (Bayley III), Gross Motor Function Classification System level (GMFCS), and vision and hearing status. Severe disability was deemed present by any of the following: Bayley III cognitive score less than 70, GMFCS level 3 to 5, blindness, or hearing loss with inability to hear commands despite amplification. Moderate disability was defined by a cognitive score of 70 to 84 and any of GMFCS level 2, treated seizure disorder, or hearing loss requiring amplification or implant to understand commands. Infants with cognitive score greater than or equal to 85 and no deficits were considered normal.

Secondary Outcomes

Prespecified secondary outcomes included death alone, severe or moderate disability only, death or profound disability (defined as severe disability with assignment of lowest possible cognitive score because infant untestable due to impairment), survival with normal outcome, each component of severe and moderate disability, and cause of death.

Safety

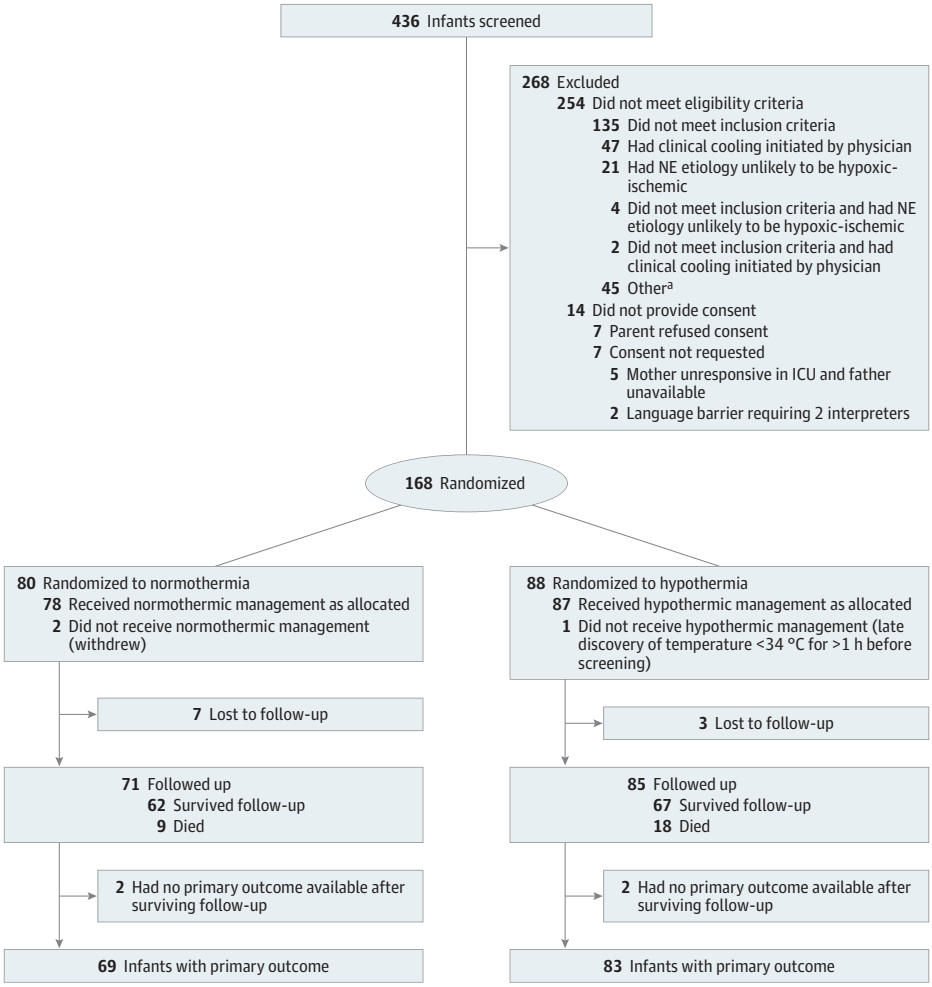
Adverse events included arrhythmia requiring treatment, persistent metabolic acidosis, thrombosis, bleeding, altered skin integrity, and death as in prior NRN hypothermia trials.[2,12,13] Additionally, intracranial hemorrhage, seizures after randomization, necrotizing enterocolitis of Bell stage greater than or equal to II,[18] spontaneous intestinal perforation, major bleeding (prompting blood product administration), thrombocytopenia (<100,000/mm^3), hypoglycemia (<30 mg/dL), hyperglycemia (>180 mg/dL), bronchopulmonary dysplasia, pulmonary hypertension, late-onset culture-proven bloodstream infection, esophageal probe injuries, receipt of extracorporeal membrane oxygenation, abnormalities of electrolytes, calcium, phosphorus, or magnesium, and other morbidities were prospectively tracked. The NRN data safety monitoring committee (DSMC) reviewed cumulative outcomes and adverse events at 6 specified intervals during the trial: after 20, 40, 60, 80, 100, and 130 infants reached NICU discharge, were alive in the NICU at 60 days, or had died by 60 days.

After its third review of cumulative data on September 17, 2017, the DSMC requested additional measures to prevent or correct Tes less than 32 °C. The following steps were implemented: (1) change precooling blanket before intervention from 5 to 15 °C, (2) immediate notification of research staff if Tes less than 32.0 °C, (3) Tes recorded every 10 minutes until target Tes attained, and (4) documentation of corrective actions.

Statistical Analysis

Intention-to-treat analyses were prespecified. Using retrospective review of NICU admission records at participating centers in 2012, the number of eligible infants for a 5-year period was estimated to approach 170. Simulations showed that the trial design had greater than 75% chance of observing final posterior probability of less than or equal to 0.80 for relative risk less than 1, when true relative risk is near 0.70. The trial was designed using bayesian principles to assess primary and other outcomes. The bayesian approach assesses probability of treatment benefit/harm based on observed data and allows for formal inclusion of any prior data.[19,20] Binary outcomes were modeled using logistic regression, and predicted outcome probabilities were postprocessed using the method of Gelman to estimate posterior distribution of relative risk and risk difference (RD).[21] Models were adjusted for level of encephalopathy and center as random effects. Posterior distributions of adjusted risk ratio (aRR) and adjusted RD (aRD) were used to estimate 95% credibility intervals (CrIs) and posterior probabilities of benefit/harm for outcomes. aRR was determined using hypothermia group results as numerator and normothermia as denominator, and aRD was determined by subtracting normothermia results from those of the hypothermia group. Neutral prior for aRR (centered on 1.0, with 50% prior probability of better outcome and 50% of worse outcome) was preselected given no preexisting trials for this intervention in the target GA range. Prespecified assessments of enthusiastic (centered on aRR 0.75) and skeptical (centered on aRR 1.1) prior probabilities were also conducted. These priors and CrIs were based on largest effect sizes identified for major outcomes in randomized trials and exclude implausible effect sizes.[22] For death or severe disability and other binary outcomes, the 3 priors were centered at −0.29, 0, and 0.10, respectively, on the log odds ratio (OR) scale, with 95% CrIs on that scale of −1.39 to 1.39 for neutral, −1.67 to 1.10 for enthusiastic, and −1.29 to 1.48 for skeptical. To produce neutral prior for aRR within a linear regression model, a normal prior with mean 0 and SD 0.71 was placed on the treatment parameter in the logistic regression. Probability of treatment benefit and harm was assessed by determining areas under the posterior probability distribution curve with aRR less than 1.0 and greater than 1.0. All analyses were conducted in SAS, version 9.4 (SAS Institute), or R, version 4.2.2 (R Project for Statistical Computing), and all models were assessed for convergence using visual observation of trace plots within SAS and Gelman-

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) Flow Diagram



[a]Other reasons for noneligibility included 14 with major anomaly, 12 unable to randomize by 6 hours postnatal age, 7 with equipment/staff unavailable, 6 moribund and not receiving intensive care, 3 with temperature lower than 34 °C for more than 1 hour, 2 requiring extracorporeal membrane oxygenation, and 1 with no acute perinatal event. ICU indicates intensive care unit; NE, necrotizing enterocolitis.

Rubin statistics based on 3 Markov chain Monte Carlo chains. Data were analyzed from March 2023 to November 2024.

Results

From July 2015 to September 2020, 168 infants were randomized (**Figure 1**), 88 to the hypothermia cohort (mean [SD] age, 34.0 [0.8] weeks' gestation; 42 female [48%]; 46 male [52%]) and 80 to the normothermia cohort (mean [SD] age, 34.1 [0.8] weeks' gestation; 35 female [44%]; 45 male [56%]). Infants in the hypothermic cohort were parent or guardian identified as the following races and ethnicities: 27 Black (31%), 15 Hispanic (17%), 52 White (59%), and 9 other (10%). Infants in the normothermic cohort were parent or guardian identified as the following races and ethnicities: 31 Black (39%), 10 Hispanic (12%), 42 White (52%), and 7 other (9%). No participant qualified by clinical seizures alone. One infant randomized to hypothermia did not receive that intervention due to late discovery of temperature less than 34 °C for more than 1 hour before screening but was analyzed as receiving hypothermia per intention to treat. Of those randomized to normothermia, 2 were withdrawn by parents immediately after randomization but before intervention and were not analyzed beyond features present at randomization.

Demographic and clinical characteristics of mother and infant before randomization were similar between the groups (**Table 1**). Mean (SD) Tes of the 2 groups during the intervention demonstrated expected differences (hypothermia, 33.4 [0.2] °C vs normothermia, 37.2 [0.2] °C) (eFigure in the Supplement 3). In the normothermia group, 16 infants met the threshold for treatment of Tes greater than 37.5 °C.

The last patient completed follow-up in December 2022. Follow-up intended for 18 to 22 months was delayed in 52 infants due to the COVID-19 pandemic-related restrictions. In those cases, data from the earliest delayed follow-up visit were used; mean (SD) corrected age for these infants was 26 (4) months (range, 23-40 months). One infant whose age exceeded Bayley III examination limit was considered lost to follow-up.

Randomization occurred at mean (SD) 4.5 (1.2) hours and 4.5 (1.3) hours for the groups with hypothermia and normothermia, respectively. The primary outcome of death or moderate/severe disability occurred in 29 of 83 infants (35%)

Table 1. Maternal and Neonatal Characteristics at Randomization

Maternal	No./total No. (%)	
	Infant	
	Hypothermic (n = 88)	Normothermic (n = 80)
Age, mean (SD), y	30.9 (6.1)	28.8 (6.4)
Married	43/88 (49)	47/80 (59)
Race[a]		
Black	27/88 (31)	31/80 (39)
White	52/88 (59)	42/80 (52)
Other[b]	9/88 (10)	7/80 (9)
Ethnicity		
Hispanic[a]	15/88 (17)	10/80 (12)
Gravida, median (IQR), No. of pregnancies	3 (2-5)	2 (2-4)
No.	87	80
Parity, median (IQR), No. of births	2 (1-3)	2 (1-3)
No.	87	80
Education		
High school or less	20/83 (24)	22/73 (30)
Any college or more	63/83 (76)	51/73 (70)
Pregnancy complications		
Preeclampsia/hypertension	32/87 (37)	31/78 (40)
Antepartum hemorrhage	25/87 (29)	21/79 (27)
Thyroid dysfunction	4/87 (5)	8/77 (10)
Diabetes	21/88 (24)	22/77 (29)
Intrapartum complications		
Fetal decelerations	69/87 (79)	57/79 (72)
Cord mishap	9/86 (10)	7/78 (9)
Uterine rupture	6/86 (7)	1/78 (1)
Maternal fever (temperature, 37.6 °C)	2/84 (2)	3/75 (4)
Placental problem (any)	38/86 (44)	36/78 (46)
Abruption	35/86 (41)	36/78 (46)
Previa	1/86 (1)	0/78 (0)
Accreta	1/86 (1)	0/78 (0)
Maternal trauma	1/86 (1)	5/79 (6)
Maternal hemorrhage	17/85 (20)	16/78 (20)
Shoulder dystocia	3/86 (4)	3/78 (4)
Rupture of membranes, yes	36/81 (44)	20/75 (27)
Duration, median (IQR), h before delivery	4.2 (0.3-27.6)	1.5 (0.1-13.3)
No.	32	19
≤18 h	22/32 (69)	16/19 (84)
>18 h	10/32 (31)	3/19 (16)
Histologic chorioamnionitis	11/59 (19)	7/45 (16)
Emergent cesarean delivery	68/88 (77)	67/80 (84)
Infant		
Gestational age, mean (SD), wk	34.0 (0.8)	34.1 (0.8)
Birth weight, mean (SD), g	2464 (634)	2371 (608)
Length, mean (SD), cm	46.0 (3.2)	45.1 (2.8)
No.	86	76
Head circumference, mean (SD), cm	32.0 (1.8)	31.7 (1.8)
No.	86	77
Male	46/88 (52)	45/80 (56)
Outborn	47/88 (53)	47/80 (59)
Delivery room resuscitation		
Intubation	56/88 (64)	50/79 (63)
Chest compressions	40/88 (46)	30/79 (38)
Epinephrine	26/88 (30)	26/79 (33)
Time to spontaneous breaths, median (IQR), min	2.0 (1.0-3.0)	2.0 (1.0-3.0)
No.	80	74
Apgar score <5		
At 5 min	54/86 (63)	48/79 (61)
At 10 min	36/70 (51)	29/67 (43)
Cord blood or if unavailable, neonatal blood gas at <1 h postnatal age		
Mean (SD), pH	6.9 (0.2	6.9 (0.2)
No.	69	68
Mean (SD), base deficit	17.7 (7.0)	17.0 (7.7)
No.	60	59
Age at randomization, mean (SD), h	4.5 (1.2)	4.5 (1.3)
Level of encephalopathy		
Moderate	61/88 (69)	57/80 (71)
Severe	27/88 (31)	23/80 (29)
Clinical seizures at randomization	14/88 (16)	11/80 (14)

[a] Race and ethnic group were reported by parent or guardian.

[b] Other race includes Asian, Native American, Pacific Islander, and unspecified.

randomized to hypothermia vs 20 of 69 infants (29.0%) randomized to normothermia (**Table 2**). aRR using neutral prior probability was 1.11 (95% CrI, 0.74-2.00), yielding probability of benefit, 26%, and of harm, 74% (**Figure 2**). eTable 1 in Supplement 3 presents analyses using skeptical and enthusiastic priors. Death occurred in 18 of 88 infants (20%) with hypothermia and 9 of 78 infants (12%) with normothermia (aRR for death alone, 1.38; 95% CrI, 0.79-2.85) with probability of benefit, 13%, and of harm, 87%. Assessment for treatment heterogeneity with hypothermia revealed benefit probability 38% for males and 25% for females, and this probability was 35% for White infants and 11% for Black infants. Stratification by GA in exploratory analysis revealed higher incidence of primary outcome in hypothermic infants at each GA and of death at each GA except 33 weeks (eTable 2 in Supplement 3).

In exploratory analysis, it was noted that 32 infants randomized to hypothermia and 1 to normothermia attained Tes less than 32 °C during the intervention (with duration <1 hour in 26). Exclusion of all such infants (eTable 3 in Supplement 3) revealed no clinically important difference between groups for the primary outcome or death alone.

Death was attributed by site investigators to asphyxial brain injury in 15 of 18 infants (83%) in the hypothermia cohort and 5 of 9 infants (56%) in the normothermia cohort. Multiorgan failure was considered cause of death in 2 of 18 infants (11%) in the hypothermia cohort and 2 of 9 infants (22%) in the normothermia cohort. Cause of death in 2 remaining infants in the normothermia cohort were pulmonary hypoplasia with chronic

Table 2. Comparison of Primary and Secondary Outcomes in Infants Using Neutral Prior[a]

Outcome	Group, No./total No. (%)		Bayesian effect	Median (95% CrI)[c,d]	Posterior probability of benefit, %[e]
	Hypothermia (n = 88)	Normothermia (n = 78)[b]			
Primary outcome					
Death or moderate or severe disability	29/83 (35)	20/69 (29)	aRD	0.04 (−0.08 to 0.18)	26
			aRR	1.11 (0.74 to 2.00)	26
Secondary outcomes[f]					
Any death	18/83 (22)	9/69 (13)	aRD	0.05 (−0.05 to 0.26)	13
			aRR	1.38 (0.79 to 2.85)	13
Survival with moderate or severe disability	11/83 (13)	11/69 (16)	aRD	−0.02 (−0.15 to 0.09)	68
			aRR	0.86 (0.46 to 1.63)	68
Death or severe disability	27/83 (32)	20/69 (29)	aRD	0.02 (−0.11 to 0.15)	38
			aRR	1.05 (0.67 to 1.82)	38
Death or moderate or severe disability with initial moderate NE	9/56 (16)	6/48 (12)	aRD	0.03 (−0.09 to 0.14)	32
			aRR	1.18 (0.59 to 2.41)	32
Death or moderate or severe disability with initial severe NE	20/27 (74)	14/21 (67)	aRD	0.06 (−0.14 to 0.26)	28
			aRR	1.09 (0.81 to 1.53)	28
Cause of death: asphyxial brain injury	15/18 (83)	5/9 (56)	aRD	0.10 (−0.13 to 0.36)	18
			aRR	1.17 (0.80 to 2.19)	18
Cause of death: multiorgan failure	2/18 (11)	2/9 (22)	aRD	−0.04 (−0.27 to 0.15)	69
			aRR	0.8 (0.32 to 2.04)	69
Clinical seizures after randomization	13/86 (15)	11/75 (15)	aRD	0.0 (−0.12 to 0.13)	47
			aRR	1.02 (0.55 to 1.92)	47

Abbreviations: aRD, adjusted risk difference; aRR, adjusted risk ratio; NE, neonatal encephalopathy; Pr, posterior probability.

[a] Models adjusted for level of encephalopathy and included center as a random effect.

[b] Excluded 2 withdrawn infants.

[c] Posterior median of probability distribution.

[d] Posterior 95% credible interval.

[e] Posterior probability of benefit due to whole body hypothermia. For relative risk, this is Pr(relative risk <1 | trial data), and for risk difference this is Pr(RD <0 | trial data). For relative risk, the comparison is whole body hypothermia over normothermia; therefore, relative risk values less than 1 indicate benefit for whole body hypothermia. For risk difference, the comparison is whole body hypothermia minus normothermia; therefore, risk difference values less than 0 indicate benefit for whole body hypothermia.

[f] Although profound disability was prespecified as a secondary outcome of interest, only 1 infant (normothermic) met criteria and results are therefore not included in the table.

pulmonary hypertension and severe bronchopulmonary dysplasia, whereas cause in the remaining infant in the hypothermia cohort was cardiomyopathy. All but 2 deaths followed decisions to redirect care or forego resuscitation. Three deaths (2 hypothermia, 1 normothermia) occurred after NICU discharge, including 1 discharged on hospice care. Bayesian analysis with neutral prior indicated 74% probability of increased death or disability and 87% probability of increased death with hypothermia.

The frequency of prespecified nondeath safety events during intervention was generally comparable in the 2 groups (**Table 3**). The posterior probability that hypothermia was beneficial in reducing these events ranged from 25 to 81%, except for hyperglycemia (5%), hyponatremia (1%), days on mechanical ventilation (1%), and hypoglycemia (87%). Details of intracranial hemorrhage on ultrasound before, during, and after the intervention during NICU course are in eTable 4 in Supplement 3. Two normothermic infants had intestinal perforation after intervention, 1 due to spontaneous intestinal perforation and 1 due to previously undiagnosed ileal atresia.

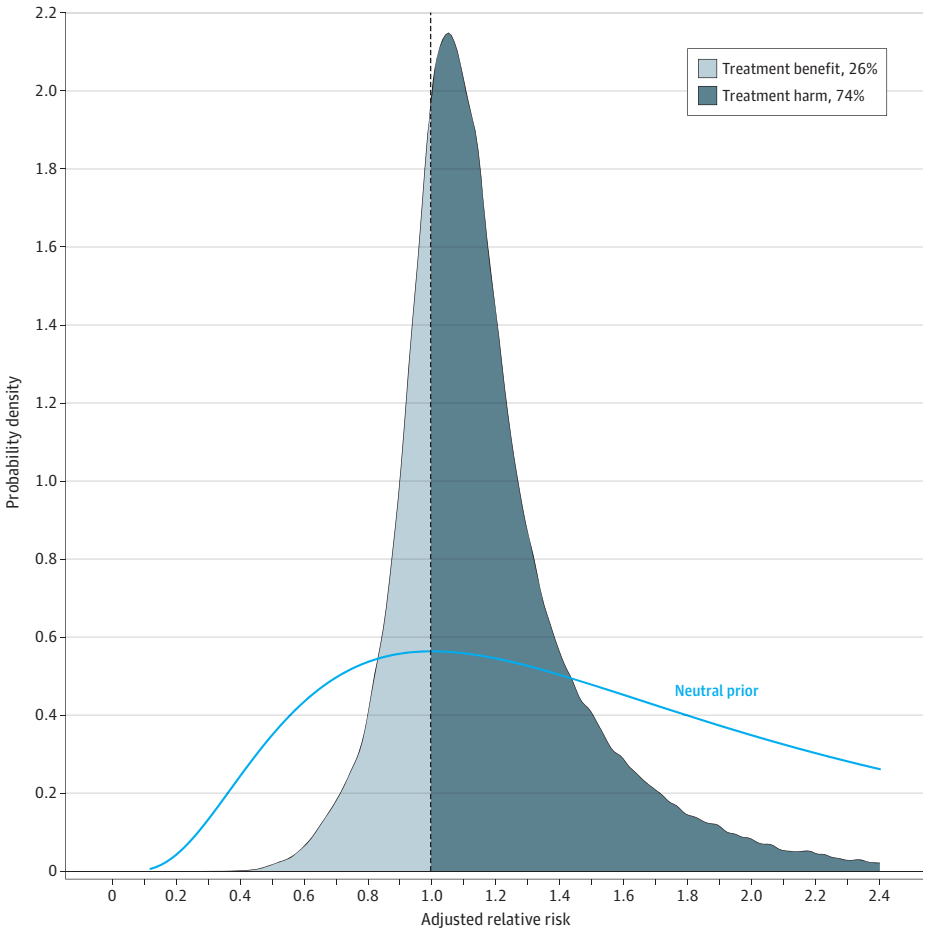
Discussion

Our findings indicate that therapeutic hypothermia initiated by 6 hours postnatal age did not reduce the primary outcome of death or moderate/severe disability or death alone at 18 or more months in infants born at 33 to 35 weeks' GA with moderate or severe neonatal encephalopathy. A 74% probability of treatment harm for the primary outcome and 87% for death alone with hypothermia was observed. Other prespecified safety events were generally comparable between groups. Although survival with moderate or severe disability appeared to be slightly better in the hypothermic group, the absolute difference was small (13 vs 16%), and this potential small benefit was accompanied by a much higher incidence of death.

Most studies demonstrating effectiveness of hypothermia for neonatal encephalopathy limited their population to 36 weeks' GA or older.[1-5] Two RCTs with follow-up at 12 to 24 months included enrollment at 35 weeks, but the publications did not specify how many such infants were included nor their outcomes.[23-25] The American Academy of Pediatrics Committee of Fetus and Newborn considered 1 of those trials in their 2014 recommendation for hypothermia in infants 35 weeks' GA and older.[26] Personal communication in 2014 with the authors of those 2 RCTS revealed the total number of 35 weeks' GA infants in those studies to be 7, with 2 randomized to control (1 death, 1 normal survivor) and 5 to cooling (2 deaths, 2 survivors with moderate disability, 1 normal survivor). Unlike those 2 trials, our trial required abnormal level of consciousness and may select sicker patients. Our findings for 48 infants born at 35 weeks' GA provide no support for hypothermia at that GA.

Reasons for absent benefit with hypothermia among preterm infants in our trial are unclear and may be multifactorial. First, developmental differences may alter risk-benefit balance with hypothermia compared with infants 36 weeks' GA or older. Second, antepartum environment and perinatal events may differ between preterm and term infants. Rates of placental abruption were more than 3-fold higher in the present study than in the nEuro trial (11.6% with placental problems, including abruption) and Late Hypothermia trial (11.3%).[5,12]

Figure 2. Posterior Probability of Relative Risk for Primary Outcome



Relative risk = probability with hypothermia/probability with normothermia.

Maternal hypertensive disorders were 2-fold higher than in the Late Hypothermia trial (17.8%).[12] Finally, protocol-directed correction of hyperthermia in the normothermic group may have altered outcomes. Noncooled comparison groups from prior RCTs that experienced higher core temperatures were associated with increased risk of death or moderate/severe disability.[15-17] The effect of measures to avoid high Tes in our normothermic infants is unclear.

The observation that many infants randomized to hypothermia attained Tes less than 32.0 °C. during the intervention is not surprising since preterm infants in general are known to have limited thermoregulatory ability. It is unclear if increased frequency of primary outcome and death alone seen in those infants reflects a direct effect of overshoot or if overshoot is simply a marker for infants who had sustained more severe hypoxic-ischemic insult and were at higher risk for adverse outcomes. Newer generations of whole-body cooling devices are reported by manufacturers to have reduced likelihood of overshoot but it is unknown if that will yield any meaningful difference in outcomes. It is noteworthy in our study that if all infants with Tes less than 32.0 °C. are excluded, there was still no notable benefit with hypothermia.

Prospective estimates of the incidence of neonatal encephalopathy among infants 33 to 35 weeks' GA are lacking. A single-center retrospective review of such infants who fulfilled inclusion criteria for a prior hypothermia trial estimated an incidence of 5 per 1000 live births.[27] Studies of neonatal encephalopathy at 33 to 35 weeks' GA will thus have limited sample size given the small number of births at these GAs compared with trials enrolling infants 36 weeks' GA and older even with multiple, large referral centers. Frequentist analysis with typical assumptions of types I and II error and outcome difference require a larger number of subjects than this multi-site study could accrue over 5 years. Bayesian analysis is particularly recommended for uncommon conditions to provide an estimate of the probability of benefit or harm due to an intervention based on trial results combined with preexisting data.[19,20] Estimating the probability of benefit or harm may yield meaningful information to clinicians, patients, and family.

Strengths and Limitations

This study offers significant information that may strongly influence clinical practice. It offers strengths of being a

Table 3. Neonatal Safety Events During Intervention Period (Relative Risk: Hypothermic/Normothermic Groups)

Adverse event during intervention	No./total No. (%)		Posterior probability of benefit, %	Posterior aRR (95% CrI)
	Hypothermic (n = 88)	Normothermic (n = 78)		
Arrhythmia needing treatment	1/88 (1.1)	1/78 (1.3)	54	0.95 (0.33-2.73)
Persistent metabolic acidosis[a]	4/88 (4.5)	5/78 (6.4)	65	0.84 (0.35-1.99)
Thrombosis	0/88 (0)	0/78 (0)	Cannot be estimated	Cannot be estimated
Intracranial bleeding[b]	6/88 (8)	5/78 (8)	53	1.03 (0.46- 2.33)
Major bleeding	1/88 (1.1)	4/78 (5.1)	81	0.65 (0.24-1.69)
Thrombocytopenia	11/88 (12.5)	12/78 (15.4)	67	0.87 (0.44-1.67)
Treatment with vasopressors	28/88 (32)	23/78 (30)	43	1.03 (0.65-1.71)
Treatment with steroids	9/75 (12)	7/70 (10)	38	1.12 (0.54-2.38)
Oliguria/anuria[c]	6/85 (7)	3/74 (4)	30	1.24 (0.53-2.98)
Liver dysfunction[d]	40/88 (46)	38/78 (49)	68	0.94 (0.67-1.26)
Serum sodium <120 mEq/L	8/88 (9)	0/78 (0)	4	2.25 (0.94-5.90)
Serum sodium >150 mEq/L	5/88 (6)	1/78 (1)	20	1.51 (0.59-3.92)
Serum potassium <3.0 mEq/L	21/88 (24)	22/78 (28)	72	0.87 (0.55-1.38)
Serum potassium >6.0 mEq/L	16/88 (18)	19/78 (24)	80	0.80 (0.47-1.34)
Serum calcium <7.0 mg/L	29/82 (35)	26/71 (37)	57	0.97 (0.66-1.43)
PPHN	5/88 (5.7)	4/78 (5.1)	48	1.03 (0.43-2.48)
Hyperglycemia	20/88 (22.7)	9/78 (11.5)	5	1.64 (0.92-3.27)
Hypoglycemia	1/88 (1.1)	5/78 (6.4)	87	0.58 (0.22-1.48)
NEC	0/88 (0)	0/78 (0)	Cannot be estimated	Cannot be estimated
Esophageal probe issue	0/88 (0)	0/78 (0)	Cannot be estimated	Cannot be estimated
ECMO	0/88 (0)	0/78 (0)	Cannot be estimated	Cannot be estimated
Altered skin integrity				
Erythema	4/88 (4)	1/78 (1)	25	1.38 (0.53-3.73)
Sclerema	0/88 (0)	0/78 (0)	Cannot be estimated	Cannot be estimated
Cyanosis	1/88 (1)	0/78 (0)	Cannot be estimated	Cannot be estimated
Subcutaneous fat necrosis	0/88 (0)	0/78 (0)	Cannot be estimated	Cannot be estimated
For entire hospitalization				
Late-onset sepsis[e]	1/88 (1)	1/78 (1)	55	0.94 (0.32-2.71)
Oxygen, median (IQR), d	4 (0-29)	2 (0-87)	55	0.98 (0.70-1.37)
Mechanical ventilation, median (IQR), d	3.5 (0-64)	2 (0-57)	1	1.43 (1.08-1.90)
Length of hospital stay in survivors, median (IQR), d	22 (7-73)	22.5 (6-115)	32	1.04 (0.87-1.24)
No.	67	60	NA	NA

Abbreviations: aRR, adjusted relative risk; CrI, credibility interval; ECMO, extracorporeal membrane oxygenation; NA, not applicable; NEC, necrotizing enterocolitis; PPHN, pulmonary hypertension.

SI conversion factor: To convert calcium to millimoles per liter, divide by 10 and multiply by 0.25; potassium and sodium to millimoles per liter, multiply by 1.

[a] Blood pH less than 2 SD and base deficit greater than 2 SD from time-specific values developing more than 3 hours after beginning of intervention period and persisting more than 3 hours.

[b] Includes intraventricular, parenchymal, and cerebellar hemorrhage found on cranial ultrasound during or after intervention period, because cannot exclude possibility that hemorrhage detected after intervention actually occurred during the intervention.

[c] Oliguria less than 0.5 mL/kg/h.

[d] Liver dysfunction any of aspartate aminotransferase level greater than 200 IU/L, alanine aminotransferase level greater than 100 IU/L, or direct bilirubin level greater than 1.5 mg/dL.

[e] Positive blood culture at greater than 3 days of age.

pragmatic randomized clinical trial conducted prospectively in 19 centers, well-defined inclusion and exclusion criteria, certified examiners to determine degree of encephalopathy at randomization, standardized interventions including steps to avoid confounding hyperthermia in the normothermic arm, systematic follow-up by certified examiners blinded to treatment assignment, and use of intention-to-treat design. Limitations include moderate sample size, inability to assign primary outcome to 11% of normothermic and 6% of hypothermic infants, loss to follow-up of more patients in the normothermic than hypothermic group, an intervention that was unblinded to clinicians (although follow-up investigators were unaware of treatment assignment), and the fact that 47 infants were excluded from the study by clinicians opting for hypothermia without randomization (mean [SD] GA, 34.8 [0.6] weeks).

Conclusions

This randomized clinical trial provided evidence for no benefit from hypothermia in infants 33 to 35 weeks' GA with moderate or severe hypoxic-ischemic encephalopathy. Indeed, our findings suggest that it may increase death or

impairment. In the absence of strong supportive evidence from future trials, use of hypothermia is not indicated in infants born with hypoxic-ischemic encephalopathy at 35 weeks' GA or younger.

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