ORIGINAL ARTICLE

Whole-Body Hypothermia for Neonates with Hypoxic–Ischemic Encephalopathy

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ABSTRACT

BACKGROUND

Hypothermia is protective against brain injury after asphyxiation in animal models. However, the safety and effectiveness of hypothermia in term infants with encephalopathy is uncertain.

METHODS

We conducted a randomized trial of hypothermia in infants with a gestational age of at least 36 weeks who were admitted to the hospital at or before six hours of age with either severe acidosis or perinatal complications and resuscitation at birth and who had moderate or severe encephalopathy. Infants were randomly assigned to usual care (control group) or whole-body cooling to an esophageal temperature of 33.5°C for 72 hours, followed by slow rewarming (hypothermia group). Neurodevelopmental outcome was assessed at 18 to 22 months of age. The primary outcome was a combined end point of death or moderate or severe disability.

RESULTS

Of 239 eligible infants, 102 were assigned to the hypothermia group and 106 to the control group. Adverse events were similar in the two groups during the 72 hours of cooling. Primary outcome data were available for 205 infants. Death or moderate or severe disability occurred in 45 of 102 infants (44 percent) in the hypothermia group and 64 of 103 infants (62 percent) in the control group (risk ratio, 0.72; 95 percent confidence interval, 0.54 to 0.95; P=0.01). Twenty-four infants (24 percent) in the hypothermia group and 38 (37 percent) in the control group died (risk ratio, 0.68; 95 percent confidence interval, 0.44 to 1.05; P=0.08). There was no increase in major disability among survivors; the rate of cerebral palsy was 15 of 77 (19 percent) in the hypothermia group as compared with 19 of 64 (30 percent) in the control group (risk ratio, 0.68; 95 percent confidence interval, 0.38 to 1.22; P=0.20).

CONCLUSIONS

Whole-body hypothermia reduces the risk of death or disability in infants with moderate or severe hypoxic–ischemic encephalopathy.

AMONG TERM INFANTS, HYPOXIC–ischemic encephalopathy due to acute perinatal asphyxia remains an important cause of neurodevelopmental deficits in childhood. Infants with moderate encephalopathy have a 10 percent risk of death, and those who survive have a 30 percent risk of disabilities. Sixty percent of infants with severe encephalopathy die, and many, if not all, survivors are handicapped.[1,2] Treatment is currently limited to supportive intensive care.

Reductions in brain temperature by 2°C to 5°C provide neuroprotection in newborn and adult animal models of brain ischemia.[3-10] Brain cooling has a favorable effect on multiple pathways contributing to brain injury, including excitatory amino acids,[11] the cerebral energy state,[12] cerebral blood flow and metabolism,[13] nitric oxide production,[11] and apoptosis.[14] Brain cooling is effective in reducing the extent of brain injury even when it is initiated up to 5.5 hours after brain ischemia in near-term sheep fetuses.[10] We have previously demonstrated the feasibility of whole-body cooling in a pilot study of neonates with hypoxic–ischemic encephalopathy.[15] Therefore, we conducted a randomized, controlled trial to evaluate whether whole-body cooling initiated before 6 hours of age and continued for 72 hours in term infants with encephalopathy would reduce death or disability at 18 to 22 months of age as compared with infants given usual care.

METHODS

A committee of the principal investigators from participating sites developed a manual of operations that specified neurologic criteria for eligibility and details of the cooling and rewarming procedure. Each principal investigator certified additional neonatologists to perform the neurologic examination, and a training session for research personnel was held to standardize all study procedures. The protocol was approved by the institutional review board at each site.

SCREENING

Infants were screened for eligibility if they had a gestational age of at least 36 weeks and were admitted to the neonatal intensive care unit at six hours of age or less with either poor respiratory effort at birth and a need for resuscitation or a diagnosis of encephalopathy.

INCLUSION CRITERIA

Infants were evaluated according to physiological criteria and subsequently by a neurologic examination.[15] Eligibility criteria included a pH of 7.0 or less or a base deficit of 16 mmol per liter or more in a sample of umbilical-cord blood or any blood during the first hour after birth. If, during this interval, a pH was between 7.01 and 7.15, a base deficit was between 10 and 15.9 mmol per liter, or a blood gas was not available, additional criteria were required. These included an acute perinatal event (e.g., late or variable decelerations, cord prolapse, cord rupture, uterine rupture, maternal trauma, hemorrhage, or cardiorespiratory arrest) and either a 10-minute Apgar score of 5 or less or assisted ventilation initiated at birth and continued for at least 10 minutes.

Once these criteria were met, all infants underwent a standardized neurologic examination performed by a certified examiner. Infants were candidates for the study when encephalopathy or seizures were present. Encephalopathy was defined as the presence of one or more signs in at least three of the following six categories (Table 1): level of consciousness, spontaneous activity, posture, tone, primitive reflexes (suck or Moro), and autonomic nervous system (pupils, heart rate, or respiration). The number of moderate or severe signs determined the extent of encephalopathy; if signs were equally distributed, the designation was based on the level of consciousness. Exclusion criteria were

Table 1. Criteria for Defining Moderate and Severe Encephalopathy.

Category	Moderate Encephalopathy	Severe Encephalopathy
Level of consciousness	Lethargic	Stupor or coma
Spontaneous activity	Decreased activity	No activity
Posture	Distal flexion, complete extension	Decerebrate
Tone	Hypotonia (focal or general)	Flaccid
Primitive reflexes		
Suck	Weak	Absent
Moro	Incomplete	Absent
Autonomic system		
Pupils	Constricted	Deviated, dilated, or nonreactive to light
Heart rate	Bradycardia	Variable
Respiration	Periodic breathing	Apnea

Table 2. Maternal and Neonatal Characteristics.*

Characteristic	Hypothermia Group (N=102)	Control Group (N=106)
Maternal		
Race — no. (%)†		
Black	32 (31)	40 (38)
White	40 (39)	32 (30)
Other	30 (29)	34 (32)
Maternal age — yr	27±6	27±7
Married — no. (%)	60 (60)	55 (53)
Gravida — median no.	2	2
Parity — median no.	2	2
Complications of pregnancy — no. (%)		
Chronic hypertension	12 (12)	14 (13)
Antepartum hemorrhage	10 (10)	20 (19)
Thyroid disease	1 (1)	1 (1)
Diabetes	8 (8)	9 (8)
Intrapartum complications — no. (%)‡		
Fetal heart rate decelerations	74 (73)	79 (75)
Cord prolapse	23 (23)	14 (13)
Uterine rupture	16 (16)	13 (12)
Maternal pyrexia	12 (12)	9 (9)
Shoulder dystocia	11 (11)	9 (8)
Maternal hemorrhage	6 (6)	8 (8)
Labor — hr	12±7	12±11
Rupture of membranes — hr	6±9	6±12
Emergency cesarean delivery — no. (%)	72 (71)	80 (75)

an inability to enroll by six hours of age, a major congenital abnormality, a severe growth restriction (birth weight of ≤1800 g), and refusal of consent by a parent or an attending neonatologist; moribund infants for whom no further aggressive treatment was planned also were excluded.

TREATMENT ASSIGNMENT

Written informed consent was obtained from the parents of 208 of 239 eligible infants. Consent was not requested from 16 mothers, parents refused consent for 10 infants, and physicians opposed the enrollment of 5 infants. After informed consent was obtained from a parent, the assignment to a treatment group was performed randomly by telephone by the data-coordinating center (RTI International). Assignments were stratified according to center and were generated by a random, permuted-block algorithm with block sizes of two and four.

Infants in the hypothermia group were placed on an infant-size blanket, 25 in. by 33 in. (64 cm by 84 cm), that was precooled to 5°C (Blanketrol II Hyper-Hypothermia System, Cincinnati Sub-Zero). Blankets and cooling systems were purchased by each site. An esophageal probe was inserted, and the esophageal temperature was lowered to 33.5°C by the blanket's servomechanism. A second blanket, 25 in. by 64 in. (64 cm by 163 cm), was attached to the cooling system. Water circulated simultaneously through both blankets to diminish the variability in the esophageal temperature.[15] Neither an overhead warmer nor any other heat source was used during the cooling period. Abdominal-wall skin temperature was monitored with a skin probe by means of either the radiant warmer (with the heater turned off) or the temperature-monitoring unit (Mon-a-therm, Mallinckrodt Medical). Esophageal and skin temperatures were monitored continuously and recorded every 15 minutes for the first 4 hours, every hour for the next 8 hours,

Table 2. (Continued.)

Characteristic	Hypothermia Group (N=102)	Control Group (N=106)
Neonatal		
Age at randomization — hr	4.3±1.3	4.3±1.2
Transferred from birth hospital — no. (%)	48 (47)	45 (42)
Male sex — no. (%)	51 (50)	67 (63)
Apgar score ≤5 — no. (%)		
At 5 min	92 (91)	97 (92)
At 10 min	80 (84)	74 (77)
Birth weight — g	3385±617	3370±645
Length — cm	51±3	51±3
Head circumference — cm	34±2	34±2
Intubation in delivery room — no. (%)	97 (95)	98 (92)
Continued resuscitation at 10 min — no. (%)	95 (93)	100 (94)
Time to spontaneous respiration ≥10 min — no. (%)	69 (71)	71 (71)
Cord blood		
pH	6.9±0.2	6.8±0.2
Base deficit — mmol/liter	18.5±6.7	19.9±8.7
Seizures — no. (%)§	44 (43)	51 (48)
Moderate encephalopathy — no. (%)§	69 (68)	66 (62)
Severe encephalopathy — no. (%)§	32 (32)	40 (38)
Inotropic support — no. (%)§	33 (33)	26 (25)
Anticonvulsants — no. (%)§	42 (44)	42 (45)

* Plus–minus values are means ±SD. Percentages are based on the number of mothers or infants for whom data were available. Because of rounding, not all percentages sum to 100.
† Race was determined by interviewing the mothers.
‡ Seventy infants (39 in the hypothermia group and 31 in the control group) had more than one intrapartum complication at birth. Intrapartum complications included antepartum hemorrhage (placenta previa, placental abruption, or threatened abortion resulting in bleeding that was external [vaginal bleeding] or occult [retroplacental clot] after 20 weeks of gestation); maternal hemorrhage (acute bleeding at delivery from placenta previa or placental abruption); and maternal pyrexia (temperature ≥37.6°C).
§ Data are for this characteristic at the time of randomization. One infant in the hypothermia group qualified with seizures but was missing a neurologic examination to permit classification of the extent of encephalopathy.

and every 4 hours during the remaining period of cooling.

After 72 hours of hypothermia, the set point of the automatic control on the cooling system was increased by 0.5°C per hour. After six hours, the esophageal probe was removed, and skin temperature was controlled by the radiant warmer's servomechanism. The temperature of the warmer was set 0.5°C higher than the skin temperature and was increased 0.5°C every hour until the set point of the warmer reached 36.5°C. Infants received routine clinical care, including the monitoring of vital signs and surveillance for organ dysfunction. Blood-gas measurements in the hypothermia group were corrected for body temperature.

Infants in the control group were cared for on overhead radiant warmers with abdominal-wall skin and esophageal temperatures recorded every four hours. Skin temperature was maintained by the servomechanism between 36.5°C and 37.0°C initially, and subsequent adjustments were made according to usual care at each center. Infants in the control group received the same monitoring of vital signs and surveillance for organ dysfunction as did the infants in the hypothermia group.

ADVERSE EVENTS

During the 72-hour intervention period, infants in both groups were monitored for cardiac arrhythmia, persistent acidosis, major-vessel thrombosis or

bleeding, skin changes, and death. Any equipment malfunction also was noted. All adverse events were reported within 72 hours to the institutional review board at the site and to the data center.

FOLLOW-UP

The primary outcome was death or disability (moderate or severe). All surviving infants were evaluated at 18 to 22 months of age; the families of those who did not return for follow-up were contacted by telephone to obtain information about the primary outcome. Data on growth, vision, and audiometric characteristics were obtained, and neurologic and developmental testing were performed by trained examiners who were blinded to intervention status. An assessment of neuromotor disability was based on the presence of cerebral palsy, and functional disability was graded according to the Gross Motor Function Classification System (GMFCS)[16] (level 1 includes children who walk independently with some gait abnormalities; level 2 includes those who are unable to walk but who can sit, pull to standing, and cruise [take steps holding on to furniture]; level 3 includes those who are unable to walk or crawl, use hands for sitting support; level 4 includes those for whom support is needed for sitting; and level 5 includes those who require adult assistance to move). Cognitive outcome was assessed with the use of the Bayley Scales of Infant Development II,[17] where a mean (±SD) score of 100±15 was normal on the Mental Development Index and Psychomotor Developmental Index. Severe disability was defined as any of the following: a Bayley Mental Development Index score more than 2 SD below the mean score (i.e., below 70), a GMFCS grade of level 3 to 5, hearing impairment requiring hearing aids, or blindness. Moderate disability was defined as a Mental Development Index score 1 to 2 SD below the mean score (i.e., 70 to 84) in addition to one or more of the following: a GMFCS grade of level 2, hearing impairment with no amplification, or a persistent seizure disorder.

STATISTICAL ANALYSIS

A requirement for a sample size of 104 infants in each group was based on a two-tailed type 1 error rate of 0.05, a statistical power of 80 percent, a 10 percent loss to follow-up, and an incidence of death or disability in the control group of 50 percent and a reduction to 30 percent in the intervention group. All data analyses were performed according to the intention-to-treat principle. The data were analyzed for treatment group differences with chi-square or Fisher's exact tests for the categorical variables and with t-tests for the continuous variables. The data for the primary and secondary outcomes were analyzed by the Mantel–Haenszel test, with adjustment according to center. An external data and safety monitoring committee monitored safety and efficacy during three interim analyses. All reported P values are two-sided and not adjusted for multiple comparisons.

RESULTS

The 15 participating centers of the National Institute of Child Health and Human Development Neonatal Research Network recruited subjects between July 2000 and May 2003. Of 798 infants who were screened, 239 were eligible and 208 were enrolled (102 in the hypothermia group and 106 in the control group). Baseline characteristics were similar in the two groups (Table 2). Cooling was initiated in the hypothermia group at a median of 35.5 minutes after randomization and at an average of 302 minutes after birth.

MONITORING OF INFANTS

The mean esophageal temperature at baseline was 36.6±1.0°C among the infants in the hypothermia group (Fig. 1A). After an initial overshoot to a mean of 32.7°C, the target temperature of 33.5°C was achieved within 90 minutes and remained constant throughout the intervention period (mean, 33.4±0.9°C; 25th and 75th percentiles, 33.2°C and 33.5°C). In the control group, the mean esophageal temperature was 37.2±0.6°C during the same interval (25th and 75th percentiles, 36.9°C and 37.5°C). Esophageal temperatures in the control group exceeded 38°C on at least one measurement in 41 infants. The mean skin temperature was 31.9±1.4°C in the hypothermia group and 36.5±0.8°C in the control group during the intervention period (Fig. 1B). The mean heart rate was similar in the two groups before the intervention. It decreased in the hypothermia group during cooling to a mean of 109 beats per minute but remained greater than 140 beats per minute in the control group (Fig. 1C). Blood pressure was similar in the two groups (data not shown).

ADVERSE EVENTS AND FOLLOW-UP

The incidence of serious adverse events was similar in the hypothermia and control groups (Table 3).

Figure 1. Mean Esophageal (Panel A) and Abdominal-Wall Skin (Panel B) Temperatures and Heart Rate (Panel C) during the 72-Hour Intervention Period.

T bars represent standard deviations. Infants in the hypothermia group were placed on precooled blankets at baseline and were rewarmed after 72 hours of cooling.

The median age at follow-up was 19.8 months in the hypothermia group (follow-up rate, 100.0 percent) and 20.2 months in the control group (follow-up rate, 95.6 percent). The follow-up visits for the study ended in December 2004.

PRIMARY OUTCOME

Primary outcome data were available for 205 of the 208 enrolled infants. Three infants in the control group were lost to follow-up. Death or moderate or severe disability occurred in 45 of 102 infants (44 percent) in the hypothermia group and 64 of 103 infants (62 percent) in the control group (relative risk after adjustment according to center, 0.72; 95 percent confidence interval, 0.54 to 0.95; number needed to treat, 6) (Table 4). The protective effect of hypothermia persisted after adjustment according to center and the severity of encephalopathy at randomization (relative risk, 0.76; 95 percent confidence interval, 0.60 to 0.97). A test of homogeneity of risk ratios across the centers revealed no significant interaction among treatments according to center (P=0.25). There was also no significant interaction between treatment and the severity of encephalopathy at enrollment (P=0.36). Results stratified according to the initial severity of encephalopathy (moderate or severe) are shown in Table 4.

There were 24 deaths in the hypothermia group and 38 deaths in the control group (relative risk, 0.68; 95 percent confidence interval, 0.44 to 1.05) (Table 4). In the hypothermia and control groups, respectively, the rates of disabling cerebral palsy were 19 and 30 percent, the rates of blindness were 7 and 14 percent, and the rates of hearing impairment requiring aids were 4 and 6 percent (the P values for all comparisons were not significant). The proportion of infants with scores of 85 or more, 70 to 84, or below 70 on either the Mental Development Index or the Psychomotor Developmental Index also did not differ significantly between the groups.

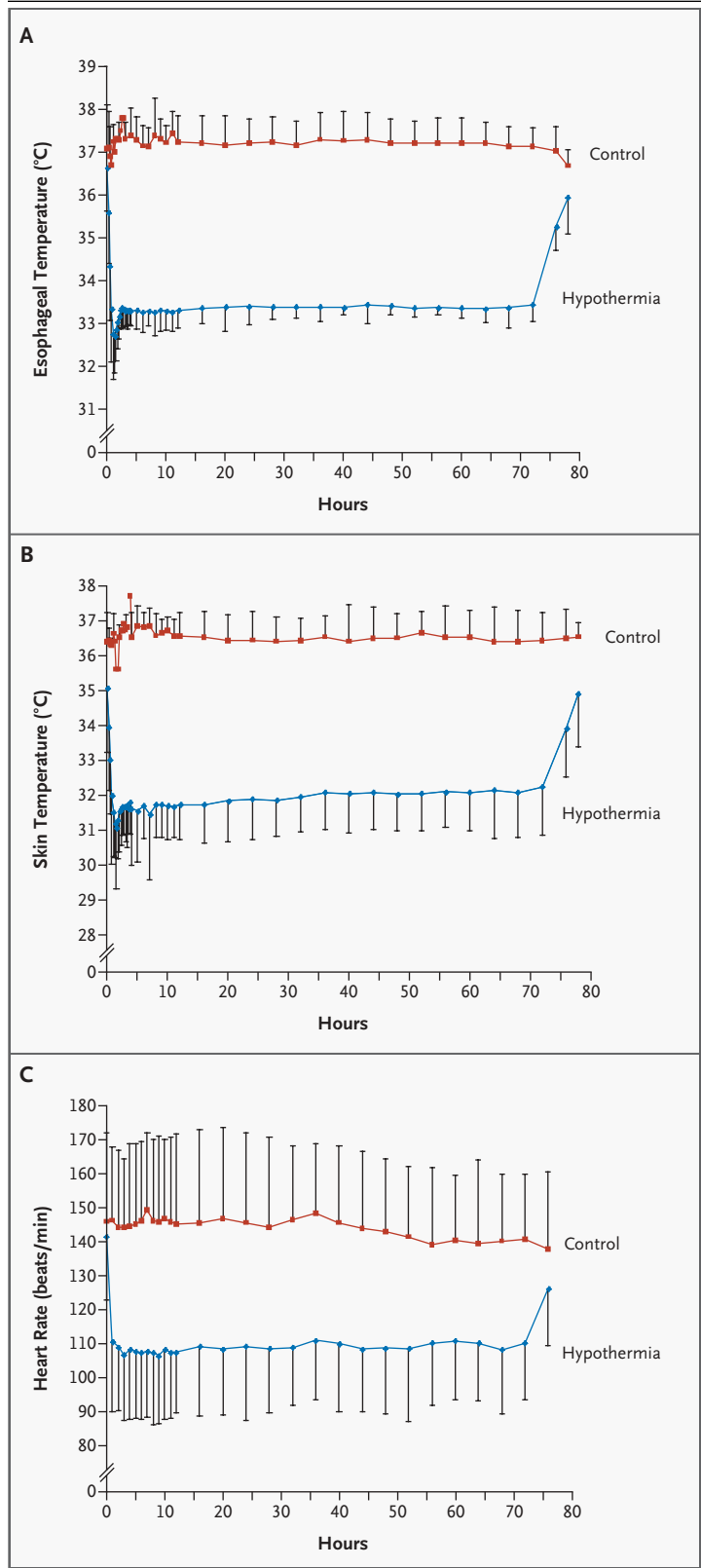The distribution of age at death according to

Table 3. Hospital Course and Status at Discharge.*		
Variable	Hypothermia Group (N=102)	Control Group (N=106)
Adverse event		
During 72-hr intervention — no. (%)		
Cardiac arrhythmia†	1 (1)	1 (1)
Persistent acidosis‡	2 (2)	0
Bleeding§	3 (3)	2 (2)
Skin changes¶	4 (4)	0
Death	13 (13)	11 (10)
During hospital course — no. (%)‖		
Hypotension treated with vasopressors	42 (42)	35 (33)
Cardiac arrhythmia†	2 (2)	1 (1)
Persistent pulmonary hypertension	25 (25)	23 (22)
Oliguria	16 (16)	23 (22)
Anuria	6 (6)	4 (4)
Hepatic dysfunction**	20 (20)	16 (15)
Bloodstream infection	5 (5)	6 (6)
Disseminated intravascular coagulopathy	18 (18)	12 (11)
Hypoglycemia††	12 (12)	16 (15)
Hypocalcemia‡‡	28 (28)	20 (19)
Death	19 (19)	29 (27)
Days receiving oxygen	8.0±11.7	8.0±8.6
Length of stay — days§§	19.9±15.0	20.9±18.0
Discharge status — no. (%)§§		
Gavage feeding	9 (11)	5 (7)
Gastrostomy tube feeding	6 (7)	12 (17)
Seizures requiring anticonvulsants	31 (38)	28 (40)

* Plus–minus values are means ±SD. Percentages are based on the number of infants for whom data were available.

† Cardiac arrhythmia was defined as sustained bradycardia (one infant in the hypothermia group) or ventricular tachycardia (one infant each in the hypothermia and control groups).

‡ Persistent acidosis was defined as metabolic acidosis with a pH of less than 7.15 that persisted for more than three hours after the initiation of intervention.

§ Bleeding was defined as overt bleeding with a platelet count of less than 40,000 per liter with abnormal results on coagulation studies.

¶ Four infants in the hypothermia group had skin changes. Erythema, sclerema (hardening of subcutaneous tissue), cyanosis, and subcutaneous fat necrosis each occurred in one infant; these changes resolved spontaneously without scarring.

‖ The hospital course was defined as the period between randomization and discharge.

** Hepatic dysfunction was defined as an aspartate aminotransferase level above 200 IU and an alanine aminotransferase level above 100 IU.

†† Hypoglycemia was defined as a blood glucose level of less than 30 mg per deciliter (1.7 mmol per liter).

‡‡ Hypocalcemia was defined as a blood calcium level less than 8 mmol per liter.

§§ This variable applies to surviving infants only; 83 infants in the hypothermia group and 77 in the control group survived to initial hospital discharge.

treatment group is shown in Figure 2. Support was withdrawn from 12 infants in the hypothermia group (9 during the 72-hour intervention and 3 later during hospitalization) and 27 in the control group (10 during the intervention period, 15 later during hospitalization, and 2 after the initial hospitalization). The most frequent diagnosis for which support was withdrawn was asphyxial brain injury (8 of 12 infants in the hypothermia group and 18 of 27 in the control group).

DISCUSSION

As compared with usual care, whole-body cooling to an esophageal temperature of 33.5°C initiated within the first 6 hours after birth and continued for 72 hours reduced the rate of death or moderate or severe disability in term newborns with encephalopathy in this study. Hypothermia has been widely studied as a neuroprotective strategy in newborn and adult animals after ischemia and hypoxia–ischemia. In perinatal animals (sheep, rats, and piglets[7-10,18,19]), hypothermia has been beneficial when implemented up to 5.5 hours after brain ischemia.[10]

The eligibility criteria for this trial were designed to include infants with acute hypoxic–ischemic encephalopathy as indicated by profound fetal acidemia or infants with the need for resuscitation after acute hypoxic events. The trial was also designed to select infants who had a high probability of a poor outcome (i.e., death or disability). In the control group, the incidence of death or disability was 48 percent in the subgroup of infants with moderate encephalopathy at enrollment and 85 percent in the subgroup of infants with severe encephalopathy. In this study, the classification of encephalopathy as moderate or severe during the first hours after birth predicted outcome as readily as assessments later in the first week.[1,2]

The brain can be cooled by cooling the body, cooling the head selectively, or cooling the head and body together. The majority of studies in animals have used whole-body cooling,[3-8,11-14,18,19] but some have used selective head cooling.[9,10,20-24] Whole-body cooling provides homogeneous cooling to all brain structures, including peripheral and central brain regions.[25] Selective head cooling provides greater cooling to the periphery of the brain than to the central brain structures[25]; head cooling combined with some body cooling minimizes temperature gradients across the brain and facilitates

Table 4. Outcome at 18 to 22 Months of Age.*

Variable	Hypothermia Group (N=102)	Control Group (N=106)	Relative Risk (95% CI)†	P Value
	no. (%)			
Primary outcome				
Death or moderate or severe disability‡	45 (44)	64 (62)	0.72 (0.54–0.95)	0.01
Secondary outcomes				
Death	24 (24)	38 (37)	0.68 (0.44–1.05)	0.08
Death or disability§				
Among infants with moderate encephalopathy	22 (32)	30 (48)	0.69 (0.44–1.07)	0.09
Among infants with severe encephalopathy	23 (72)	34 (85)	0.85 (0.64–1.13)	0.24
Survival	78 (76)	68 (66)		
Bayley Mental Development Index score¶				
≥85	39 (52)	25 (40)	1.24 (0.83–1.83)	0.27
70–84	17 (23)	13 (21)	1.08 (0.57–2.05)	0.81
<70	19 (25)	24 (39)	0.71 (0.43–1.17)	0.18
Bayley Psychomotor Developmental Index score‖				
≥85	46 (62)	34 (55)	1.10 (0.82–1.48)	0.53
70–84	8 (11)	6 (10)	1.19 (0.38–3.76)	0.77
<70	20 (27)	22 (35)	0.80 (0.48–1.33)	0.39
Disabling cerebral palsy**	15 (19)	19 (30)	0.68 (0.38–1.22)	0.20
Blindness††	5 (7)	9 (14)	0.50 (0.17–1.44)	0.20
Severe hearing impairment **	3 (4)	4 (6)	0.54 (0.10–3.02)	0.47

* Percentages are based on the number of infants for whom data were available.
† Relative risks shown are adjusted according to center. CI denotes confidence interval.
‡ Data were unobtainable for three patients in the control group. Severe disability was defined as any of the following: Mental Development Index score below 70, Gross Motor Function Classification System (GMFCS) grade level 3 to 5, hearing impairment requiring hearing aids, or blindness. Moderate disability was defined as a Mental Development Index score of 70 to 84 and one or more of the following: GMFCS grade of level 2, hearing impairment with no amplification, or a persistent seizure disorder.
§ Sixty-nine infants in the hypothermia group and 63 in the control group had moderate encephalopathy, and 32 infants in the hypothermia group and 40 in the control group had severe encephalopathy.
¶ Data were unavailable for 3 of 78 infants who survived in the hypothermia group and 6 of 68 who survived in the control group.
‖ Data were unavailable for four infants in the hypothermia group and six in the control group.
** Data were unavailable for one infant in the hypothermia group and four in the control group.
†† Data were unavailable for three infants in the hypothermia group and five in the control group.

the cooling of central regions.[24] Given the propensity for hypoxic–ischemic injury to affect deep-brain structures such as the thalamus, internal capsule, and basal ganglia in the human neonate,[26-28] we chose whole-body cooling to achieve a consistent reduction in brain temperature in such structures. The target temperature of 33.5°C was selected on the basis of studies in animals[3] that showed attenuation of brain injury at this temperature without the adverse effects (e.g., myocardial injury) that occur at lower temperatures.[29]

The cooling system used in this study was easily initiated, achieved the target temperature rapidly, and required minimal effort by providers to monitor the temperature. These features are important, given that the intervention was initiated within a defined time interval and maintained for 72 hours. Cooling was well tolerated and not associated with an increase in death or serious adverse events.

If esophageal temperature is a proxy for the core temperature of the brain, the observation that more than one third of the infants in the control group had an elevated esophageal temperature on at least one occasion suggests that brain temperatures may
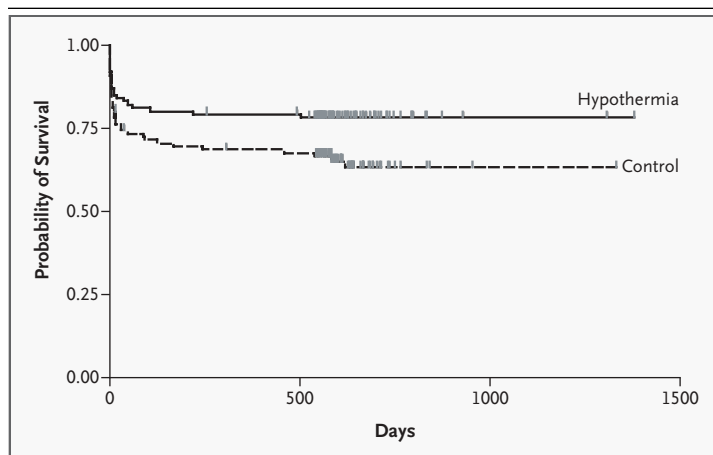
Figure 2. Kaplan–Meier Estimates of Survival.

The relative risk of death in the hypothermia group as compared with the control group was 0.68 (95 percent confidence interval, 0.44 to 1.05; P=0.08). Data for all infants who did not die were censored; censoring is indicated by tick marks. In the hypothermia group, 19 infants died from the following causes during the initial hospitalization: asphyxial brain injury (12 infants), multiorgan failure (2), asphyxial brain injury and multiorgan failure (2), persistent pulmonary hypertension of the newborn (1), disseminated intravascular coagulopathy and asphyxial brain injury (1), and unknown (1). Five infants died from the following causes after hospital discharge: sudden infant death syndrome (1), respiratory failure or aspiration pneumonia (2), multiorgan failure (1), and unknown (1). In the control group, 29 infants died from the following causes during the initial hospitalization: asphyxial brain injury (22), multiorgan failure (1), persistent pulmonary hypertension of the newborn (2), meconium aspiration syndrome (1), asphyxial brain injury and meconium aspiration syndrome (1), and sepsis (2). Nine infants died from the following causes after hospital discharge: respiratory failure or aspiration pneumonia (5), multiorgan failure (1), and unknown (3).

have risen intermittently in these infants. This study cannot establish a causal relationship between an elevated esophageal temperature and brain injury. An elevated brain temperature may result from brain injury, and conversely, a moderate increase in brain temperature can exacerbate hypoxic–ischemic brain injury.[30,31]

A concern with any therapy that reduces mortality among infants at high risk of death and disability is the possibility of an increase in the number of infants who survive with disabilities. In our study, there was no evidence of increased rates of moderate or severe disability at 18 to 22 months of age among infants treated with hypothermia. The rates of disabling cerebral palsy were 19 percent in the hypothermia group and 30 percent in the control group, and the rates of a Mental Development Index below 70 were 25 percent and 39 percent, respectively.

Recently, the results of a large, randomized, controlled trial of selective head cooling with systemic hypothermia (rectal temperature, 34°C to 35°C for 72 hours) (the Cool-Cap Trial)[32] and a pilot trial of body cooling (rectal temperature, 33°C for 48 hours)[33] have been published. The Cool-Cap Trial demonstrated a benefit associated with selective head cooling among infants with moderate abnormalities on an amplitude-integrated electroencephalogram (aEEG) at enrollment,[32] whereas the pilot trial of body cooling showed protection among all infants studied.[33] The eligibility criteria in our study did not make use of the aEEG, although data are accumulating to support the possibility that aEEG results predict outcomes after perinatal hypoxia–ischemia.[34,35] The criteria we used for eligibility are assessed easily by clinicians and do not require the availability of aEEG equipment.

In summary, our findings demonstrate the safety and effectiveness of whole-body cooling in reducing the risk of death or disability among infants with moderate or severe encephalopathy. Rigorous criteria were used to define moderate and severe encephalopathy, and we used certified examiners and trained personnel to implement and monitor the study interventions and outcome.

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