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Outcomes of Safety and Effectiveness in a Multicenter Randomized, Controlled Trial of Whole-Body Hypothermia for Neonatal Hypoxic-Ischemic Encephalopathy

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Abstract

Background—Whole-body hypothermia reduced the frequency of death or moderate/severe disabilities in neonates with hypoxic-ischemic encephalopathy in a randomized, controlled multicenter trial.

Objective—Our goal was to evaluate outcomes of safety and effectiveness of hypothermia in infants up to 18 to 22 months of age.

Design/Methods—A priori outcomes were evaluated between hypothermia (n = 102) and control (*n* = 106) groups.

Results—Encephalopathy attributable to causes other than hypoxia-ischemia at birth was not noted. Inotropic support (hypothermia, 59% of infants; control, 56% of infants) was similar during the 72-hour study intervention period in both groups. Need for blood transfusions (hypothermia, 24%; control, 24%), platelet transfusions (hypothermia, 20%; control, 12%), and volume expanders (hypothermia, 54%; control, 49%) was similar in the 2 groups. Among infants with persistent pulmonary hypertension (hypothermia, 25%; control, 22%), nitric-oxide use (hypothermia, 68%; control, 57%) and placement on extracorporeal membrane oxygenation (hypothermia, 4%; control, 9%) was similar between the 2 groups. Non–central nervous system organ dysfunctions occurred with similar frequency in the hypothermia (74%) and control (73%) groups. Rehospitalization

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What's Known on This Subject: Term infants with moderate or severe encephalopathy caused by acute perinatal asphyxia are at risk for death and disability in childhood. Hypothermia, either whole-body cooling or selective head cooling, has been found to provide neuroprotection.

What This Study Adds: There are possible adverse effects of cooling in neonates. For the NICHD trial of whole-body cooling for neonatal HIE, we report on outcomes of safety and effectiveness during cooling and at up to 18 months of age.

occurred among 27% of the infants in the hypothermia group and 42% of infants in the control group. At 18 months, the hypothermia group had 24 deaths, 19 severe disabilities, and 2 moderate disabilities, whereas the control group had 38 deaths, 25 severe disabilities, and 1 moderate disability. Growth parameters were similar between survivors. No adverse outcomes were noted among infants receiving hypothermia with transient reduction of temperature below a target of 33.5°C at initiation of cooling. There was a trend in reduction of frequency of all outcomes in the hypothermia group compared with the control group in both moderate and severe encephalopathy categories.

Conclusions—Although not powered to test these secondary outcomes, whole-body hypothermia in infants with encephalopathy was safe and was associated with a consistent trend for decreasing frequency of each of the components of disability.

Keywords

hypoxic-ischemic encephalopathy; whole-body hypothermia; safety; effectiveness

Among term infants, hypoxic-ischemic encephalopathy (HIE) caused by acute perinatal asphyxia remains an important cause of neurodevelopmental deficits in childhood.[1,2] Currently, there is increasing evidence that mild or moderate brain hypothermia reduces brain injury caused by hypoxia and ischemia.[3–7] We have demonstrated that whole-body hypothermia reduces the risk of death or disability in infants with moderate or severe HIE.[6] However, enthusiasm regarding the beneficial effects of hypothermia has been tempered by concerns of safety. These concerns have focused on potential complications involving coagulation and immunologic defects, cardiovascular and pulmonary compromise, metabolic adverse effects, and hematologic effects.[8–13]

In the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network's randomized, controlled trial of whole-body cooling for neonatal HIE, very few adverse events were noted during the 72-hour intervention period.[6] We noted 2 cases of cardiac arrhythmia (1 case in the hypothermia group and 1 in the control group), 2 cases of persistent acidosis (in the hypothermia group), 5 cases of bleeding (3 infants in the hypothermia group and 2 infants in the control group), skin changes (in 4 cooled infants), and 24 deaths (13 in the hypothermia group and 11 in the control group). The objective of the present study was to report other secondary outcomes of safety and effectiveness of whole-body cooling in the trial participants up to 18 to 22 months of age. The trial was not designed to assess harm or adverse events; we acknowledge the limited power to assess adverse events that are infrequent.

Patients and Methods

Data from the NICHD Neonatal Research Network whole-body hypothermia trial were used for this analysis.6 Neonates with either moderate or severe encephalopathy based on a modified Sarnat scoring14 were randomly assigned to whole-body cooling or usual care. Total-body cooling to a temperature of 33.5°C was maintained for 72 hours in the cooled group followed by rewarming at 0.5°C every hour for 6 hours. The primary outcome of the study was either death or moderate or severe disability at 18 to 22 months of age. Severe disability was defined as a Mental Developmental Index (MDI) on the Bayley Scales of Infant Development II[15] of <70 or Gross Motor Functional Classification System (GMFCS)16 rating of 3 to 5 or bilateral blindness or deafness requiring amplification. Moderate disability included an MDI of 70 to 84 and a GMFCS level of 2, a hearing deficit without amplification, or a seizure disorder requiring anticonvulsive therapy at 18 months of age.

To monitor for potential adverse effects of hypothermia, data collected during the 72-hour intervention and rewarming period included blood pressure support and transfusion needs,10

as well as effects of anticonvulsant and analgesic/sedation medications[12,13] on target temperature. In addition, changes in oxygen requirements among those infants diagnosed with persistent pulmonary hypertension of the newborn (PPHN) were collected during the study intervention and rewarming period.

During the hospital stay, our evaluation also included a detailed review of medical charts to identify other potential causes of encephalopathy aside from hypoxia-ischemia that have been noted by other investigators, including infectious, metabolic, and neuromuscular causes or major congenital anomalies.[17,18] In addition, we documented the frequency of multiorgan injury other than the central nervous system (CNS).[2,17,19] Pulmonary involvement included meconium-aspiration syndrome, PPHN (including use of inhaled nitric oxide and placement on extracorporeal membrane oxygenation [ECMO]), chronic lung disease, and/or pulmonary hemorrhage. Cardiac involvement included cardiomegaly, cardiac failure and cardiac dysfunction indicated by echocardiography, cardiac ischemia indicated by electrocardiography, or elevated enzyme levels, hypotension, hypertension, and/or arrhythmia. Renal involvement included oliguria, anuria, and/or dialysis. Gastrointestinal involvement included hepatic dysfunction or necrotizing enterocolitis. Infectious diseases included bloodstream infection, meningitis, or encephalitis. Hematologic dysfunction included disseminated intravascular coagulopathy, and metabolic dysfunction included hypoglycemia, hypocalcemia, and/or hypomagnesemia.

After NICU discharge, data were collected on hospitalizations, growth parameters, and neurologic and developmental outcome (as defined above) at 18 to 22 months of age. Microcephaly was defined as a head circumference below the 10 percentile.

Dichotomous data were compared by using Fisher's exact test, and continuous data were analyzed by linear regression analysis. Relative risks and 95% confidence intervals were obtained by using the Mantel-Haenszel test, with adjustments accounting for center differences. A significance level of $<.05$ was used for comparisons between the 2 treatment groups.

Results

Hospital Stay in the NICU

The diagnosis of encephalopathy at enrollment was confirmed by review of status at death or NICU discharge for all study participants. None of the study infants were diagnosed to have malformations or metabolic or neuromuscular disorders as a cause of encephalopathy despite routine screening with cranial sonography and MRI and intensive assessments before NICU discharge.

In the hypothermia group, the esophageal temperature was noted to be transiently reduced with the initiation of cooling to below the target temperature of 33.5°C.[6] The mean time to initially surpass 33.5°C was 0.9 ± 0.5 hours (range: 0.25–3.50 hours). The mean maximum overshoot below the target temperature was −1.4°C ± 0.6°C (range: 0.0°C−4.1°C). The mean time to maximum overshoot below the target temperature was 1.3 ± 1.0 hours (range: 0.25–8.00 hours). The mean time to equilibration after overshoot (defined as within 0.1°C of target temperature) was 1.9 ± 3.6 hours (range: 0.0–21.0 hours) after initiation of cooling. We noted some unexpected findings: (1) 1 infant never achieved equilibration, and (2) there were 40 temperatures recorded to be <32.0°C after the initial overshoot. There were 27 infants with temperatures of <32.0°C after the initial overshoot and 10 infants who had temperatures of <32.0°C after equilibration.

During the study intervention period, among the infants who were cooled, there were no significant differences in the median or first- and third-quartile esophageal temperatures among

infants who received anticonvulsants and those who did not receive these medications. At 24, 48, and 72 hours, the mean esophageal temperatures were, respectively, 33.4°C, 33.3°C, and 33.4°C among those who received anticonvulsants and 33.3°C, 33.4°C, and 33.3°C among those who did not receive these medications. Similar esophageal temperatures were recorded at 24, 48, and 72 hours among infants who received sedatives and those who did not receive sedatives. In the hypothermia group at the end of the 72-hour intervention of cooling, the mean esophageal temperature was 33.4°C ± 0.4°C. At 76 hours of study intervention, during the rewarming phase, the mean esophageal temperature was 35.3°C ± 0.6°C. At the end of the rewarming phase, at 78 hours of study intervention, the mean esophageal temperature was 35.9°C ± 0.8°C. Because esophageal temperatures were not recorded every 4 hours after 78 hours, information is lacking as to when infants in the hypothermia group reached "normal" esophageal temperatures.

Events that occurred and therapies that were provided during the NICU stay are noted in Table 1. The use of inotropic agents, volume expanders, blood transfusions, or platelet transfusions during the study intervention period was comparable among infants in the hypothermia and control groups. The platelet count at 72 hours of study intervention was a median of 132 in the hypothermia group (quartile 1 to 3: 77–194) and 129 in the control group (quartile 1 to 3: 78–195). The minimum platelet count during the 72-hour period was a median of 139 (quartile 1 to 3: 62–211) and 156 (quartile 1 to 3: 87–202) in the hypothermia and control groups, respectively. The number of infants with clinical seizures at baseline and at 48 and 72 hours of study intervention were similar in the hypothermia group compared with the control group (Table 1). At 24 hours of study intervention, fewer infants in the hypothermia group had seizures as compared with those in the control group.

The number of infants who had any of the 7 organ systems (pulmonary, cardiac, renal, gastrointestinal, infectious, hematologic, and metabolic) involved, in addition to the CNS, was 76 infants in the hypothermia group and 77 in the control group. One-organ-system involvement, in addition to the CNS, was noted among 25 infants in the hypothermia group and 36 in the control group; 2-organ-system involvement was noted among 23 in the hypothermia group and 13 in the control group; and 3-organ-system involvement was noted among 14 in the hypothermia group and 15 in the control group. Seven infants in the hypothermia group had 4 systems involved compared with 10 infants in the control group, and >4-system involvement occurred in 7 infants in the hypothermia group compared with 3 in the control group.

The number of infants diagnosed with PPHN was 25 in the hypothermia group and 23 in the control group (Table 1). The mean fraction of inspired oxygen (FiO_2) requirement among infants with PPHN during the 72-hour intervention period was similar between groups; at 24, 48, and 72 hours, the requirement was, respectively, 0.97, 0.97, and 0.94 in the hypothermia group and 0.90, 0.65, and 0.53 in the control group. The number of infants who received inhaled nitric oxide or who were placed on ECMO was also comparable between the 2 groups.

Nineteen infants had major surgery before NICU discharge; these surgeries included ECMO cannulation in 1 infant in the hypothermia group and 2 in the control group; other procedures among the 16 infants are listed in Table 1.

Rehospitalization and Growth Parameters at 18 Months of Age

The number of infants who were rehospitalized was comparable in both the hypothermia and control groups (Table 2). Growth parameters were also comparable in infants in the hypothermia and control groups. The number of infants who had microcephaly was 22 (30%) of 74 in the hypothermia group and 17 (27%) of 62 in the control group ($P = .77$); microcephaly

noted was observed only at the 18-month visit, because the growth parameters at birth were in the normal range.[6]

Death or Disabilities at 18 Months of Age

The study's primary outcome was death or moderate or severe disabilities at 18 months of age (Table 3). There were 24 deaths in the hypothermia group and 38 in the control group, and there were 19 infants in the hypothermia group diagnosed with a severe disability, whereas 25 infants in the control group were noted to have a severe disability. Severe disabilities among these 44 infants included 34 with an MDI of <70 and at least 1 of the other components of severe disability, 9 infants with only an MDI of <70, and 1 infant with an MDI of 70 to 84 with deafness. Only 3 infants had a moderate disability; 2 infants in the hypothermia group (1 infant with an MDI of 70–84 and hearing impairment with no amplification and the other with an MDI of 70–84 and a GMFCS level 2) compared with 1 infant in the control group (MDI of 70–84 and seizure disorder at 18 months). Among the 29 infants with quadriplegia, additional neurologic findings included truncal hypotonia ($n = 6$), truncal hypotonia with athetosis (2 infants), generalized hypotonia (1 infant), generalized hypertonia (1 infant), athetosis (1 infant), and dystonia (1 infant).

Relationship of Severity of Encephalopathy at Randomization to Outcome at 18 Months of Age

Data were missing from the 3 infants in the control group (lost to follow-up) and 1 infant in the hypothermia group (this infant qualified for study eligibility with seizures at <6 hours of age but did not have a neurologic examination at randomization) (Table 3). Although the study was not powered to evaluate death or disability separately among infants designated as having moderate encephalopathy and severe encephalopathy, there was a consistent trend in the decrease in frequency of disability in the infants in the hypothermia group compared with those in the control group.

Association of Variables Evaluated for Safety with Outcome at 18 to 22 Months of Age

Among the infants in the hypothermia group, the mean time to maximum overshoot at the onset of cooling was not related to the primary outcome (1.2 ± 0.5 hours in infants with the primary outcome compared with 1.4 ± 1.3 hours among those without the primary outcome [$P = .23$]). The mean time to equilibration of target temperature after maximum overshoot also did not impact outcome (2.3 ± 4.1 vs 1.5 ± 3.2 hours with primary outcomes versus without the primary outcome, respectively [$P = .29$]). Last, the outcome of infants in the hypothermia group with an esophageal temperature recorded below 33.5°C was not related to the primary outcome: those with the primary outcome spent 45 ± 21 hours below 33.5°C, whereas those without the primary outcome spent 51 ± 16 hours below 33.5°C (P = not significant).

The presence of non-CNS organ dysfunction during the neonatal course (in addition to HIE) was related to the primary outcome. The risk varied with the organ system involved: pulmonary involvement ($n = 63$) was associated with primary outcome in 65% vs 48% with no pulmonary involvement ($P = .02$). Renal involvement ($n = 44$) was associated with a primary outcome in 68% vs 49% with no renal involvement ($P = .03$); there was a trend for cardiac involvement ($n = 91$) to be associated with the primary outcome in 60% vs 48% with no cardiac involvement ($P = .09$). Gastrointestinal, hematologic, or metabolic problems, in addition to HIE, did not increase the risk of the primary outcome.

Among the outcomes assessed at follow-up, the presence of microcephaly was not associated with treatment group; however, microcephaly was significantly associated with primary outcome in both groups. In the hypothermia group, 82% of the infants with microcephaly had the primary outcome present compared with 6% without microcephaly, whereas in the control

group, 71% with microcephaly had the primary outcome present compared with 27% without microcephaly (all $P < .01$).

Discussion

The data we have presented support the safety of whole-body hypothermia for infants with moderate and severe HIE when adhering to strict entry criteria and cooling initiated within 6 hours of age at participating centers. A relative risk of < 1.0 was identified for death and each of the components of severe disability at 18 to 22 months of age. Our data support the safety of hypothermia during the period of cooling as well as during the NICU hospitalization and follow-up through 18 to 22 months of age.

We did not find any decrease in platelet counts or increase in bleeding episodes among infants in our study. Our protocol did not include investigations to evaluate the coagulation profile or blood viscosity status for all participants. Eicher et al[10] noted a low platelet count on each day of cooling with an increase in platelet count on the fourth day. However, no clinical manifestations of coagulopathy were found in that study. In the same trial, treatment was used for hypotension among more infants in the cooled group as compared with the control group. It should be noted that 77% of the infants who were enrolled in the Eicher et al trial had severe encephalopathy at the time of enrollment, and 75% of the infants were outborn. In the other 2 larger randomized, controlled trials, the CoolCap study and the NICHD trial, infants with severe encephalopathy comprised ~33% of enrolled infants and fewer were outborn compared with the Eicher et al trial.[4,6]

The cardiovascular complications associated with hypothermia in adult cooling trials include pulmonary vasoconstriction, sinus bradycardia, cardiac arrhythmia, and increased blood viscosity.[20–22] All the neonatal cooling studies have documented sinus bradycardia during the period of cooling without significant cardiovascular effects.[4–7,10] A recent study has documented that in term neonates undergoing hypothermia for HIE, cardiac output and stroke volume are both lower during the period of hypothermia and slowly increase to baseline during the rewarming phase.[23] Investigators have also noted that the QT interval can be prolonged with cooling, and hypotension can occur during cooling.[24] We have reported previously that there was no difference between systolic and diastolic blood pressure throughout the period of study intervention.[6] In this study, we observed similar use of inotropic agents, blood transfusions, and volume expanders during the study period in the 2 groups. The number of infants who required aggressive therapy for PPHN, including inhaled nitric oxide or ECMO, was not higher among infants who were cooled as compared with control infants in our study. In addition, we did not find that administration of anticonvulsant drugs or analgesics/sedatives produced decreases in temperature during cooling as noted by others.[12,13] This lack of influence of medications on esophageal temperature may be a result of the cooling system that was servo-controlled and adjusted cooling to maintain a stable temperature.

Hypothermia has profound immunosuppressive and antiinflammatory effects and in adults is associated with increased risk of infectious complications such as pneumonia and bloodstream infection.[20–22] We did not find an increase in the rate of bloodstream infection among the infants who were cooled, either during the intervention period or during the entire hospitalization course.

In this study, we found that fewer infants in the hypothermia group had clinical seizures after 24 hours of study intervention as compared with the control group. We are unable to explain this finding, which is different from the findings of Eicher et al.[10] Video electroencephalography recording was not a part of the protocol; hence, it is likely that the incidence of seizures was underestimated. Recent preclinical studies have noted that

hypothermia delays onset of seizures and reduces seizure incidence and severity, and there have been no experimental data to suggest that hypothermia increases seizures.[25]

Conclusions

The safety of whole-body cooling initiated within 6 hours of age to a depth of 33.5°C for 72 hours' duration has been demonstrated. However, the rate of death and disability continues to be high, even with this safe method of cooling. In the NICHD trial, hypothermia to 33.5°C for 72 hours reduced death and disability of infants with moderate HIE to 32% and severe HIE to 72%. Preclinical data suggest that cooling earlier and to a greater depth may be more effective.[8,26,27] However, the safety of cooling during transport of infants to a referral center has not been evaluated yet.

At the present time, no pharmacologic agent is ready for clinical trials in neonates with HIE.[28] The method of cooling we have described needs to be improved with no/minimal overshoot and rapid achievement and stability of the target temperature. The observation of unexplained transient decreases in esophageal temperature to <32°C during cooling using servo control emphasizes the need to have trained staff available who are well versed with all potential technical problems associated with a cooling regimen. It is also apparent that monitoring of temperatures needs to be continued beyond 6 hours after cessation of cooling and initiation of rewarming, because it is unclear when normal temperature is achieved. We suggest that clinical trials in the future be focused on defining the optimal degree and duration of cooling and rewarming strategies as neuroprotection for neonatal encephalopathy.

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Abbreviations

HIE	hypoxic-ischemic encephalopathy
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
MDI	Mental Developmental Index
GMFCS	Gross Motor Functional Classification System
PPHN	persistent pulmonary hypertension of the newborn
CNS	central nervous system
ECMO	extracorporeal membrane oxygenation

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Table 1

Acute Outcome in the NICU

Parameter	Hypothermia (*N* = 102)	Control Group (*N* = 106)	RR (95% CI)
During study intervention, *n* (%)			
No BP support at any time[a]	41 (41)	44 (44)	0.91 (0.67–1.24)
BP support at any of the 4 time points: baseline or 24, 48, or 72 h	58 (59)	55 (56)	1.07 (0.86–1.34)
BP support throughout 72 h	19 (19)	18 (18)	1.09 (0.60–1.95)
1 medication at each time point	11 (12)	8 (9)	1.31 (0.55–3.11)
1 medication at some time points, >1 at other time points	4 (4)	6 (6)	0.69 (0.21–2.31)
≥2 medications at each time point	4 (4)	4 (4)	1.29 (0.31–5.43)
Volume expanders at any time	55 (54)	52 (49)	1.14 (0.88–1.47)
Blood transfusion at any time	24 (24)	25 (24)	0.98 (0.59–1.61)
Platelet transfusion at any time	20 (20)	13 (12)	1.60 (0.82–3.14)
Seizures, *n* (%)			
At baseline	44 (43)	51 (48)	0.92 (0.70–1.21)
At 24 h	19 (20)	34 (34)	0.62 (0.38–0.99)[b]
At 48 h	13 (14)	20 (22)	0.67 (0.36–1.27)
At 72 h	8 (9)	12 (13)	0.78 (0.33–1.82)
During hospitalization			
PPHN, *n* (%)	25 (25)	23 (22)	1.16 (0.72–1.88)
Among infants with PPHN, *n* (%)			
Inhaled nitric oxide	17 (68)	13 (57)	1.37 (0.85–2.21)
ECMO	1 (4)	2 (9)	0.62 (0.08–4.92)
Bloodstream infection[c]	5 (5)	6 (6)	
Surgery			
Gastric fundoplication	1	0	
Gastrostomy	3	6	
Gastric fundoplication and Gastrostomy	0	4	
Tracheostomy, fundoplication and gastrostomy	0	1	
Other	0	1	

[a] Three hypothermia-group infants and 7 control-group infants had data missing at ≥1 time point.

[b] $P < .05$; the rest were all nonsignificant.

[c] Bloodstream infection includes 1 in hypothermia group and 2 in the control group from samples drawn before study enrollment.

Table 2

Status at 18 Months of Age

Parameter	Hypothermia (*N* = 78)	Control (*N* = 68)	Value
Rehospitalizations, *n* (%)[a]			
Any	21 (27)	26 (42)	0.67 (0.42 to 1.07)[b]
1	8 (12)	14 (28)	0.48 (0.21 to 1.10)[b]
2–3	10 (13)	6 (11)	1.31 (0.52 to 3.29)[b]
>3	3 (4)	6 (10)	0.38 (0.09 to 1.58)[b]
Growth parameters, mean ± SD			
Weight, kg[c]	11.4 ± 1.8	11.0 ± 2.3	0.31 (−0.37 to 0.98)[d]
Height, cm[c]	81.7 ± 5.9	80.0 ± 10.6	1.73 (−1.10 to 4.56)[d]
Head circumference, cm[e]	46.9 ± 5.3	46.7 ± 2.5	0.19 (−1.24 to 1.62)[d]

[a] NICU discharge to follow-up visit. Missing hospitalization data for 6 infants in the control group.

[b] Data shown are RRs (95% CIs).

[c] Data missing for 2 hypothermia and 6 control group infants.

[d] Data shown are the adjusted mean differences.

[e] Data missing for 2 hypothermia and 5 control group infants.

Table 3
Death and Disability at 18 Months

Parameter	Hypothermia (*N* = 102), *n* (%)	Control (*N* = 106), *n* (%)	RR (95% CI)
Death	24 (24)	38 (37)	0.68 (0.44–1.05)
Severe disability	19 (24)	25 (38)	0.67 (0.41–1.10)
Moderate disability	2 (3)	1 (3)	1.11 (0.14–8.45)
Disabling cerebral palsy	15 (19)	19 (30)	0.68 (0.38–1.22)
Spastic quadriplegia	14 (93)	15 (79)	
Hemiplegia	1 (7)	1 (5)	
Triplegia	0 (0)	1 (5)	
Truncal hypotonia and dystonia	0	1	
Generalized hypotonia	0	1	
Completely normal	32 (32)[a]	22 (22)	1.40 (0.88–2.22)
Moderate HIE	69	63	
Death	9 (13)	14 (21)	0.55 (0.25–1.21)
Disabling CP	8 (14)	10 (21)	0.64 (0.25–1.65)
MDI of <70	12 (21)	14 (30)	0.74 (0.35–1.55)
MDI of 70–84	15 (33)	12 (36)	0.87 (0.49–1.54)
Blindness	3 (5)	5 (11)	0.50 (0.12–2.07)
Hearing impairment	7 (12)	5 (10)	1.13 (0.37–3.43)
Deafness	1 (2)	3 (6)	0.24 (0.02–2.54)
Seizures	9 (15)	10 (21)	0.69 (0.27–1.76)
Multiple impairments	9 (15)	10 (20)	0.73 (0.29–1.83)
Completely normal	26 (39)	19 (32)	1.17 (0.73–1.87)
Severe HIE	32	40	
Death	15 (47)	24 (60)	0.80 (0.46–1.40)
Disabling CP	7 (41)	9 (56)	0.70 (0.33–1.51)
MDI of <70	7 (41)	10 (67)	0.71 (0.38–1.33)
MDI of 70–84	2 (20)	1 (20)	
Blindness	2 (13)	4 (25)	0.69 (0.16–2.93)
Hearing impairment	3 (18)	1 (6)	4.00 (0.36–44.11)
Deafness	2 (12)	1 (6)	2.00 (0.13–31.98)
Seizures	4 (24)	4 (29)	0.79 (0.22–2.90)
Multiple impairments	6 (35)	9 (56)	0.70 (0.33–1.51)
Completely normal	5 (16)	3 (8)	1.67 (0.43–6.56)

Primary outcome was missing for 3 control infants. MDI was unavailable for 3 hypothermia-group and 6 control-group infants. CP and deafness information was unavailable for 1 hypothermia-group and 4 control-group infants and blindness information was missing for 3 hypothermia-group and 5 control-group infants. Multiple impairments include 2 or more of the following: disabling CP, MDI of <70, blindness, or deafness. Completely normal was defined as MDI and Psychomotor Developmental Index scores of ≥85 with normal neurologic examination and normal hearing and vision. CP indicates cerebral palsy.

[a] One infant in the hypothermia group qualified for study with seizures but was missing a neurologic examination to permit classification of extent of encephalopathy.