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Systemic Hypothermia After Neonatal Encephalopathy: Outcomes of neo.nEURO.network RCT

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KEY WORDS
hypothermia, hypoxic-ischemic encephalopathy, neonates, developmental outcome, asphyxia

ABBREVIATIONS
aEEG—amplitude-integrated electroencephalography
CI—confidence interval
EEG—electroencephalography
HIE—hypoxic-ischemic encephalopathy
OR—odds ratio

Drs Simbruner and Mittal contributed equally to this work.

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WHAT'S KNOWN ON THIS SUBJECT: Hypothermia as selective head or total-body cooling is neuroprotective. However, the efficacy varies in studies published to date, and some studies show no benefit in severe HIE.

WHAT THIS STUDY ADDS: In the neo.nEURO.network trial, hypothermia with morphine as cotreatment had a statistically significant neuroprotective effect, even for neonates with aEEG/EEG evidence of severe HIE, and greater efficacy, characterized by a lower OR than in previously published trials.

abstract

OBJECTIVE: Mild hypothermia after perinatal hypoxic-ischemic encephalopathy (HIE) reduces neurologic sequelae without significant adverse effects, but studies are needed to determine the most-efficacious methods.

METHODS: In the neo.nEURO.network trial, term neonates with clinical and electrophysiological evidence of HIE were assigned randomly to either a control group, with a rectal temperature of 37°C (range: 36.5–37.5°C), or a hypothermia group, cooled and maintained at a rectal temperature of 33.5°C (range: 33–34°C) with a cooling blanket for 72 hours, followed by slow rewarming. All infants received morphine (0.1 mg/kg) every 4 hours or an equivalent dose of fentanyl. Neurodevelopmental outcomes were assessed at the age of 18 to 21 months. The primary outcome was death or severe disability.

RESULTS: A total of 129 newborn infants were enrolled, and 111 infants were evaluated at 18 to 21 months (53 in the hypothermia group and 58 in the normothermia group). The rates of death or severe disability were 51% in the hypothermia group and 83% in the normothermia group ($P = .001$; odds ratio: 0.21 [95% confidence interval [CI]: 0.09–0.54]; number needed to treat: 4 [95% CI: 3–9]). Hypothermia also had a statistically significant protective effect in the group with severe HIE ($n = 77$; $P = .005$; odds ratio: 0.17 [95% CI: 0.05–0.57]). Rates of adverse events during the intervention were similar in the 2 groups except for fewer clinical seizures in the hypothermia group.

CONCLUSION: Systemic hypothermia in the neo.nEURO.network trial showed a strong neuroprotective effect and was effective in the severe HIE group. *Pediatrics* 2010;126:e771–e778

A series of randomized controlled trials and meta-analyses have demonstrated that mild hypothermia after perinatal hypoxic-ischemic encephalopathy (HIE) reduces neurologic sequelae without significant adverse effects.[1–6] However, those trials used different methods to achieve hypothermia and different inclusion criteria, target temperatures, and cotreatments.[1–4] In some of those trials, the effectiveness of hypothermia was dependent on the severity of HIE in the neonatal patients.[1,7] Our study protocol, which was written in 2001 and was based on the protocol of the Cool Cap trial reported by Gluckman et al,[1] used electroencephalography (EEG) criteria for enrollment but differed in target temperature, method of administering hypothermia, and rigorous cotreatment with morphine for both cooled and noncooled neonates. The objectives of this randomized, controlled, multicenter study (the neo.nEURO. network trial) were (1) to determine whether induction of systemic hypothermia to 33°C to 34°C in term neonates with HIE decreased the proportions of infants who died or survived with severe disability, compared with neonates maintained at normal body temperature, (2) to determine whether the protective effect of hypothermia was related to the severity of HIE, and (3) to evaluate the safety of hypothermia.

METHODS

Study Period

The neo.nEURO.network trial was conducted in 24 centers between January 2001 and April 2006, when, after reports of hypothermia being neuroprotective, the trial was terminated earlier than planned because of ethical concerns regarding control subjects.[1,2] The ethics committee from each center approved the protocol before enrollment of patients.

Enrollment of Patients

Inclusion and exclusion criteria are presented in Table 1. Briefly, newborn infants who were born at ≥36 weeks of gestation and were admitted to the NICU of a participating hospital were eligible for the trial if they met the inclusion criteria for moderate or severe HIE. The inclusion criteria were based on stepwise evaluation of (1) evidence of birth asphyxia, (2) clinical evidence of encephalopathy, and (3) electrophysiological findings of encephalopathy with either amplitude-integrated EEG (aEEG) or standard EEG.

Recording and Classification of aEEG or Standard EEG Findings

aEEG was performed with a cerebral function monitor (MT2-5330 system [Lectromed, Letchworth, Hertfordshire, England]), and standard EEG was performed according to the International 10–20 classification. Classification of the aEEG and EEG results was based on the reports by al Naqeeb et al[8] and Lamblin et al,[9] respectively, and yielded 2 subgroups, that is, moderately abnormal aEEG/EEG findings associated with mild/moderate encephalopathy and suppressed aEEG/EEG findings associated with severe encephalopathy. This classification was used for adjustment and subgroup analysis.

Consent, Randomization, and Intervention

Randomization was performed after informed consent was obtained from ≥1 parent. The assignment to the groups was performed through stratified block randomization, with center and severity of HIE as strata, by using sealed envelopes according to the grade of encephalopathy (moderate or severe), in ascending order. The assigned intervention was started as soon as possible after assignment, with the aim of starting no more than 6 hours after birth.

TABLE 1. Inclusion and Exclusion Criteria for Enrollment in Study

Criteria
Inclusion
≥1 of criteria A (birth asphyxia)
Apgar score of <5 at 10 min after birth
Continued need for resuscitation (including endotracheal intubation or mask ventilation) at 10 min after birth
Umbilical cord pH or any arterial pH of <7.00 within 60 min after birth
Base deficit of >16 mmol/L within 60 min after birth
AND criteria B (encephalopathy), with lethargy, stupor, or coma and ≥1 of following:
Hypotonia
Abnormal reflexes, including oculomotor or pupillary abnormalities
Absent or weak suck
Clinical seizures
AND abnormal standard EEG or aEEG findings
Exclusion
Infants >5.5 hours of age at time of random assignment
Administration of high-dose anticonvulsant therapy (phenobarbitone at >20 mg/kg)
Birth weight of <1800 g or gestational age of <36 wk
Head circumference of <3rd percentile for gestational age if birth weight and length are in >3rd percentile
Major congenital malformations with poor developmental prognosis
Imperforate anus
Gross hemorrhage
Infant "in extremis"

All 3 inclusion criteria needed to be fulfilled for enrollment of the neonate in the study. The fulfillment of any 1 of the exclusion criteria resulted in exclusion of the neonate from the study.

Temperature Control

All infants were nursed naked in an open care unit and were treated according to the usual standards of postnatal care in both groups. Body temperature was measured as rectal temperature, with either a thermistor probe or a standard thermometer inserted to a depth of 2 cm from the anus. In the control group, a normal body temperature (ie, rectal temperature of 37°C [range: 36.5–37.5°C]) was maintained.

In the hypothermia group, a rectal temperature of 33.5°C (range: 33.0–34.0°C) was intended to be induced within 60 minutes after the start of

cooling and maintained with a manually adjusted, water-perfused, cooling mattress (Tecotherm TS Med 200 [TecCom, Halle, Germany]) for 72 hours. Rewarming was achieved by setting the perfusion temperature 2°C higher in a stepwise manner, which allowed the rectal temperature to increase ≤0.5°C per hour to reach a normal rectal temperature. The infant then was treated according to routine care standards.

Cotreatments

All infants in the hypothermia and control groups received 0.1 mg/kg morphine every 4 hours or an equivalent dose as a continuous infusion. Fentanyl in an equivalent dosage was also allowed. Opioids were administered to reduce discomfort attributable to encephalopathy and to counteract the stress response induced by hypothermia, which might reduce the effectiveness of hypothermia.[10]

Patient Care

Respiratory, cardiovascular, nutritional, and other management was performed according to standard care standards. Abnormal renal function was defined as urine output of <0.5 mL/kg per hour for ≥24 hours after birth and maximal serum creatinine levels of >0.09 mmol/L. Clinical seizures were treated according to the judgment of the clinicians.

Adverse Effects

Abnormal organ functions were monitored in both treatment groups, according to a checklist (see Table 4), to detect potential adverse effects of hypothermia. Severe adverse events attributable to hypothermia needed to be reported immediately to the data safety monitoring committee.

Follow-up Evaluations

All infants were evaluated at day 7 and at 6, 12, and 18 to 21 months. The follow-up evaluations consisted of (1) neurologic assessment on the basis of Thompson score[11] and cranial ultrasound scans at 7 ± 1 postnatal days, (2) gross neurologic assessment and measurement of body weight, length, and head circumference at 6 months by a neurologist who was blinded to the random assignment, (3) Denver developmental questionnaire at 12 months, and (4) final follow-up evaluation at 18 to 21 months of age. The final follow-up evaluation consisted of a neurologic examination and determination of the development quotient as the Griffiths general quotient or Brunet-Lezine quotient[12] (used in France). Persistent abnormal neurologic signs and handicaps consistent with a central motor deficit were classified according to the 5-level classification described by Palisano et al.[13] The neurologists who conducted the final follow-up evaluations were blinded to the treatment allocation of the patients and were instructed not to ask the accompanying parents about it.

Primary Outcome Measure

The primary outcome was defined as death or severe disability at postnatal age of 18 to 21 months. Severe disability was defined as a neurologic deficit with a functional score of 3 to 5, as defined by Palisano et al,[13] a development quotient of <2 SD, a severe bilateral cortical visual deficit, or any combination of the aforementioned findings.

Statistical Analyses

The intended sample size of 2 times 75 patients was determined on the basis of the assumptions of a study with 80% statistical power with a 1-sided type I error rate of 5% for Fisher's exact test, loss to follow-up monitoring of 20%, and rates of death or severe disability of 83% in the normothermia group and 61% in the hypothermia group, both with a ratio of moderate/severe HIE cases of 60:40.[8,14,15] In an amendment, the analysis was changed to logistic regression to allow for adjustment for severity of HIE and to use the international standard of 5% in 2-sided testing. An associated loss of power was accepted because of the conservativeness of this change. Frequencies are given for categorical data and means (with SDs) and/or medians (with ranges) for continuous variables. Baseline differences were compared by using Student's *t* tests, Wilcoxon tests, or Fisher's exact tests, respectively. The effect of the treatment was analyzed confirmatorily for the primary outcome through logistic regression analysis with adjustment for HIE severity. All other analyses were performed in an exploratory manner, with a 2-sided significance level of 5%. The analyses were performed by using SAS 8.2 (SAS Institute, Cary, NC).

RESULTS

Patients

A total of 129 newborn infants were enrolled, after meeting the inclusion and exclusion criteria. Four neonates were excluded from the trial within the first 7 days; parents withdrew consent for 2 neonates, and no data regarding intervention period were available for 2 neonates. Therefore, 125 neonates constituted the set for safety analyses (Fig 1). The baseline characteristics of the mothers and the neonates did not differ significantly between the normothermia group and the hypothermia group except for the temperature at admission and the age at randomization, both of which were lower in the normothermia group (Table 2). The proportions of neonates who were outborn or had severe encephalopathy were >60% in both groups (Table 2).

Intervention Period

The ages of neonates at randomization were 4.6 ± 1.2 hours in the hypother-

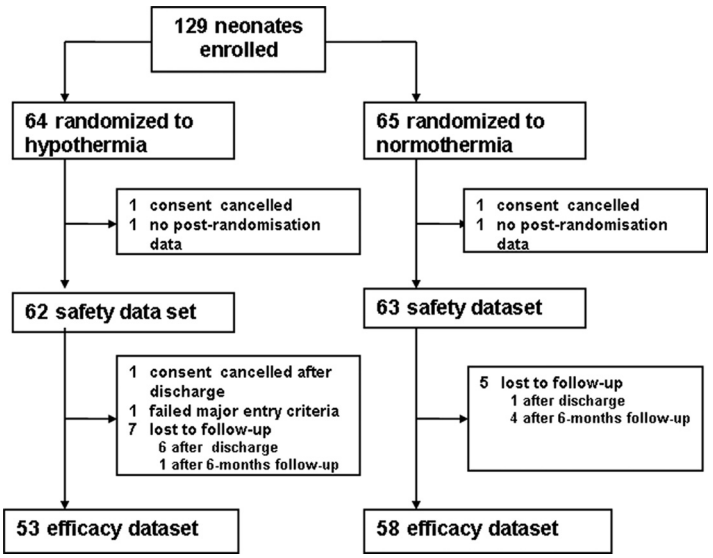

FIGURE 1
Study flow.

mia group and 4.1 ± 1.4 hours in the normothermia group, and the baseline temperatures were 36.0 ± 1.2°C and 35.7 ± 1.7°C, respectively (Table 3). Fifteen neonates were assigned randomly between 5.5 and 6 hours after birth, and 7 were assigned randomly between 6 and 6.5 hours after birth; all were included in the analyses. Cooling was started at an average postnatal age of 5.0 ± 1.1 hours in the hypothermia group, earlier for inborn neonates than for outborn infants (4.6 ± 1.1 vs 5.2 ± 1.0 hours; $P = .03$). The average time from the start of cooling to the achievement of the targeted temperature range was 1.6 ± 1.5 hours (median: 1.2 hours [range: 0.0–8.9 hours]). Infants in the 2 groups reached the target temperature at similar postnatal ages (Table 3), inborn infants (6.1 ± 2.5 hours in the hypothermia group and 6.4 ± 4.1 hours in the control group) slightly earlier than outborn infants (6.9 ± 1.8 hours in the hypothermia group and 7.7 ± 4.7 hours in the control group).

TABLE 2. Maternal and Neonatal Characteristics

Characteristics	Hypothermia ($N = 62$)	Normothermia ($N = 63$)	P
Maternal			
Maternal age, mean ± SD, y	30.8 ± 5.5	30.1 ± 5.6	.51
Chronic maternal illness, *n* (%)	1 (1.6)	0 (0)	.50
Clinical signs of intrauterine infection, *n* (%)	5 (8.2)	6 (9.7)	1.00
Emergency cesarean section, *n* (%)	35 (56.5)	44 (71.0)	.13
Prolapse of umbilical cord, *n* (%)	7 (11.9)	6 (10.3)	1.00
Placental abruption, *n* (%)	6 (10.3)	12 (21.1)	.13
Fetofetal or fetomaternal transfusion, *n* (%)	2 (3.4)	2 (3.5)	1.00
Uterine rupture, *n* (%)	3 (4.8)	8 (12.7)	.21
Cord around neck, *n* (%)	4 (6.5)	4 (6.4)	1.00
Meconium-stained liquor, *n* (%)	15 (26.3)	18 (29.5)	.84
Neonatal			
Gestational age, mean ± SD, wk	39.2 ± 1.6	39.4 ± 1.6	.42
Birth weight, mean ± SD, kg	3.3 ± 0.5	3.3 ± 0.6	.40
Length, mean ± SD, cm	50.6 ± 2.8	50.6 ± 3.7	.98
Head circumference, mean ± SD, cm	34.5 ± 1.5	34.5 ± 1.8	.96
Male, *n* (%)	31 (50.0)	33 (52.4)	.86
Outborn, *n* (%)	39 (65.0)	42 (67.7)	.85
Apgar score at 5 min, mean ± SD	3.4 ± 2.4	3.2 ± 2.4	.53
Apgar at 5 min of 0–5, *n* (%)	44 (75.9)	46 (79.3)	.82
Apgar score at 10 min, mean ± SD	4.9 ± 2.4	4.3 ± 2.4	.22
Apgar score at 10 min of 0–5, *n* (%)	33 (57.9)	36 (65.5)	.44
Umbilical pH, mean ± SD	6.9 ± 0.2	6.9 ± 0.2	.33
Umbilical base deficit, mean ± SD, mmol/L	19.4 ± 6.2	19.5 ± 4.8	.94
Temperature at admission, mean ± SD °C	35.9 ± 1.1	35.3 ± 1.7	.01
Moderate HIE, *n* (%)[a]	24 (38.7)	17 (27.0)	.19
Severe HIE, *n* (%)[a]	38 (61.3)	46 (73.0)	.19
Age at randomization, mean ± SD, h	4.6 ± 1.2	4.1 ± 1.4	.02
Continued need for resuscitation at 10 min, *n* (%)	55 (91.7)	59 (95.2)	.49

[a] Classified on the basis of aEEG or EEG findings.

The total duration of cooling was 72.8 ± 3.4 hours (median: 72.0 hours [range: 69.2–92.3 hours]). During the intervention period, body temperature fluctuations outside the targeted range occurred in both groups, because of difficulties in temperature regulation among neonates with very severe HIE, very low temperatures during transport, and difficulty in rewarming of the neonates. In the hypothermia group, a total of 52 infants had a body temperature outside the target range, compared with 38 in the normothermia group. Details are given in Table 3. Eight patients in the normothermia group experienced ≥1 episode of temperature of >38°C during the intervention period (median highest recorded temperature: 38.5°C [range: 38.2–39.3°C]).

Almost all infants in both groups received the recommended dose of morphine or fentanyl as cotreatment (Table 3). Sixty-three percent of infants in the hypothermia group received anticonvulsants during the intervention, compared with 75% in the normothermia group (Table 3), with phenobarbital being the most-commonly administered drug (alone or in combination

TABLE 3. Details of Intervention Period

	Hypothermia ($N = 62$)	Normothermia ($N = 63$)
Age at start of cooling, mean ± SD, h	5.0 ± 1.1	
Temperature before intervention, mean ± SD, °C	36.0 ± 1.2	35.7 ± 1.7
Age when target temperature reached, mean ± SD, h	6.7 ± 2.1	7.4 ± 4.5
Time between start of cooling and achieving target temperature, h		
Mean ± SD	1.6 ± 1.5	
Median (range)	1.2 (0–8.9)	
Completed intervention period, *n* (%)[a]	54 (87.1)	50 (79.4)
Death during intervention, *n* (%)	5 (8.1)	13 (20.6)
Total duration of cooling, mean ± SD, h)[b]	72.8 ± 3.4	
Neonates with an episode below target range, *n*/*N* (%)[b]	47/54 (87.0)	37/49 (75.6)
Neonates with an episode above target range, *n*/*N* (%)[b]	33/54 (61.1)	19/49 (38.8)
Lowest rectal temperature during intervention, mean ± SD, °C[b]	32.2 ± 0.9	35.5 ± 1.5
Highest rectal temperature during intervention, mean ± SD, °C[b]	34.3 ± 0.7	37.6 ± 0.6
Time below target range, mean ± SD, h[b]	5.0 ± 6.2	8.9 ± 14.9
Time above target range, mean ± SD, h[b]	2.5 ± 4.3	2.5 ± 6.8
Anticonvulsants during intervention, *n*/*N* (%)	39/62 (62.9)	47/63 (74.6)
Morphine/fentanyl during intervention, *n*/*N* (%)	60/62 (96.8)	60/63 (95.2)
Length of stay, mean ± SD, d	18.4 ± 9.6	29.9 ± 19.4

The target temperature range was 33–34°C in the hypothermia group and 36.5–37.5°C in the normothermia group.

[a] Three neonates in the hypothermia group did not complete the intervention period because of withdrawal of therapy by the attending physicians.

[b] Data are given for infants who completed the intervention period ($N = 104$); for 1 neonate from the normothermia group, temperature data were not available.

TABLE 4. Adverse Effects During Intervention Period in Hypothermia and Normothermia Groups

Adverse Effects	*n* (%)		*P*
	Hypothermia ($N = 62$)	Normothermia ($N = 63$)	
Systemic hypotension (mean blood pressure of <40 mm Hg)	33 (53.2)	28 (44.4)	.421
Metabolic acidosis (base deficit of ≥10 mmol/L)	26 (41.9)	28 (44.4)	.915
Seizures, clinical	17 (27.4)	31 (49.2)	.004
Seizures on aEEG or EEG	29 (46.8)	35 (56.5)	.242
Intracranial hemorrhage	2 (3.2)	5 (7.9)	.235
Major venous thrombosis	0 (0)	1 (1.6)	.353
Overt bleeding	3 (4.8)	5 (7.9)	.580
Coagulopathy	9 (14.5)	14 (23.0)	.339
Thrombocytopenia (platelet count of <100 000 cells per μL)	16 (25.8)	21 (34.4)	.303
Hemoconcentration (hematocrit level of >65%)	2 (3.2)	3 (5.0)	.504
Systemic infection	7 (11.3)	10 (15.9)	.395
Cardiac arrhythmia	3 (4.8)	4 (6.3)	.735
Hypoglycemia (<40 mg/dL)	8 (12.9)	11 (7.5)	.486
Hypocalcemia (<1.8 mmol/L)	8 (12.9)	11 (17.5)	.328
Hyponatremia (<130 mmol/L)	23 (37.1)	21 (33.3)	.570
Elevated liver enzyme levels (AST level of >200 IU; ALT level of >100 IU)	13 (22.4)	17 (29.8)	.449
Pathologic renal function	16 (26.2)	26 (41.9)	.059
Initiation of ventilatory support after beginning of intervention	13 (21)	15 (23.8)	.624
Need for nitric oxide	4 (6.5)	10 (15.9)	.144
Death during intervention period	5 (8.1)	13 (20.6)	.108

No difference was observed between the 2 groups except for the number of neonates with clinically evident seizures, which was significantly lower in the hypothermia group. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase.

with other drugs). Infants in the hypothermia group had a lower incidence of clinically evident seizures, compared with those in the normothermia group ($P = .004$) (Table 4).

No increased incidence of adverse effects was observed with hypothermia (Table 4). During the intervention period, 5 neonates in the hypothermia group and 13 neonates in the normothermia group died. The majority of deaths occurred during the first month of life (20 in the hypothermia group and 29 in the normothermia group). The most-common cause of death was withdrawal of support because of lack of improvement in the neonate's neurologic status (70% in the hypothermia group and 66.7% in the normothermia group) (Table 5).

Follow-up Data

Outcome data at 18 to 21 months were available for 111 (88.8%) of 125 newborns in the safety data set. Fourteen patients were not included; 12 infants were lost to follow-up monitoring, and 2 were excluded because of withdrawal of parental consent and diagnosis of a major congenital abnormality that affected neurologic status at 3 weeks of age (Fig 1). These 111 patients constituted the efficacy data set, with 53 infants in the hypothermia group and 58 in the control group (Fig 1).

Primary Outcome

The rate of death or severe disability was significantly lower for the infants treated with hypothermia (51%), compared with normothermia (83%; $P = .001$; odds ratio [OR]: 0.21 [95% confidence interval [CI]: 0.09–0.54]; number needed to treat: 4 [95% CI: 3–9]) (Table 6). This confirmatory result was adjusted for the severity of HIE. An additional, exploratory, extended logistic regression analysis, performed as recommended by the US Food and Drug

TABLE 5. Causes of Death in Hypothermia and Normothermia Groups

Cause of Death	*n* (%)	
	Hypothermia	Normothermia
Withdrawal of support, poor neurologic outcome	14 (70.0)	22 (66.7)
Withdrawal of support, multiorgan failure	4 (20.0)	1 (3.0)
Death despite maximal support	1 (5.0)	6 (18.2)
Late death after discharge	0 (0)	3 (9.1)
Missing data	1 (5)	1 (3)
Total	20 (100)	33 (100)

Administration by including seizures at baseline, age at randomization, Apgar score at 5 minutes, birth weight, and gender, showed persistence of the positive effect of hypothermia in reducing the incidence of death or severe disability ($P = .002$; OR: 0.15 [95% CI: 0.05–0.48]). In addition, the severity of encephalopathy significantly affected the outcome ($P = .005$), whereas the other parameters had no significant effect.

Secondary Outcomes

The rates of death were 38% in the hypothermia groups and 57% in the normothermia group, which were not significantly different (Table 6). Among the survivors, the rates of severe disability were 21.2% in the hypothermia group and 60.0% in the control group ($P = .004$; OR: 0.18 [95% CI: 0.06–0.57]), independent of the severity of encephalopathy ($P = .635$). Therefore, hypothermia did not result in an increased proportion of survivors with severe disability, especially in the severe HIE group. Subgroup analysis revealed that hypothermia had a statistically significant protective effect in the severe HIE group but not in the moderate HIE group, probably because of the smaller sample size (Table 6). Hypothermia-treated survivors had a lower incidence of developmental quotients of <2 SD, disabling cerebral palsy, cortical blindness, and severe hearing loss requiring cochlear implants (Table 6).

Adverse Effects of Hypothermia

During the intervention period, there was no significant difference in the frequency of adverse events between the 2 intervention groups except for clinical seizures (Table 4). Pathologic renal function also was less frequent in the hypothermia group.

DISCUSSION

We report that whole-body hypothermia for newborns with HIE safely decreases the rates of death or severe disability for neonates with moderate or severe HIE. This is in contrast to the study by Gluckman et al[1] and the Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trial[4] but is in agreement, with respect to showing an overall benefit, with studies by Shankaran et al[2] and Eicher et al.[3] In addition, hypothermia had a statistically significant protective effect in the severe HIE group.

In our study, the OR for death or severe disability of 0.21 (95% CI: 0.09–0.54) was lower than those in previously published trials (Gluckman et al,[1] OR: 0.61 [95% CI: 0.34–1.09]; Shankaran et al,[2] OR: 0.48 [95% CI: 0.26–0.87]; Azzopardi et al,[4] OR: 0.74 [95% CI: 0.48–1.14]), which might indicate a stronger neuroprotective effect of hypothermia when it is administered according to the neo.nEURO.network protocol. A reason for the difference in effectiveness of hypothermia might be the proportions of neonates with moderate or severe HIE. In our study, however, the proportion of neonates with severe HIE was larger than that reported in other studies,[1,2] probably because of a larger proportion of outborn infants, who are known to have higher mortality rates than neonates born in a tertiary care center.[3] Furthermore, comparison of the control

TABLE 6. Outcomes for Neonates Treated With and Without Hypothermia, at 18 to 21 Months of Age

Outcome	*n*/*N* (%)		Adjusted OR (95% CI)[a]	*P*
	Hypothermia (*N* = 53)	Normothermia (*N* = 58)		
Primary outcome: Death or severe disability	27/53 (50.9)	48/58 (82.8)	0.21 (0.09–0.54)	.001
Death or severe disability in severe HIE group	21/34 (61.8)	39/43 (90.7)	0.17 (0.05–0.57)	.045
Death or severe disability in moderate HIE group	6/19 (31.6)	9/15 (60.0)	0.31 (0.08–1.28)	.103
Death	20/53 (37.7)	33/58 (56.8)	0.48 (0.21–1.13)	.092
Developmental quotient of <2 SD[b]	7/33 (21.2)	13/23 (56.5)	0.21 (0.06–0.67)	.009
Disabling cerebral palsy[b]	4/32 (12.5)	10/21 (47.6)	0.15 (0.04–0.60)	.007
Bilateral cortical visual deficit[b,c]	1/32 (3.1)	1/20 (5.0)	Not done	Not done
Severe hearing loss[b,c]	0/30 (0)	2/17 (11.8)	Not done	Not done

The primary outcome and death are reported for the whole group. Developmental outcomes, disabling cerebral palsy, bilateral cortical visual deficits, and severe hearing loss are reported for survivors.

[a] ORs were adjusted for the severity of encephalopathy.

[b] Thirty-three infants survived at 18 to 21 months in the hypothermia group and 25 in the normothermia group; data are not available for all infants.

[c] Statistical analysis was not meaningful because of the low incidence of the outcome variable.

groups of published trials with our control group (to assess the similarity of the populations studied) revealed that the incidence rates of death or severe disability were similar in both severe and moderate HIE groups.[1,2,4] In conclusion, differences in case mix of patients do not explain the greater effectiveness of hypothermia in our trial.

The target temperatures in both the hypothermia and control groups and the duration of cooling were similar to those in other studies with whole-body hypothermia.[2,4] Therefore, the greater effectiveness of hypothermia could be explained only in comparison with the Cool-Cap trial[1] and not those that used the same target temperature.[2,4] Inadvertent multiple episodes of elevated body temperature in the control group may result in worse neurodevelopmental outcomes,[16] thereby relatively "improving" the effect of hypothermia and the outcomes in the hypothermia group. However, the target temperature ranges of the control groups in 4 trials[1–4] were very similar to ours. It is difficult to determine to what extent these inadvertent higher temperatures might have had an impact on outcomes, and only trials that controlled the temperatures strictly in both the hypothermia and control groups could answer this question. The practical consequence is that inadvertent higher body temperatures should be avoided through close, continuous monitoring of body temperature and should be treated as outlined by Eicher et al,[17] through the use of a hypothermia blanket, acetaminophen or unswaddling, to avoid increased odds of unfavorable outcomes.

The greater effectiveness of hypothermia in our study, compared with other studies, may be a result of the relatively small number of patients ($N = 111$), compared with the studies by Gluckman et al[1] ($N = 218$), Shankaran et al[2] ($N = 205$), and Azzopardi et al[4] ($N = 325$). The effect may be overestimated because of a greater variation in effect estimation. The CIs of the ORs overlap to a certain extent in all of the aforementioned studies. Therefore, although the effect of hypothermia in our study is significant, it cannot be presumed to be better than in other studies.

Finally, the consistent use of opioid analgesics as a cotreatment in our study might have made a difference, as reported by Thoresen et al,[10] who found a lack of hypothermia neuroprotection in unsedated newborn pigs with severe HIE. Opioids have neuroprotective properties,[18,19] demonstrate increased levels in mammals during the natural process of hibernation,[20] and might have a more-pronounced effect during hypothermia by blunting the stress[10] and the metabolic and hormonal responses to hypothermia.[10,21] In addition, morphine levels are increased during hypothermia because of altered pharmacokinetic characteristics and decreased elimination.[22] The effects and role of morphine during hypothermia need to be validated in additional trials. Our study confirmed the reports from previous trials that hypothermia in the temperature range of 33°C to 34°C and for the duration of 72 hours is safe, reduces the incidence of seizures, and might have a protective effect on the kidneys.

CONCLUSIONS

We conclude that whole-body hypothermia is a safe, effective therapy for neonates with evidence of moderate/severe encephalopathy attributable to perinatal asphyxia. Hypothermia is effective for infants with severe HIE and results in decreased (not increased) rates of severe neurologic impairments in survivors.

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Systemic Hypothermia After Neonatal Encephalopathy: Outcomes of neo.nEURO.network RCT

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