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Whole-Body Hypothermia for Term and Near-Term Newborns With Hypoxic-Ischemic Encephalopathy

A Randomized Controlled Trial

Susan E. Jacobs, MD; Colin J. Morley, MD; Terrie E. Inder, MD; Michael J. Stewart, MD; Katherine R. Smith, MBiostat; Patrick J. McNamara, MD; Ian M. R. Wright, MD; Haresh M. Kirpalani, MD; Brian A. Darlow, MD; Lex W. Doyle, MD; for the Infant Cooling Evaluation Collaboration

Objective: To determine the effectiveness and safety of moderate whole-body hypothermia in newborns with hypoxic-ischemic encephalopathy born in hospitals with and without newborn intensive care facilities or complicated hypothermia equipment.

Design: Multicenter, international, randomized controlled trial.

Setting: Neonatal intensive care units in Australia, New Zealand, Canada, and the United States (N = 28) from February 2001 through July 2007.

Participants: Newborns of 35 weeks' gestation or more, with indicators of peripartum hypoxia-ischemia and moderate to severe clinical encephalopathy, randomly allocated to hypothermia (n = 110) or standard care (n = 111).

Intervention: Whole-body hypothermia to 33.5°C for 72 hours or standard care (37°C). Infants who received hypothermia were treated at ambient environmental temperature by turning off the radiant warmer and then applying refrigerated gel packs to maintain rectal temperature at 33°C to 34°C.

Main Outcome Measures: Death or major sensorineural disability at 2 years of age.

Results: Therapeutic hypothermia reduced the risk of death or major sensorineural disability at 2 years of age: 55 of 107 infants (51.4%) in the hypothermia group and 67 of 101 infants (66.3%) in the control group died or had a major sensorineural disability at 2 years (risk ratio, 0.77 [95% confidence interval, 0.62-0.98]; *P* = .03). The mortality rate decreased, and the survival rate free of any sensorineural disability increased. Adverse effects of hypothermia were minimal.

Conclusions: Whole-body hypothermia is effective and appears to be safe when commenced within 6 hours of birth at the hospital of birth in term and near-term newborns with hypoxic-ischemic encephalopathy. This simple method of hypothermia could be used within strict protocols with appropriate training on correct diagnosis and application of hypothermia in nontertiary neonatal settings while awaiting retrieval and transport to the regional neonatal intensive care unit.

Trial Registration: anzctr.org.au Identifier: ACTRN12606000036516

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Author Affiliations are listed at the end of this article.
Group Information: The members of the Infant Cooling Evaluation Collaboration are listed on page 699.

PERIPARTUM ASPHYXIA COMPLICATED by hypoxic-ischemic encephalopathy (HIE) remains an important cause of mortality worldwide[1-3] and of long-term sensorineural impairments and disabilities.[4-8] Animal models demonstrate a therapeutic "window of opportunity" of approximately 6 hours after hypoxia-ischemia in the newborn before the delayed phase of neuronal loss. They also show that this secondary neuronal injury can be prevented or reduced by a mild reduction in brain temperature.[9-13] Accumulating evidence supports the neuroprotective benefit of therapeutic hypothermia in term newborns with HIE.[14-20]

Commencing therapeutic hypothermia before 6 hours of age is considered critical; however, few babies throughout the world are admitted to tertiary neonatal intensive care units (NICUs) before this time. The Infant Cooling Evaluation (ICE) trial was a pragmatic trial to determine the

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effect of moderate whole-body hypothermia to 33.5°C for 72 hours in newborns with HIE on the composite outcome of mortality or major sensorineural disability at 2 years of age. The ICE trial differed from other hypothermia trials by combining clinical criteria to identify infants at risk of brain injury after peripartum hypoxia-ischemia with a simple, inexpensive method of systemic hypothermia commenced at the birth hospital by dedicated neonatal retrieval teams for infants born in nontertiary settings (hereafter referred to as outborn infants). If effective and safe, the ICE method of therapeutic hypothermia will be widely applicable.

METHODS

DESIGN

The ICE trial was a multicenter randomized controlled trial for term and near-term infants with moderate or severe HIE in which whole-body hypothermia to 33.5°C for 72 hours was compared with maintaining normal body temperature at 37.0°C. The protocol was approved by the human research and ethics committee at each participating site. The ICE steering committee supervised the conduct of the trial. An independent data monitoring committee provided advice on the study's progress.

PARTICIPANTS

Eligible infants were 35 weeks' gestation or more at birth, could have hypothermia initiated within 6 hours of birth, had moderate or severe encephalopathy and indicators of peripartum hypoxia-ischemia, had informed written parental consent, and were managed in (hereafter referred to as inborn infants) or transported to (ie, outborn infants) a participating NICU. Encephalopathy was defined according to modified Sarnat criteria (lethargy, stupor, coma, abnormal tone, and/or seizures).[4,21] A diagnosis of peripartum hypoxia-ischemia was given if an infant had at least 2 of the following clinical characteristics: an Apgar score of 5 or less at 10 minutes, continued need for mechanical ventilation at 10 minutes, and/or metabolic acidosis (cord pH $<$ 7.00; an arterial, venous, or capillary pH $<$ 7.00; or a base deficit of $\geq$12 within 60 minutes of birth). Potentially eligible outborn infants were identified at the time of referral to the participating center or the regional transport service. Inborn infants were assessed for eligibility by site investigators in participating NICUs who obtained parental consent, and outborn infants were assessed at the birth hospital by either a study investigator or a member of the retrieval team who had received education about the ICE trial.

Infants were excluded if hypothermia could not start within 6 hours of birth, if the birth weight was less than 2 kg, if major congenital abnormalities were suspected, if there was overt bleeding, if the infant required more than 80% inspired oxygen,[22] if death was imminent (refractory hypotension or acidosis unresponsive to treatment), or if therapeutic hypothermia had commenced before assessment.

RANDOMIZATION

Assignment to treatment group was by sequentially numbered, sealed opaque envelopes containing computer-generated random numbers in a 1:1 ratio with variable block sizes. Randomization was stratified by study center and performed by a statistician independent of the trial analysis.

INTERVENTION

All infants had their core temperature measured continuously by a thermistor inserted at least 5 cm into the rectum (per rectum). Hypothermia to the target core temperature of 33.5°C (range, 33°C-34°C) was achieved by turning the radiant warmer (or transport incubator) off and exposing the infant to the ambient temperature. Two refrigerated gel packs were applied across the chest and/or under the head and shoulders if the temperature was above 35.5°C at initiation of hypothermia and sequentially removed when the temperature fell below 35°C and then 34.5°C. The radiant warmer heater output (or transport incubator temperature) was manually adjusted every 15 to 30 minutes if the temperature was below 33.5°C. Gel packs were also applied when the temperature was above 34.0°C during the maintenance period of hypothermia between 6 and 72 hours after randomization. After 72 hours, infants were rewarmed over 8 to 12 hours by 0.5°C every 2 hours. Control infants were also nursed under a radiant warmer with their core temperature maintained at 37°C (range, 36.8°C-37.3°C) for the 72-hour intervention period.

For 84 hours after randomization, infants were monitored for continuous core temperature, arterial blood pressure, oxygen saturation, heart rate, respiration rate, and urine output and were also monitored by electrocardiogram. The following parameters were measured or tested daily (or more frequently if the result was abnormal): blood gases (not corrected for temperature); lactate, glucose, electrolyte, urea, and creatinine levels; liver function; complete blood cell count including platelets; coagulation profile; and calcium and magnesium levels.

Other aspects of medical management, including the use of sedatives and analgesics, were not standardized. Decisions to withdraw treatment because of poor neurological prognosis or inevitable death were made by the clinical team independent of the trial.

OUTCOME MEASURES

The primary composite outcome was mortality or major sensorineural disability at 2 years of age. Surviving infants were assessed by trained developmental pediatricians and psychologists masked to treatment allocation. Major sensorineural disability comprised neuromotor delay (cerebral palsy [CP] in which the child was not walking [moderate CP] or was unlikely to walk [severe CP] at 2 years, a Psychomotor Development Index score on the Bayley Scales of Infant Development II [BSID-II] of less than −2 SDs, a Motor Composite Scale score on the BSID-III of less than −2 SDs, or a disability level on the Gross Motor Function Classification System [GMFCS] of 2-5), developmental delay (a Mental Development Index score on the BSID-II of less than −2 SDs or a Cognitive Scale score or a Language Composite Scale score on the BSID-III of less than −2 SDs), blindness (vision worse than 20/200 in both eyes), and/or deafness requiring amplification or worse (ie, the infant does not respond to amplification and is in need of a cochlear implant).[23-26] Fifteen survivors were assessed with the BSID-III, which was introduced in 2006. Because the motor and cognitive scores of the BSID-II and the BSID-III are not equivalent, BSID-III scores were not pooled and developmental delay on BSID-III scores was categorized according to published data from Australian normal-birthweight term infants at 2 years of age.[27]

Secondary outcomes at 2 years included mortality, major sensorineural disability and its individual components (neuromotor delay, developmental delay, blindness, deafness requiring amplification, or worse), and survival free of any sensorineural disability (no neuromotor delay [no CP or a GMFCS disability level of 0 and a BSID-II Psychomotor Development Index of greater than −1 SD or a BSID-III Motor Composite Scale score of greater than −1 SD], no developmental delay [a BSID-II

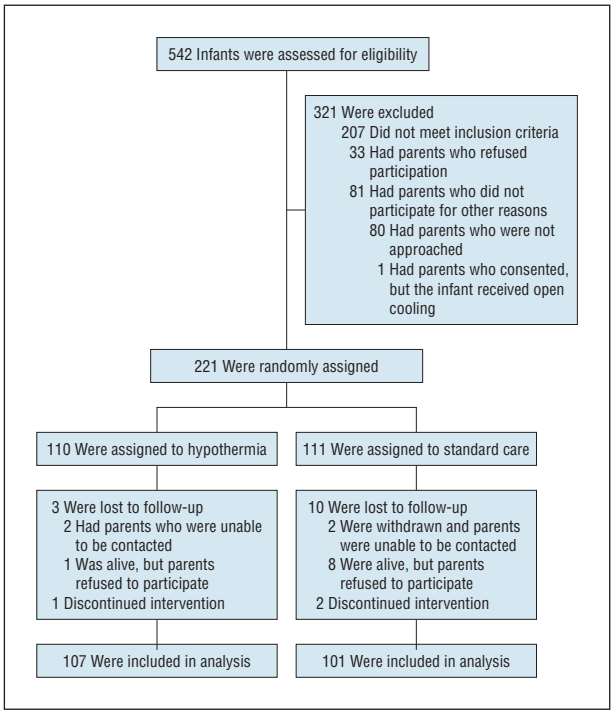

Figure 1. Consort diagram of enrollment and follow-up of infants with peripartum hypoxia-ischemia in the Infant Cooling Evaluation trial.

Mental Development Index score of greater than –1 SD or BSID-III Cognitive and Language Composite Scale scores of greater than –1 SD], no blindness, and no deafness).

Adverse effects and outcomes from therapeutic hypothermia included any cardiac arrhythmia that required medical treatment, prolonged QT interval (>98th centile for heart rate and age[28]), hypotension treated with inotropes, overt bleeding, thrombosis or coagulopathy treated with fresh frozen plasma and/or cryoprecipitate, hypoxia in 100% inspired oxygen that resulted in the hypothermia regimen being discontinued, thrombocytopenia (platelet count, $<150\times10^3$/μL [to convert to $\times10^9$/L, multiply by 1.0]), oliguria (urine output, <1.0 mL/kg/h on day 2 or day 3), hepatic dysfunction (alanine aminotransferase level, >100 U/L [to convert to microkatals per liter, multiply by 0.0167]), rectal bleeding or necrotizing enterocolitis, sepsis, and mortality.

STATISTICAL ANALYSIS

The sample of 150 infants in each group was based on a 2-sided type I error rate of 5%, statistical power of 80%, 10% of infants being lost to follow-up, and a rate of death or major sensorineural disability of 35% in the control infants and 20% in the infants who received hypothermia. The conservative estimate in control infants of 35% was based on anticipated recruitment of fewer severely encephalopathic infants than in other randomized controlled trials, with the combination of encephalopathy and very low Apgar scores and/or significant acidemia predicting between 30% and 80% mortality or major disability in survivors.[29-32]

Analyses were by intention to treat. Risk ratios with 95% confidence intervals (CIs) were used to compare proportions between infants who received hypothermia (the cooled group) and infants who received standard care (the control group) for dichotomous outcomes (including the primary outcome), and risk differences and the number needed to treat were calculated for the primary outcome and for 2-year mortality. Means were compared using the *t* test. Heart rate and rectal temperature during the 6 to 72 hours after randomization were compared using linear mixed models to allow for potential correlation of measurements within infants. Gompertz regression was used to compare mortality between the groups between birth and 2 years, with the result expressed as a hazard ratio. Initially, a Cox proportional hazards model was fitted. However, a check of predicted against observed values showed that model fit was poor, especially for the cooled group, so we considered whether a parametric survival model might fit better. We investigated using an exponential, Weibull, log-logistic, log-normal, or Gompertz distribution and found that the Gompertz model was the best fitting. A gamma distribution was also investigated, but this model did not converge.[33]

Children with missing values for a particular outcome or covariate were not included in analyses using that outcome and/or covariate. The 9 children who were known to be alive at 2 years but whose families refused to attend the 2-year assessment were included as survivors to 2 years with missing neurodevelopmental outcome. We did not perform any type of imputation of missing values, with the exception that children who had a positive primary outcome component (such as death, GMFCS disability level of 2-5, moderate or severe CP, Bayley motor delay, Bayley cognitive delay, legally blind, or deafness requiring amplification) were included as having the primary outcome, regardless of any missingness in the other primary outcome components. The 6 survivors who were assessed as "normal" at 2 years on neurodevelopmental assessment for motor, visual, and auditory outcome but who did not have the Bayley motor or cognitive assessments performed were assumed to have normal cognition and were therefore normal for the primary outcome. Another 6 survivors with data on all primary outcome components except for GMFCS disability level were considered to have normal motor outcome (because none had CP or psychomotor delay measured on the Bayley score).

For the primary outcome, adjusted risk ratios and CIs were estimated using multivariable regression to control for the potentially confounding effects of the severity of encephalopathy at assessment for eligibility, age at randomization, and outborn status. Statistical interactions between each of these 3 covariates and randomization group were investigated.

All *P* values are 2-sided, with $P\leq.05$ considered to be statistically significant. Analyses were performed using Stata version 11 (StataCorp, College Station, Texas).

RESULTS

From February 14, 2001, through July 27, 2007, a total of 542 infants with peripartum hypoxia-ischemia were assessed for eligibility, with 221 infants from 28 participating hospitals in Australia (n=132), New Zealand (n=24), Canada (n=60), and the United States (n=5) randomly assigned to either the cooled group (n=110) or the control group (n=111) (**Figure 1**). Recruitment was stopped by the ICE steering committee on July 27, 2007, on the basis of accumulating external evidence in favor of hypothermia,[17-19,34-36] with loss of equipoise.[37-39] With randomization, an acceptable balance was achieved on both maternal and neonatal baseline demographic variables between the cooled infants and the control infants (**Table 1**).

PRIMARY OUTCOME

The primary composite outcome of death or major sensorineural disability is reported for 208 of 221 randomly assigned infants (94.1%) and 139 of 152 survi-

vors (91.4%), assessed at a median age of 24.6 months (interquartile range, 24.1-26.1 months). Therapeutic hypothermia significantly reduced the risk of death or major sensorineural disability at 2 years of age (**Table 2**), with an absolute reduction of 15% (95% CI, 2%-28%) ($P=.03$). Treating 7 newborns (95% CI, 4-59) with HIE with hypothermia prevented 1 infant from dying or surviving with a major disability. The protective effect of hypothermia persisted in the sensitivity analysis, which excluded the 42 infants recruited with mild encephalopathy at assessment for eligibility (risk ratio, 0.75 [95% CI, 0.60-0.94]; $P=.01$).

Adjusted analyses of the primary outcome demonstrated a significant association between severity of encephalopathy at assessment for eligibility and death or major sensorineural disability at 2 years of age ($P<.001$). The protective effect of hypothermia persisted after adjustment for severity of encephalopathy at assessment for eligibility (risk ratio, 0.83 [95% CI, 0.68-1.00]; $P=.05$). There were no significant interactions between therapeutic hypothermia and the stage of encephalopathy at assessment for eligibility ($P=.16$), between hypothermia and outborn status ($P=.85$), or between hypothermia and age at randomization ($P=.22$) that provided evidence that the effect of hypothermia differed within these subgroups.

SECONDARY OUTCOMES

Mortality

Mortality at 2 years of age was significantly reduced in cooled infants compared with control infants (Table 2) (risk difference, −14% [95% CI, −26% to −1%]; $P=.03$) (number needed to treat, 7 [95% CI, 4-100]). Most deaths occurred within 4 weeks, with the hazard ratio for mortality with hypothermia of 0.58 (95% CI, 0.36-0.94) ($P=.03$). End-of-life discussions preceded 65 of 69 deaths (94.2%), with decisions made to withdraw life-sustaining treatment and provide palliative management (for 22 of 27 cooled infants [81.5%] and 30 of 42 control infants [71.4%]) or to not escalate treatment (for 4 of 27 cooled infants [14.8%] and 9 of 42 control infants [21.4%]).

Neurodevelopmental Outcome

There was no statistically significant effect of hypothermia on major sensorineural disability or its components for survivors assessed at 2 years (Table 2). More cooled infants survived without any sensorineural disability than did control infants (Table 2) (risk difference, 17% [95% CI, 4%-29%]; $P=.008$) (number needed to treat, 6 [95% CI, 4-23]).

Temperature Monitoring

The mean (SD) core temperature at randomization was 36.4°C (1.1°C). All infants randomly assigned to hypothermia reached the 33°C to 34°C target range by a median time of 2 hours (interquartile range, 1-3 hours). During the 6 to 72 hours' maintenance phase, the mean (SD) temperature was 33.8°C (0.4°C) for cooled infants and 36.9°C (0.3°C) for control infants (mean difference, −3.2 [95% CI, −3.3 to −3.1]; $P<.001$) (**Figure 2**A). There was no significant difference in core temperature between inborn and outborn infants in whom retrieval teams commenced the intervention and continued it during transport to the NICU (Figure 2B).

A total of 106 infants were treated with gel packs (105 cooled infants and 1 control infant who was hyperther-

Table 1. Maternal and Neonatal Baseline Characteristics in the Infant Cooling Evaluation Trial[a]

Characteristic	No. (%) Cooled Group (n=110)	No. (%) Control Group (n=111)
Maternal		
Age, mean (SD), y	30.6 (5.6)	30.8 (5.7)
Primigravida	54 (49.1)	42 (37.8)
Multiple pregnancy	2 (1.8)	1 (0.9)
Intrapartum complications		
Temperature ≥38.5°C	2 (1.8)	5 (4.5)
Cord prolapse	10 (9.1)	11 (9.9)
Shoulder dystocia	8 (7.3)	15 (13.5)
Antepartum hemorrhage	20 (18.2)	20 (18.0)
Other sentinel event	34 (30.9)	29 (26.1)
Suspected fetal compromise on electronic fetal CTG[b]	79 (92.9)	69 (93.2)
Cesarean delivery	50 (45.5)	56 (50.5)
Neonatal		
Gestation, wk, mean (SD)	39.0 (1.8)	39.2 (1.7)
Birth weight, g, mean (SD)	3348 (598)	3515 (611)
Male	61 (55.5)	66 (59.5)
Outborn[c]	68 (61.8)	66 (59.5)
Apgar score, median (IQR)		
At 1 min	1 (0-2)	1 (0-2)
At 5 min	3 (1-4)	3 (1-4)
At 10 min	4 (3-5)	4 (3-5)
Resuscitation		
Ventilation	110 (100)	111 (100)
Cardiac compressions	69 (62.7)	69 (62.2)
Epinephrine	43 (39.1)	50 (45.0)
Intravenous fluid	64 (58.2)	74 (66.7)
Peripartum hypoxia-ischemia		
Apgar score ≤5 at 10 min	87 (82.1)	92 (86.0)
Resuscitation or ventilation ≥10 min	105 (95.5)	107 (96.4)
Cord or gas within 1 h of birth, pH, mean (SD)[d]	6.9 (0.2)	6.9 (0.2)
Base excess, mmol/L, mean (SD)[e]	−20.4 (7.7)	−19.0 (9.2)
Encephalopathy at assessment for eligibility[f]		
Mild	17 (15.5)	25 (23.2)
Moderate	63 (57.3)	54 (50.0)
Severe	30 (27.3)	29 (26.9)
Clinical seizures	36 (32.7)	38 (34.2)
Age at randomization, h, mean (SD)	4.0 (1.3)	3.9 (1.3)
Temperature at randomization, °C, mean (SD)	36.3 (1.2)	36.6 (1.0)

Abbreviations: CTG, cardiotocograph; IQR, interquartile range.
[a] Because of rounding, percentages may not always add to 100% exactly.
[b] Data were unavailable for 25 infants in the cooled group and 37 infants in the control group.
[c] Outborn infants were born in nontertiary settings and transported to participating neonatal intensive care units.
[d] Data were unavailable for 16 infants in the cooled group and 19 infants in the control group.
[e] Data were unavailable for 17 infants in the cooled group and 25 infants in the control group.
[f] Data were unavailable for 3 infants in the control group.

Table 2. Outcome at 2 Years for Infants in the Infant Cooling Evaluation Trial

Outcome	Cooled Group		Control Group		RR (95% CI)	*P* Value
	No. (%)	Total No.	No. (%)	Total No.		
Primary outcome of death or major disability	55 (51.4)	107	67 (66.3)	101	0.77 (0.62-0.98)	.03
Encephalopathy at assessment for eligibility						.16[a]
Mild	4 (25.0)	16	8 (38.1)	24	0.53 (0.17-1.66)	
Moderate	26 (42.6)	61	34 (66.7)	51	0.64 (0.45-0.91)	
Severe	25 (83.3)	30	24 (88.9)	27	0.94 (0.76-1.15)	
Moderate or severe	51 (56.0)	91	58 (74.4)	78	0.75 (0.60-0.94)	
Secondary outcomes						
Death	27 (25.0)	108	42 (38.5)	109	0.65 (0.43-0.97)	.04
Major sensorineural disability	28 (35.0)	80	25 (42.4)	59	0.83 (0.54-1.26)	.37
Neuromotor delay	23 (29.1)	79	19 (32.2)	59	0.90 (0.55-1.50)	.70
Cerebral palsy	21 (26.6)	79	17 (28.8)	59	0.92 (0.54-1.59)	.77
Moderate or severe cerebral palsy	16 (20.3)	79	13 (22.0)	59	0.92 (0.48-1.76)	.80
GMFCS disability level 2-5	16 (20.3)	79	12 (20.7)	58	0.98 (0.50-1.91)	.95
Motor score on Bayley scales <–2 SDs	19 (26.0)	73	14 (28.0)	50	0.93 (0.52-1.68)	.81
Developmental score on Bayley scales <–2 SDs	17 (23.3)	73	14 (28.0)	50	0.83 (0.45-1.53)	.55
Legal blindness	1 (1.3)	78	0 (0)	58		.99
Deafness requiring amplification	2 (2.5)	79	2 (3.4)	58	0.73 (0.11-5.06)	.75
Survival free of any disability	42 (39.6)	106	22 (22.7)	97	1.75 (1.13-2.70)	.01

Abbreviations: CI, confidence interval; GMFCS, Gross Motor Function Classification System; RR, risk ratio.
[a] *P* value for interaction between treatment group and stage of encephalopathy at assessment for eligibility.

mic at randomization). Among the 110 infants allocated to hypothermia, gel packs were used on 93 (84.5%) during the first 6-hour initiation phase of hypothermia and on 86 (78.2%) in the maintenance phase between 6 and 72 hours. A total of 64 infants had at least 1 core temperature reading that was below 33°C: 62 cooled infants (56.4%) with a core temperature reading ranging from 29.8°C to 32.9°C (55 [50.0%] with a reading of 29.8°C-32.9°C; 5 [4.5%] with a reading of 31°C-31.9°C; 1 [0.9%] with a reading of 30°C-30.9°C; and 1 [0.9%] with a reading of <30°C) and 2 control infants (1.8%) with a core temperature reading ranging from 32.7°C to 32.9°C. The overshoot below 33°C mostly occurred during the first 6-hour initiation phase of hypothermia. Sixteen control infants (14.4%) had a temperature of 38.0°C or higher at some stage, which was associated with a trend toward increased mortality ($P=.08$).

Other Effects of Therapeutic Hypothermia

The mean (SD) heart rate from 6 to 72 hours after randomization was 114 (16) beats per minute for cooled infants and 139 (18) beats per minute for control infants (mean difference, –25 [95% CI, –29 to –20]; $P<.001$). Cooled infants had a significantly prolonged QT interval compared with control infants, but they had no arrhythmia requiring treatment or discontinuation of hypothermia (**Table 3**).

Therapeutic hypothermia was discontinued in 6 infants. Three infants had overt bleeding, 1 was withdrawn from the study at parental request, and 2 were withdrawn by clinicians. There were no statistically significant differences in other complications or outcomes assessed at 2 years (Table 3). No significant adverse effects were seen in either inborn or outborn infants treated with hypothermia.

COMMENT

This randomized controlled trial of systemic hypothermia to 33.5°C, commenced within 6 hours of birth at the birth hospital and continued for 72 hours in term and near-term infants with HIE, showed a reduction in the combined rate of death or major sensorineural disability at 2 years of age by 15%. Treatment of 7 infants with HIE (which can be identified by using simple clinical criteria) with a pragmatic, readily available and inexpensive method of hypothermia would prevent 1 infant from dying or surviving with major disability. Mortality was also significantly reduced, without any increase in major sensorineural disability or its components in survivors assessed at 2 years. More cooled infants than control infants survived without any sensorineural disability.

The 15% reduction in the composite primary outcome of death or major sensorineural disability is both statistically significant and clinically important. This is consistent with the results of the other 3 major randomized controlled trials,[14,16,20] although the reductions were not statistically significant in 2 of the trials.[14,16] The ICE trial determined outcome at 24 months of age, which may be more predictive of permanent outcomes than the 18 months used in the other randomized controlled trials. The ICE trial is the only individual trial to demonstrate reduced mortality in cooled infants, consistent with pooled analyses in published systematic reviews.[17-19,40]

The lack of a significant effect of hypothermia on the other components of 2-year sensorineural outcomes is also consistent with the CoolCap and National Institute of Child Health and Human Development (NICHD) trials.[16,20] However, the largest trial (the Total Body Hypothermia for Neonatal Encephalopathy [TOBY] trial) reported a significant reduction in CP in cooled survi-

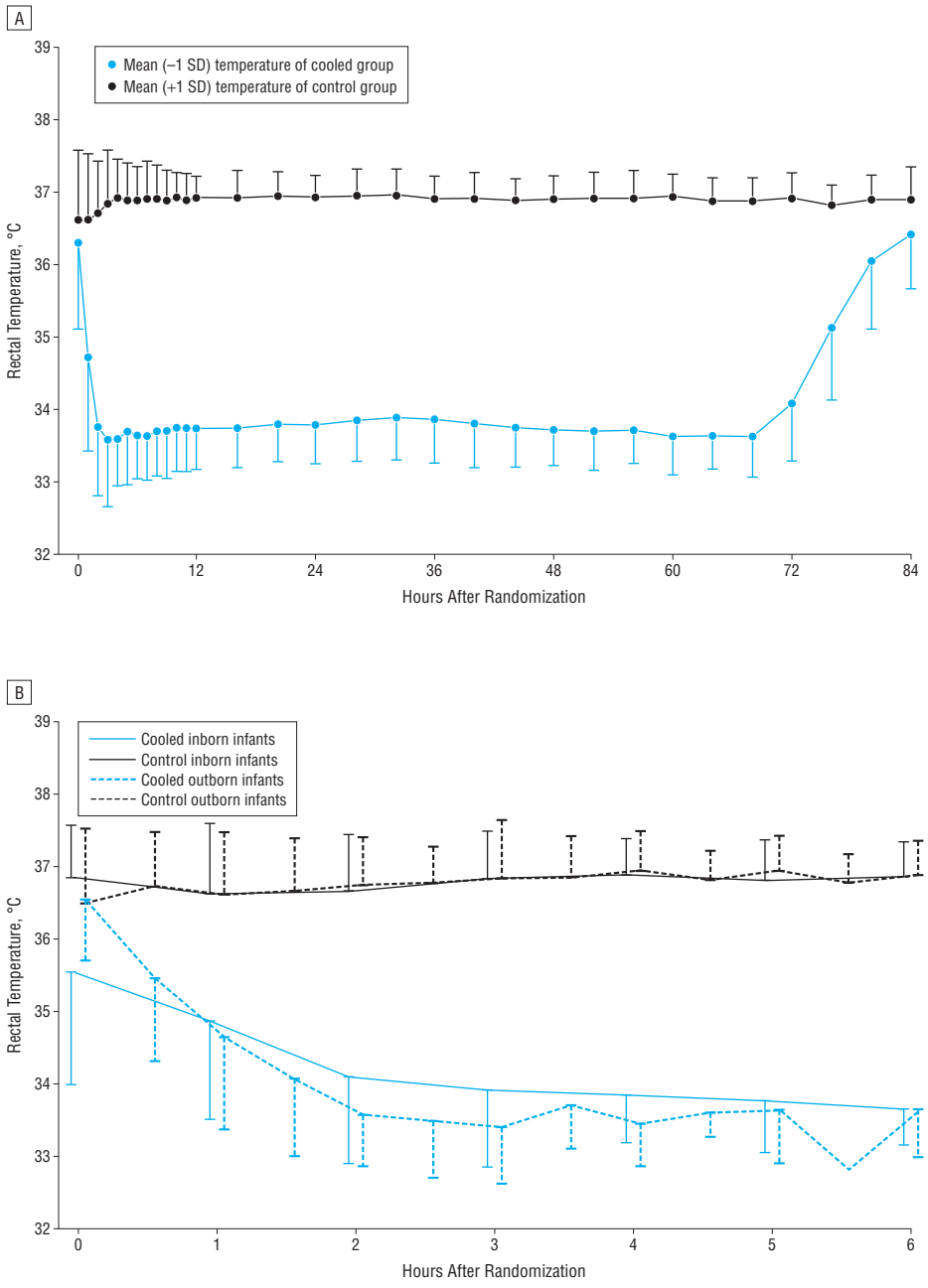

Figure 2. A, Temperature during the 72-hour intervention period and during rewarming. B, Temperature during transport and during the 6-hour initiation of the intervention period, by birth hospital status. The error bars indicate 1 SD. Inborn infants were managed in participating neonatal intensive care units (NICUs), and outborn infants were born in nontertiary settings and transported to participating NICUs.

vors at 18 months (28% of cooled infants vs 44% of noncooled infants; risk ratio, 0.67 [95% CI, 0.47-0.96]; $P = .03$]).[14] Increased survival without any neurologic disability was also reported in the TOBY trial.[14]

No significant major adverse effects of hypothermia were identified in the ICE trial, similar to the other randomized controlled trials.[14,16,20] There were also no significant differences in outcomes or adverse effects of hypothermia seen in the 60% of outborn infants. The ICE trial is therefore unique in demonstrating the apparent safety of commencing whole-body therapeutic hypothermia using a strict protocol in nontertiary settings by dedicated retrieval teams with continuation during transport to the NICU.

The method of therapeutic hypothermia used in the ICE trial is uncomplicated, pragmatic, and inexpensive, and therefore it is widely applicable. The technique achieves whole-body hypothermia primarily by exposing the infant to the ambient environmental temperature, with refrigerated gel packs applied as needed. Most infants were cooled to attain the target temperature range of 33°C to 34°C by a median time of 2 hours. Slight overshoot below 33°C was common during the initiation phase, similar to the other trials,[14,20] even when a servomechanism was used.[20]

Table 3. Other Outcomes of Therapeutic Hypothermia for Infants in the Infant Cooling Evaluation Trial

Outcome	Cooled Group		Control Group		RR (95% CI)	*P* Value
	No. (%)	Total No.	No. (%)	Total No.		
During intervention period						
Arrhythmia requiring treatment		0		0		
Prolonged QT interval	31 (43.0)	72	13 (19.7)	66	2.19 (1.26-3.81)	.006
Hypotension treated with inotropes	51 (46.4)	110	52 (47.3)	110	0.98 (0.74-1.30)	.89
Overt bleeding or thrombosis	3 (2.7)	110	0	110	Not applicable	.25[a]
Treated coagulopathy	20 (18.2)	110	12 (10.9)	110	1.67 (0.86-3.24)	.13
Platelet count $<150\times10^3/\mu L$	56 (50.9)	110	49 (45.4)	108	1.12 (0.85-1.48)	.41
Hypoxia in fraction of inspired oxygen 1.0		0		0		
Oliguria	32 (34.0)	94	24 (27.0)	89	1.26 (0.81-1.97)	.30
Hepatic dysfunction	36 (34.6)	104	47 (44.8)	105	0.77 (0.55-1.09)	.14
Gastrointestinal tract impairment[b]	4 (3.6)	110	2 (1.8)	110	2.00 (0.37-10.70)	.42
Death	13 (11.8)	110	19 (17.3)	110	0.68 (0.36-1.32)	.26
Primary hospitalization						
Mortality	23 (20.9)	110	35 (31.8)	110	0.66 (0.42-1.04)	0.07
Sepsis[c]	6 (5.5)	110	8 (7.3)	110	0.75 (0.27-2.10)	.59
Survivors sucking all feeds at discharge	60 (87.0)	69	47 (88.7)	53	0.98 (0.86-1.12)	.77
2-y Postnatal age						
Anticonvulsants	6 (7.6)	79	2 (3.4)	58	2.20 (0.46-10.52)	.32
Feeding support since discharge	11 (13.9)	79	9 (15.5)	58	0.90 (0.40-2.02)	.79

Abbreviations: CI, confidence interval; RR, risk ratio.
SI conversion factor: To convert platelet count to $\times10^9$/L, multiply by 1.0.
[a] Analyzed using the Fisher exact test.
[b] Defined as sloughing of gastrointestinal tract mucosa, rectal bleeding, or necrotizing enterocolitis.
[c] Septicemia was diagnosed on initial blood culture in 7 infants, 4 allocated to hypothermia and 3 to the control group. Late-onset sepsis was diagnosed in 7 infants, 2 allocated to hypothermia and 5 to the control group.

The ICE trial also demonstrated the ability to identify infants at risk of adverse outcome, with 66.3% of control infants either dying or surviving with major disability. Although higher than the conservative baseline estimate of 35%, it is similar to the combined rate of death or sensorineural disability of 62% in the NICHD trial that also used clinical criteria, as well the rates of the CoolCap (66%) and TOBY (53%) trials that used additional amplitude-integrated electroencephalographic criteria.

The ICE trial planned to recruit 300 infants but stopped at 221, reducing the power of the study from 80% to 61%. Following the publication in 2005 of the pilot studies of Eicher et al[15,41] and the CoolCap[16] and NICHD[20] trials,[16,20] a growing body of evidence had accumulated for the efficacy of therapeutic hypothermia. Clinical equipoise was questioned, and ethical concerns were raised about randomly assigning further newborns with HIE to normothermia who might benefit from hypothermia.[37-39] In February 2007, the ICE data monitoring committee reviewed the evidence from published hypothermia trials together with the in-hospital data on adverse events of 150 ICE recruits, agreeing with expert international opinion not to halt recruitment at that time.[34-36] Three systematic reviews were published later in 2007, with investigators in the ICE trial also authors of the updated Cochrane systematic review.[17-19] Following this, the ICE steering committee concluded that clinical equipoise within the neonatal medical community was lost and, therefore, they ceased recruitment before the planned sample size was reached[42] but continued neurodevelopmental follow-up of survivors to 2 years of age.[43]

A further limitation of the ICE trial (and a protocol violation as well) is the recruitment of 19% of infants with mild HIE. Although education was provided to participating centers and retrieval services, this may represent the lack of a standardized neurologic assessment tool to assess encephalopathy for the ICE trial, compared with the TOBY trial,[14] and the lack of formal certification of the transport medical staff who assessed encephalopathy at the birth hospital, as in the NICHD trial.[20] It may also represent the pragmatic nature of the ICE trial, which was performed in multiple centers and environments, and the imprecision in the diagnosis of encephalopathy. Importantly, the benefit of hypothermia persists when only infants with moderate or severe HIE at assessment for eligibility are analyzed.

In summary, the results of our multicenter, international, randomized controlled trial demonstrate that whole-body hypothermia commenced at the birth hospital within 6 hours of birth is effective and appears safe in term and near-term newborns with HIE, reducing the risk of death or disability at 2 years of age. Clinical criteria can be used soon after birth to identify infants who may benefit from therapeutic hypothermia. The simple method of hypothermia used in the ICE trial could be used in nontertiary settings while awaiting retrieval and transport to the regional NICU.

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Author Affiliations: Neonatal Services, Royal Women's Hospital (Drs Jacobs, Morley, Stewart, and Doyle), the Newborn Emergency Transport Service (Drs Jacobs and Stewart), Departments of Obstetrics and Gynaecology (Drs Morley and Doyle) and Paediatrics (Dr Doyle), University of Melbourne, the Neonatal Department, Royal Children's Hospital (Dr Stewart), and the Clinical Epidemiology and

Biostatistics Unit, Murdoch Children's Research Institute (Ms Smith), Melbourne, and Kaleidoscope Neonatal Intensive Care Unit, John Hunter Children's Hospital and Hunter Medical Research Institute, Newcastle (Dr Wright), Australia; Departments of Pediatrics, Radiology, and Neurology, St Louis Children's Hospital, Washington University, St Louis, Missouri (Dr Inder), and Division of Neonatology, Children's Hospital of Philadelphia, Pennsylvania (Dr Kirpalani); Division of Neonatology, Hospital for Sick Children, Toronto, Ontario, Canada (Dr McNamara), and Department of Clinical Epidemiology, McMaster Children's Hospital, Hamilton, Ontario, Canada (Dr Kirpalani); and Department of Paediatrics, Christchurch School of Medicine and Health Sciences, University of Otago, Christchurch, New Zealand (Dr Darlow).

Correspondence: Susan E. Jacobs, MD, Neonatal Services, Royal Women's Hospital, Corner Grattan Street and Flemington Road, Parkville, Victoria, Australia 3052 (sue.jacobs@thewomens.org.au).

Author Contributions: Dr Jacobs had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Jacobs, Morley, Inder, Stewart, and Doyle. *Acquisition of data:* Jacobs, Stewart, McNamara, Wright, Kirpalani, and Darlow. *Analysis and interpretation of data:* Jacobs, Inder, Smith, McNamara, Wright, Kirpalani, Darlow, and Doyle. *Drafting of the manuscript:* Jacobs, Inder, Smith, McNamara, Wright, and Kirpalani. *Critical revision of the manuscript for important intellectual content:* Jacobs, Morley, Inder, Stewart, McNamara, Wright, Kirpalani, Darlow, and Doyle. *Statistical analysis:* Smith. *Obtained funding:* Jacobs, Morley, Inder, and Doyle. *Administrative, technical, and material support:* Stewart, McNamara, Wright, Kirpalani, Darlow, and Doyle. *Study supervision:* Inder, McNamara, Wright, and Kirpalani.

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