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Original Articles

Moderate Hypothermia in Neonatal Encephalopathy: Efficacy Outcomes

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Therapeutic hypothermia holds promise as a rescue neuroprotective strategy for hypoxic-ischemic injury, but the incidence of severe neurologic sequelae with hypothermia is unknown in encephalopathic neonates who present shortly after birth. This study reports a multicenter, randomized, controlled, pilot trial of moderate systemic hypothermia (33°C) vs normothermia (37°C) for 48 hours in neonates initiated within 6 hours of birth or hypoxic-ischemic event. The trial tested the ability to initiate systemic hypothermia in outlying hospitals and participating tertiary care centers, and determined the incidence of adverse neurologic outcomes of death and developmental scores at 12 months by Bayley II or Vineland tests between normothermic and hypothermic groups. Thirty-two hypothermic and 33 normothermic neonates were enrolled. The entry criteria selected a severely affected group of neonates, with 77% Sarnat stage III. Ten hypothermia (10/32, 31%) and 14 normothermia (14/33, 42%) patients expired. Controlling for treatment group, outborn infants were significantly more likely to die than hypoxic-ischemic infants born in participating tertiary care centers (odds ratio 10.7, 95% confidence interval 1.3-90). Severely abnormal motor scores (Psychomotor Development Index < 70) were recorded in 64% of normothermia patients and in 24% of hypothermia patients. The combined outcome of death or severe motor scores yielded fewer bad outcomes in the hypothermia group (52%) than the normothermia group (84%) ($P = 0.019$). Although these results need to be validated in a large clinical trial, this pilot trial provides important data for clinical trial design of hypothermia treatment in neonatal hypoxic-ischemic injury.

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Introduction

Neuroprotective strategies that may improve outcomes after hypoxic-ischemic injuries are attracting substantial clinical interest. Many pharmacologic investigations have not consistently improved outcomes in animals and humans, perhaps because of the complexity of secondary processes that extend hypoxic-ischemic injury. Although several therapies have shown promise in a preventative strategy, few have demonstrated merit in a postischemic intervention strategy for hypoxic-ischemic disease.

Rescue treatment of neonatal hypoxic-ischemic injury with induced hypothermia is currently being investigated in several multicenter trials around the globe, after extensive animal research established an impressive and consistent record of neuroprotection [1-3]. Hypothermia delayed up to 6 hours after hypoxic-ischemic injury has

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resulted in improvement of secondary energy failure, infarct volume, and functional outcomes in neonatal animals [4-7]. After performing a feasibility study with five neonates, we conducted this randomized, controlled, multicenter pilot trial of moderate hypothermia in hypoxic-ischemic neonates to determine incidence of adverse neurologic outcomes in neonates who meet entry criteria within 6 hours of birth or hypoxic-ischemic event, randomized to either hypothermia or normothermia; to test uniformity of treatment initiation in different clinical situations; and to provide evidence-based, sample size estimates for a large-scale clinical trial.

Methods

Institutional Review Boards of seven participating institutions approved this study. Informed consent was obtained before enrollment. The National Institute for Neurologic Disorders and Stroke appointed a Data and Safety Monitoring committee, which provided oversight of this multicenter pilot trial. Sixty-five infants were enrolled from January 1998 through January 2001 with a 12-month follow-up period.

Entry Criteria

Infants qualified for the study if they were ≥35 weeks gestation, ≥2000 gm birth weight, were ≤6 hours after birth or hypoxic-ischemic insult and manifested one clinical sign *and* two neurologic findings of hypoxia-ischemia.

Clinical signs of hypoxia-ischemia were defined as: cord gas pH ≤ 7.0 or base deficit ≥ 13, initial infant gas pH < 7.1, Apgar score ≤ 5 at 10 minutes, continued resuscitation after 5 minutes, fetal bradycardia with heart rate < 80 beats/min lasting ≥15 minutes, or postnatal hypoxic-ischemic event with oxygen desaturation < 70% or arterial oxygen tension < 35 mm Hg for 20 minutes with evidence of ischemia (chest compressions, hypotension, hemorrhage).

Neurologic findings of hypoxia-ischemia (two required) included posturing, seizures, autonomic dysfunction, or increased /decreased abnormalities of tone, reflexes, or state of consciousness.

Exclusion criteria: Neonates with clinical sepsis, maternal chorioamnionitis, weight or head circumference less than 10th percentile for gestation age, or congenital abnormalities were excluded.

Randomization System

Infants with an abnormal neurologic examination or who required resuscitation at delivery were screened for eligibility. Qualifying neurologic examinations were performed by neonatologists and general pediatricians at community hospitals or by study investigators at tertiary care centers. Infants were enrolled and randomized if they were born or referred to a participating study center with qualifying criteria within 6 hours of birth or hypoxic-ischemic event, after obtaining informed consent. We designed and implemented a de novo, web-based randomization system for online randomization, which was used by all the centers in this pilot trial [8]. Because treatment benefit may differ between those neonates born in the participating tertiary care centers (inborn), those transported in (outborn), and neonates with hypoxic-ischemic injury after birth (postnatal), we employed a block randomization design stratified by these three groups, to ensure that these variables were balanced between cases and controls. With the small numbers in this pilot trial, we were not able to stratify within the 0- to 6-hour enrollment window or by center.

Treatment Protocol

Treatment was instituted initially in a participating institution's delivery room or at an outlying hospital by the transport team after they had assumed care of the infant at an outlying hospital. If randomized to normothermia, rectal temperatures were maintained at 37 ± 0.5 °C by servo-controlled, overhead warmers, per standard neonatal intensive care unit practice. If randomized to hypothermia, plastic bags filled with ice wrapped in a washcloth were applied to the head and body for approximately 2 hours, then the infant was placed on an adult-size cooling blanket, servo-controlled at 33 ± 0.5 °C for 48 hours at the participating tertiary care center (Cincinnati Sub-Zero Blanketrol II, Cincinnati, OH). All patients had rectal temperature probes, indwelling central lines, pulse oximetry and cardiorespiratory monitoring, and urinary catheters. Rewarming by 0.5°C per hour was begun after 48 hours of hypothermia, if euvolemia and normocalcemia were present. Morphine was used for analgesia at the attending physician's discretion, or fentanyl if cardiovascular compromise was significant. Seizures were treated with phenobarbital, and lorazepam or phenytoin if required.

An attending physician or fellow performed daily neurologic examinations for the first 5 days. Head ultrasounds were obtained on enrollment and at 3 days of age for detection of malformation, bleeds, or cerebral edema. Electroencephalographic recordings were obtained at 72 hours of age. Bayley II, Clinical Adaptive Test/Clinical Linguistic Auditory Milestone Scale (CAT/CLAMS), and Vineland Gross motor tests were performed by developmentalists blinded to study treatment group at 12 months (range 12-18 months of age).

The attending physicians counseled parents about neurologic sequelae of hypoxic-ischemic injury. In particular, we emphasized with parents that their right to decide on withdrawal of support at any time was not affected by participation in this study.

Patients were withdrawn from treatment if they had any of the following: sepsis/meningitis by positive blood or cerebrospinal fluid culture obtained at birth, or pneumonia by chest radiograph in the first 36 hours of life; uncontrolled disseminated intravascular coagulopathy; sustained bradycardia < 70 beats/min with hypotension and acidosis on inotropic medications, which did not respond to rewarming to 34°C; or parental request.

Outcome Measures

Primary outcome variables were the incidence of abnormal neurodevelopmental scores by Bayley II (Mental Development Index and Psychomotor Development Index), CAT/CLAMS, or Vineland examinations at 12 months of age, or death, and time to target temperature in hypothermic infants. Neurodevelopmental test scores were categorized by severity of abnormality, based on the population mean of 100 ± 15. Severely abnormal scores were defined as >2 standard deviations from mean (S.D.), moderately abnormal as >1 and ≤2 S.D., and mildly abnormal to normal as ≤1 S.D. on neurodevelopmental tests of motor function (Bayley Psychomotor Development Index, Vineland gross motor) and cognitive function (Bayley Mental Development Index, CAT/CLAMS) in both groups.

Statistical Analysis

Chi-square statistical tests were performed for all categorical variables, unless cell size was less than 5, when Fisher exact test was performed. For continuous variables, pooled or Satterthwaite *t* tests were performed, depending on analysis of equality of variances. Median test for significance was performed by Kruskal-Wallis test. Logistic regression was used to evaluate effects of outborn or inborn status on outcome controlling for treatment group. All outcomes were analyzed with intent-to-treat inclusion of all randomized patients.

Table 1. Demographics at enrollment

	Hypothermia (n = 32)	Normothermia (n = 33)	Total
Sex			
Male	17	18	35 (54%)
Female	15	15	30 (46%)
Ethnic group			
Caucasian	17	20	37 (57%)
Afro-American	13	11	24 (37%)
Other	2	2	4 (6%)
Entry strata			
Inborn @ level III	6	8	14 (22%)
Postnatal asphyxia	0	2	2 (3%)
Outborn (transported)	26	23	49 (75%)
Gestational age	38.8 ± 1.9 wk	39.1 ± 1.4 wk	$P = 0.5$
Birth weight	3241 ± 775 gm	3550 ± 819 gm	$P = 0.1$
Clinical status at enrollment			
Chest compressions	21	20	41 (66%)
Mean cord pH	6.95 ± 0.19	6.96 ± 0.23	$P = 0.9$
Mean cord base deficit	−18 ± 8.3	−16 ± 7.5	$P = 0.6$
Median Apgar @ 5 min	2	2	$P = 0.6$
Median Apgar @ 10 min	4	3	$P = 0.9$
Sarnat stage III	25	25	50 (77%)
Sarnat stage II	5	5	10 (15%)
Sarnat stage I	1	1	2 (3%)
Normal exam (withdrawn)	1	0	1 (2%)
Sarnat data incomplete	0	2	2 (3%)

Results

Demographics

Six participating sites enrolled 65 infants, 32 randomized to hypothermia, 33 to normothermia. Sixty-three infants were screened but not enrolled for the following reasons: Only one abnormality on neurologic examination (16), gestation <35 weeks (10), maternal chorioamnionitis (8), referral after the 6-hour window (14), in utero growth retardation (1), encephalopathy without clinical sign of hypoxic-ischemic injury (2), chromosomal malformation (2), parental refusal of consent (3), inadequate staff or physician refusal (3), and unspecified (4).

Three hypothermia infants were withdrawn after randomization but before completion of hypothermia treatment. One patient had an abnormal neurologic examination by the pediatrician in the community hospital that returned to normal upon arrival at the tertiary care center. One patient was withdrawn by parental request because they reconsidered their decision to enroll in the study. (This patient survived, but no developmental data are available.) A third patient was withdrawn from hypothermia treatment owing to the parental request to return to community hospital where the infant died.

Two normothermia patients were withdrawn between 24-36 hours of age because of sepsis, which was unknown at enrollment, and only determined when their blood cultures, obtained at birth, became positive at 24 hours of age. All analyses are intent-to-treat and include these outcomes, if known.

The mean time from birth to enrollment ranged from 3.1 to 4.6 hours for the six centers. There were no significant differences in gestation, birth weight, sex, race, numbers of inborn vs outborn, or condition on enrollment (chest compressions, cord pH, cord base deficit, Apgar, or Sarnat stage) between hypothermia and normothermia groups (Table 1).

Our entry criteria required increased or decreased reflexes or tone on the neurologic examination, potentially recruiting Sarnat stage I patients. However, 77% of neonates in this pilot trial presented in Sarnat stage III at enrollment, indicating a severely affected group of neonates.

Ice was an effective and reliable way to institute hypothermia treatment in tertiary care centers, outlying hospitals, and during transport. In this pilot trial, we tested our ability to effectively institute hypothermia in outlying hospitals, while on transport, and in tertiary care centers using the same protocol of ice bags to head and body for 2 hours before being placed on a servo-controlled cooling blanket. Hypothermia patients had a mean rectal temperature of 32.8 ± 1.4 °C at 2 hours after enrollment, and all hypothermia patients were at target temperature within 5 hours of enrollment.

Time to achieve target temperature of 33°C for hypothermia neonates born at outlying hospitals was compared with those born in the participating tertiary care centers (Table 2). Outborn infants tended to reach target temperature sooner. There was significantly less time required to attain target temperature in those who died (mean 70 ± 23 minutes) than in those who survived (129 ± 81 minutes, $P = 0.0013$).

More temperature variability was observed in the hypothermia group than in the normothermia group on both

Table 2. Hypothermia group: time to target temperature (32.5–33.5°C)

	Outborn (n = 23)	Inborn (n = 6)	
Mean time to target temperature	111 ± 78 min	156 ± 116 min	$P = 0.3$
Median time to target temperature	80 min	142 min	$P = 0.2$
Range of time to target temperature	30–300 min	49–300 min	

days of treatment (Table 3). Day 1 of treatment includes some hypothermia infants who were not yet at target temperature, but variability was increased in the hypothermia group compared with the normothermia group even on day 2 of treatment. These data reveal an increase in temperature variability of ±0.3°C over the estimated variability of ±0.5°C for the hypothermia group in the pilot trial protocol. The numbers of patients with fever at any time are included in Table 3, as this temperature variation may influence outcome.

Death and Neurodevelopmental Follow-up

Death. The overall study death rate was 37% (24/65), with only one death occurring after hospital discharge (Table 4). This death rate is in keeping with the severity of enrolled neonates who present early and who are largely Sarnat stage III [9]. Using intent-to-treat analyses, 10 of 32 (31%) hypothermia infants expired, vs 14 of 33 (42%) normothermia infants, $P = 0.35$.

Greater deaths in outborn neonates. Outborn hypoxic-ischemic infants in the present study had a significantly greater incidence of death compared with those inborn, regardless of treatment group. Twenty-two of 24 deaths occurred in the outborn stratum (92% total deaths) vs 1 inborn death and 1 death in the postnatal hypoxic-ischemic group. Forty-five percent of all infants born in an outlying hospital with hypoxic-ischemic injury (22/49) died compared with 7% (1/14) of inborn patients ($P = 0.007$). Using logistic regression to control for treatment group, hypoxic-ischemic neonates who died were 10 times more likely to have been outborn than inborn (odds ratio [OR] = 10.7, 95% confidence interval [CI] 1.3-90, $P = 0.03$).

Because fluid resuscitation has been demonstrated to be an important predictor of survival in community pediatric/neonatal septic shock [10], we compared mean volume of fluid boluses received before enrollment. No difference was observed in mean volume of fluid boluses in those who expired (48 ± 36 cc/kg) compared with those who survived (44 ± 23 cc/kg, $P = 0.6$). We also detected no difference in either the number of patients who received volume (27 hypothermia group, 26 normothermia group) or the mean volume of fluid boluses (46 ± 30 cc/kg in hypothermia group, 44 ± 26 cc/kg in normothermia group, $P = 0.8$).

Description of deaths. We were aware that the unblinded nature of this trial could have a positive effect on parental hope for recovery with a delay in the consideration of withdrawal of support. As the brainstem recovers from the hypoxic-ischemic insult, the infant regains control of vital functions, and withdrawal of support then becomes a withdrawal of intravenous fluid, a much harder decision for families. In addition, the treating physician was also a study investigator in some cases. Therefore several biases toward hope for recovery with hypothermia treatment may have been responsible for the decreased rate of death in the hypothermia group. We analyzed the circumstances around the study deaths and characterized them as to withdrawal of support with poor neurologic prognosis or multi-organ system failure (defined as failure of two or more organ systems despite maximal medical support) (Table 5). Nine deaths in each group were due to parental withdrawal of support, with or without multi-organ system failure. Therefore we conclude that with adequate counseling concerning severity of hypoxic-ischemic injury, 48 hours of moderate hypothermia treatment does not negatively influence parental options for withdrawal of support.

Neurodevelopmental outcomes. Twelve patients (5 hypothermia group, 7 normothermia group) had no 12-month developmental follow-up after discharge, including the two hypothermia patients who were withdrawn from treatment (Table 4). After deaths and lost-to-follow-ups, 17 hypothermia and 12 normothermia patients were avail-

Table 3. Temperature variations: difference in high and low daily rectal temperatures

	Hypothermia	Normothermia	
Mean temperature difference			
2 to 24 hr after enrollment	2.5 ± 1.1°C (n = 29)	1.7 ± 0.9°C (n = 31)	$P = 0.003$
25 to 48 hr after enrollment	1.6 ± 0.6°C (n = 28)	1.0 ± 0.5°C (n = 29)	$P < 0.001$
Range of temperature variation			
25 to 48 hr after enrollment	0.6-2.7°C	0.3-2.1°C	
Temperature ≥ 39°C at any time	7	5	

Table 4. Enrollment numbers and follow-up

	Hypothermia	Normothermia	Total
Total enrollment	32	33	65
Expired	10	14	24 (37%)
Withdrawn—no 12-month development data	2	0	2 (3%)
Lost or incomplete developmental follow-up	3	8	11 (17%)
Total with known 12-month motor development data	17	11	28 (43%)

able for neurodevelopmental testing at 12 months. One normothermia patient, who had moved after study entry and returned for the Bayley test, inadvertently had the Mental Development Index portion of the Bayley test performed but not the Psychomotor Development Index (incomplete motor developmental data, omitted for Psychomotor Development Index, in Table 4). Two infants were too impaired to score by the Bayley with quadriplegic cerebral palsy and neurologic devastation, and were recorded as severely abnormal motor and cognitive outcomes. One hypothermia patient was normal by neurologic physical examination and CAT/CLAMS testing at 12 months but did not stay to have the Bayley test performed.

Motor and cognitive developmental scores. Among survivors with known developmental outcomes at 12 months, there were fewer infants with severely abnormal Psychomotor Development Index/motor scores in the hypothermia group: incidence of 24% hypothermia (4/17, 95% CI 0.04-0.44) compared with 64% normothermia (7/11, 95% CI 0.52-0.76), $P = 0.053$ (Table 6).

The outcome of death or severe motor scores at 12 months yielded significantly fewer severe outcomes in the hypothermia group. Fifty-two percent of death or severe motor scores were observed in the hypothermia group (14/27, 95% CI 0.43-0.61) compared with 84% in the normothermia group (21/25, 95% CI 0.77-0.91), $P = 0.019$.

Twenty-four percent (4/17) of the hypothermia group, vs 42% (5/12) of the normothermia group had severely abnormal cognitive scores ($P = 0.4$) (Table 5). Using logistic regression to control for treatment group, there were no significant differences in severe motor scores (OR: 0.7, 95% CI 0.2-3.3, $P = 0.7$) or cognitive scores (OR: 0.4, 95% CI 0.1-1.6, $P = 0.2$) between infants delivered outborn or inborn.

Lost to follow-up. This multicenter pilot trial was designed to determine the incidence of adverse neurologic outcome measures to generate sample size estimates for a large clinical trial. With 17% of the patients in the present study lost to follow-up (8 normothermia, 5 hypothermia), our treatment effect could be overestimated, if many of the missing developmental scores were normal. Therefore outcome analysis was also performed treating the lost-to-follow-up patients as missing data and designating an expected outcome according to both treatment group and their Sarnat-matched group who did complete follow-up. With these estimated outcomes, we would expect 2/5 hypothermia and 5/8 normothermia lost-to-follow-up patients to have death or severe motor scores. If these outcomes are added to the known outcomes, treatment effect in death or severe motor abnormalities changes to 50% hypothermia, 79% normothermia. Using the same group and treatment matching, one would expect 1/5 hypothermia and 3/8 normothermia patients who were lost to follow-up to have severely abnormal motor scores, and estimated treatment effect changes to 23% hypothermia, 53% normothermia for severely abnormal motor scores.

Other outcome measures. Two hypothermia cases and three normothermia cases of hearing loss were documented, with one hypothermia and one normothermia patient requiring hearing aids. There was one normothermia case of cortical blindness in a child who had sepsis at birth and multiple severe disabilities. Cortical visual deficits were reported in two hypothermia patients. Two hypothermia patients and one normothermia patient re-

Table 5. Description of deaths

	Hypothermia (n = 10)	Normothermia (n = 14)
Withdrawal of support, poor neurologic prognosis	5	7
Withdrawal of support with MOSF	4	2
Death from MOSF without withdrawal of support	0	4
Death with do not resuscitate order	1	0
Late death after discharge	0	1

Abbreviation:
MOSF = Multi-organ system failure of two or more organ systems

Table 6. Developmental scores At 12 months

	Hypothermia	Normothermia	Total
Motor Developmental Index	n = 17	n = 11	
Severe (<70)	4 (24%)	7 (64%)	11 (39%)
Moderate (70–84)	5 (29%)	0	5 (18%)
Mild (>84)	8 (47%)	4 (36%)	12 (43%)
Cognitive Developmental Index	n = 17	n = 12	
Severe (<70)	4 (24%)	5 (42%)	9 (31%)
Moderate (70–84)	2 (11%)	1 (8%)	3 (10%)
Mild (>84)	11 (65%)	6 (50%)	17 (59%)

quired glasses. One hypothermia group patient had a seizure disorder at 12 months of age.

Length of hospitalization was not significantly different between groups, although one patient in the hypothermia group was hospitalized for 3 months before withdrawal of support. We therefore compared median lengths of stay, which were 16.5 days for the hypothermia group and 15 days for the normothermia group ($P = 0.3$).

Electroencephalographic abnormalities. Electroencephalograms were taken at 72 hours of age, after rewarming was completed. Ninety-two percent (24/26) of electroencephalograms in hypothermia patients were abnormal, compared with 78% (18/23) in normothermia patients ($P = 0.23$). Abnormal electroencephalograms were grouped into four categories: nonspecific encephalopathy (6 in hypothermia group, 2 in normothermia group), burst suppression (8 in hypothermia group, 9 in normothermia group), low-voltage (10 in hypothermia group, 6 in normothermia group), and isoelectric (1 in hypothermia group, 1 in normothermia group).

Length of time to enrollment. We analyzed whether a longer time from birth to enrollment might influence hypothermia's effectiveness and therefore limit the window for successful therapy. Hypothermia still significantly improved the outcomes of death or severe motor disability for those who were enrolled after 3 hours of age (death or severe motor disability in 50% [8/16] hypothermia vs 100% [8/8] normothermia, $P = 0.02$).

Discussion

This pilot trial provides important data for designing large hypothermia trials in neonatal hypoxic-ischemic injury. Using our entry criteria of two neurologic examination abnormalities for neonates who presented within 6 hours of hypoxic-ischemic injury, mainly severely affected Sarnat stage III neonates were enrolled, although Sarnat stage I infants could potentially be enrolled. They are also primarily outborn, and had a higher death rate compared with the inborn hypoxic-ischemic neonates. Those who died were 10 times more likely to have been outborn than inborn, controlling for treatment group. These findings may be due to lack of experienced personnel, more difficult resuscitations, or problems with stabilization after resuscitation. Nevertheless, stratification by outborn or inborn status will continue to be important in the design of future hypothermia trials.

The predominance of outborn hypoxic-ischemic neonates reflects the unexpected nature and diverse demographics of hypoxic-ischemic injury, emphasizing that one of the challenges of providing effective neuroprotection is in the application of the therapy in front-line community hospitals. Animal data from Tooley and other investigators clearly indicate that neuroprotection is decreased with even a few hours of delay in initiation of hypothermia [11]. Systemic hypothermia permits rapid induction of therapy in community hospitals, potentially reducing the time to initiation of therapy by several hours over other interventions that can only be begun at tertiary care centers. This pilot trial protocol provided a good test of systemic hypothermia applied in a nonintensive care setting. Transport teams effectively induced systemic hypothermia with ice bags to the head and body, demonstrating that hypothermia in an outlying hospital setting can be provided with guidance from tertiary care centers.

The group identified by these entry criteria may include some neonates with hypoxic-ischemic injury too severe or chronic to be remediated by hypothermia. Excluding these neonates may improve responsiveness to neuroprotective therapy, but identifying this group prospectively is challenging, considering the need to begin therapy quickly in the community. Therefore entry criteria for a large trial would also benefit from exclusion criteria consisting of tests or examinations that can be performed by pediatricians at outlying hospitals. Simple entry criteria and treatment protocols that are easily applied to clinical practice will allow rapid initiation of therapy in a setting where neonatal hypoxia-ischemia occurs most frequently.

Hypothermia trials cannot be blinded to treatment and must deal with several inherent biases. In some cases, the study investigator is also the treating physician, potentially creating bias in recommendations for withdrawal of support and possibly in patient care. Precise management protocols may help minimize the later bias, but cannot accommodate parental feelings about withdrawal of support or the subtleties of the doctor–patient relationship. Withdrawal of support bias can be analyzed post hoc, and failure to withdraw moribund infants should increase survival of severely abnormal infants in the treatment group. No evidence of this bias was demonstrated in our pilot trial of 48 hours of hypothermia, but larger clinical trials, particularly those involving longer treatment periods, need to continue to address this potential bias.

In statistical considerations for large trials, there is little data in the literature to base sample size estimates of treatment effect and predict the incidence of adverse neurologic sequelae in infants who present within 6 hours of hypoxic-ischemic injury. Only one study has addressed neurologic outcome predicted by time of presentation, a retrospective multivariate analysis [9]. Our pilot trial provides helpful information in the choice of the best outcome variable for evaluating hypothermia's treatment effect. We observed an improvement in the most serious outcomes of death or severe motor scores at 12 months of age. Also, severely abnormal motor outcomes alone were decreased in the hypothermia group compared with the normothermia group, even with the predominantly Sarnat stage III neonates, whom we expected to be less responsive to treatment. Cognitive scores in this pilot trial did not seem as sensitive to hypothermia treatment effects as motor scores. Based on the pilot trial data, specific primary outcomes of death or severe motor scores may be superior to a global neurologic functioning score that combines multiple diverse outcomes.

In evaluating the significance of the improvement in outcome from these pilot data, the high lost-to-follow-up rate must be considered. These missing data may influence the true incidence of adverse neurologic outcomes and, therefore, sample size estimates in Phase III trials. Clinical trial design may benefit from being more conservative in this regard, so as not to be underpowered for the primary outcome variable.

The incidence of death and severe motor scores at 12 months in this pilot trial indicate that hypothermia may be helpful even in severe neonatal hypoxic-ischemic injury. The efficacy, optimal length of hypothermia therapy, and an assessment of the risk-benefit of hypothermia will be determined in future clinical trials. The favorable results of this pilot trial offer important considerations for the design of hypothermia trials in neonatal hypoxic-ischemic injury.

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