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Acute Perinatal Sentinel Events, Neonatal Brain Injury Pattern and Outcome of Infants Undergoing a Trial of Hypothermia for Neonatal Hypoxic-Ischemic Encephalopathy

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Abstract

Infants with perinatal sentinel events in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network Hypothermia for Encephalopathy Trial had more basal ganglia and thalamus lesions on brain magnetic resonance imaging but similar neurodevelopmental outcomes at 18 months of age than infants without perinatal sentinel events. Outcomes correlated with the neonatal magnetic resonance imaging findings.

Keywords

Intrapartum event; Magnetic Resonance Imaging; Neurodevelopment

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The authors declare no conflicts of interest.

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Trial registration ClinicalTrials.gov: NCT00005772

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Specific acute clinical events which occur close to the time of delivery or are the primary reason for delivery are called perinatal sentinel events (PSE). Prior to the era of therapeutic hypothermia, PSE that result in neonatal hypoxic-ischemic encephalopathy (HIE) have been associated with basal ganglia and thalamic (BGT) lesions and less frequently with watershed (WS) injury on a magnetic resonance imaging (MRI).¹ Hypothermia for neonatal encephalopathy is currently the standard of care² because therapy initiated within 6 hours of age at 33–34°C and continued for 72 hours decreases death or disability at 18 to 24 months of age^{3–6} and increases the number of normal survivors.^{7, 8} Following the initiation of hypothermia for neonatal encephalopathy, a recent single center study noted that infants with a PSE had a higher mortality rate and more severe injury on brain MRI compared with infants without PSE.⁹

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NICHD NRN) described brain MRI findings among 136 of 208 participants in a randomized controlled trial (RCT) of hypothermia compared with usual intensive care among neonates with HIE.¹⁰ These findings were found to correlate with death or survival with moderate or severe disability at 18 months of age¹⁰ and with childhood outcome at 6 to 7 years of age.¹¹ Using the detailed information on PSE that is available in this trial database, we designed the present study to examine whether PSE are associated with MRI findings that are linked to death or disability.

METHODS

The NICHD NRN Trial of whole-body hypothermia for neonatal encephalopathy recruited 208 subjects between July 2000 and May 2003 in the 15 participating centers (ClinicalTrials.gov: NCT00005772). Term infants were eligible if they had an umbilical cord or first pH within 1 hour of birth that was ≥ 7.0 or they required resuscitation following an acute perinatal event and had moderate or severe encephalopathy within 6 hours of birth. After informed consent was obtained from a parent, infants were randomly assigned to whole body hypothermia at 33.5°C for 72 hours or usual intensive care. MRIs were performed at 44 weeks postmenstrual age or when clinically feasible, but within 60 days of age. T1 and T2 weighted sequences with 1.5 or 3.0 Tesla conventional images were obtained. The data collection form captured areas of injury and location of signal abnormalities as described in Table I. The MRI scans were read by a single central reader (PDB) and the Hypothermia study subcommittee created an injury pattern where each level reflected a greater involvement of brain injury: 0 = normal MRI; 1A = minimal cerebral lesions only with no involvement of the BGT, anterior or posterior limbs of the internal capsule (ALIC, PLIC), or WS infarction; 1B = more extensive cerebral lesions with no involvement of BGT, ALIC, PLIC, or WS infarction, 2A = any BGT, ALIC, PLIC, or WS infarction noted without any other cerebral lesions; 2B = 2A and cerebral lesions; and 3 = cerebral hemispheric devastation.¹⁰ All infants were coded on the pattern of injury without knowledge of treatment intervention status or outcome.

PSE in this study was defined as any of the following: umbilical cord mishap (either cord prolapsed, knotted, torn, ruptured or compressed), uterine rupture, placental abruption, shoulder dystocia and major maternal hemorrhage, trauma, cardiorespiratory arrest or

seizures immediately preceding delivery. The primary outcome was death or moderate/severe disability at 18 to 22 months of age. Severe disability was defined as any of the following: Bayley Scales of Infant and Toddler Development version II¹² Mental Developmental Index <70, Gross Motor Function Classification System Level 3 to 5¹³ reflecting moderate or severe cerebral palsy, deafness or blindness despite amplification. Moderate disability was defined as a Mental Developmental Index score of 70 to 84 and any of the following: Gross Motor Function Classification System Level 2, hearing impairment or active seizures at 18 months. The outcome at 6–7 years of age (death or IQ assessed by the Wechsler Preschool and Primary Scale of Intelligence or the Wechsler Scale of Intelligence for Children) was assessed among children who had data on neonatal MRI and 6–7 year outcome¹¹. The RCT protocol was approved by the institutional review board of the NRN centers.

Statistical analyses

The study cohort included participants with data on neonatal MRI and neurological and developmental outcome at 18 to 22 months of age. Data was analyzed at RTI International with SAS Version 9.2. The maternal and neonatal characteristics of the infants who were part of the study cohort and those who were not in the study (absent MRI or outcome) were compared to evaluate for bias using Fisher exact test for categorical variables and t- tests for continuous variables. MRI findings by brain region were compared between infants with and without PSE with the Fisher's exact test. The relationship between the neonatal MRI findings (pattern 0, 1A, 1B, 2A, 2B, 3) among infants with and without acute PSE, and the primary outcome and components of the primary outcome was assessed by Cochran-Armitage trend tests, with the NICHD NRN pattern of injury used as a six-level variable (0, 1A, 1B, 2A, 2B, 3).¹⁰ The impact of cooling therapy on brain injury among infants with and without PSE was also examined by treatment groups (hypothermia and control) with the Fisher's exact test. For the 6–7 year outcomes, only comparisons of primary outcome (IQ <70) were evaluated between children with and without PSE. This study involved exploratory analyses of an existing data set, which limited the sample size. There are no corrections made for multiple comparisons. Statistical significance was considered as p values of <.05.

RESULTS

Of the 208 infants enrolled in the original RCT, 136 infants had a MRI and 84 had a history of PSE (Table I).

Maternal characteristics were comparable between PSE and no PSE except that antepartum hemorrhage was higher in the PSE group. The neonatal characteristics at <6 hours of age were similar in the two groups except that 5 and 10 minute Apgar scores were lower and rates of delivery room intubation were higher in the PSE group compared with those without a PSE (data not shown).

The MRI findings by region and pattern of injury in the groups with and without a PSE are noted in Table I. Infants with a PSE had more BGT lesions and the lesions were more likely to be moderate compared with infants without a PSE. Lower cord pH was correlated with

increased BGT injury (cord pH for normal BGT : 6.93 ± 0.17 ; minimal injury: 6.88 ± 0.21 ; moderate injury: 6.77 ± 0.18 ; severe injury 6.79 ± 0.24 ; correlation -0.34 , $p=0.0008$). Lower pH on the first postnatal gas showed a trend toward correlation with BGT injury (normal: 7.10 ± 0.20 ; minimal injury: 7.20 ± 0.23 ; moderate injury: 7.14 ± 0.18 ; severe injury: 6.9 ± 0.24 ; correlation -0.17 , $p=0.06$).

Among infants with PSE, 26 of 48 (54%) who were cooled and 12 of 36 (33%) who were in the control group had a normal MRI ($p=0.08$). Among those without a PSE 12 of 25 (48%) who were cooled and 10 of 27 (37%) controls had a normal MRI, $p=0.58$.

The frequency of the primary outcome (death or moderate/severe disability at 18 to 22 months) was similar among infants with and without a PSE. The components of the primary outcome (Table II), including the Mental Developmental Index categories and moderate or severe cerebral palsy were also comparable. At 6–7 years of age, 79 children in the PSE group and 45 in the no PSE group had outcome data; death or IQ <70 were similar in the 2 groups (Table II)

There was a significant relationship between the NICHD MRI pattern of brain injury and death or moderate/severe disability or survival with disability among infants with and without a PSE (Table III; available at www.jpeds.com).

DISCUSSION

In this study evaluating 136 of 208 trial participants of hypothermia vs. normothermia therapy for neonatal moderate or severe HIE, infants with a PSE had a higher frequency of BGT injury on MRI than infants without a PSE; however at both 18–22 months and 6–7 years there was no difference in neurodevelopmental outcomes between the PSE and no-PSE groups

Results of brain MRI studies of infants undergoing hypothermia for neonatal HIE from other RCTs have been reported. In the Total Body Hypothermia for Neonatal Encephalopathy trial (TOBY), 131 of 325 infants had imaging studies. Fewer abnormalities in the BGT, PLIC and white matter were noted among cooled infants and the imaging studies were predictive of outcome at 24 months of age.¹⁴ In the Infant Cooling Evaluation (ICE) trial, 127 of 221 trial participants had neonatal MRI; fewer infants in the hypothermia group had moderate or severe white or cortical gray matter injury. In the entire cohort, injury in the PLIC and BGT were predictive of death or major disability at 2 years of age.¹⁵ The present study extends our report correlating neonatal MRI and outcome¹⁰ by evaluating the impact of PSE on MRI findings; none of the other trials of hypothermia for neonatal HIE have examined associations of PSE, MRI and outcome.

Infants with a PSE in this study were sicker than those without a PSE, with lower Apgar scores at 5 and 10 minutes and higher rates of intubation in the delivery room; however outcomes were similar between groups both in infancy and childhood. This is reassuring information that is important for counselling families.

This study noted a higher frequency of BGT injury in infants with a PSE compared with infants with no-PSE. Okerefor et al identified 48 infants with a PSE and neonatal encephalopathy in the pre-hypothermia era who had MRI studies and follow up to a minimum of 12 months of age. The authors noted BGT injury associated with severe white matter damage among 14% of infants, BGT with mild or moderate white matter changes among 56%, isolated thalamic injury in 5%, moderate white matter damage only in 2% and mild white matter changes or normal findings among 23% of infants. More severe brain injury was associated with disability at follow-up.

The frequency of neonatal encephalopathy resulting from PSE was 25% among infants in regional cohorts^{16, 17} and 15% in the neonatal encephalopathy registry of the Vermont Oxford international centers.¹⁸ Two single center studies have reported rates of 12.8% in the pre-hypothermia era¹ and 12% evaluating obstetric antecedents to hypothermia treatment of neonates.¹⁹ In the present study which included only infants enrolled in a trial of moderate/severe encephalopathy with an MRI, the rate of PSE was 62%.

The average age of imaging in our study was 15 days; there are 2 reports of PSE and early MRI. The first study with MRI at 5 days among infants receiving hypothermia noted that 8 of 25 cooled and 2 of 35 historical control infants had PSE; 5 of 8 cooled infants had normal imaging, 2 had WS predominant lesions and 1 had a BGT predominant lesion; no follow-up data are available.²⁰ Another study⁹ noted outcomes of death or abnormal MRI (BG, cortical white matter and subcortical white matter injury extending beyond the WS area among survivors) were higher in infants with PSE (n=39, 69%) compared with infants without PSE (n=38; 55%). In our study, 55% of PSE and 58% of no-PSE infants had abnormal imaging; mortality rates were similar in both groups.

This study adds the following new information to the literature; 1) the rate of PSE among term infants with birth acidosis/need for resuscitation is 62%, 2) 45% of infants with a PSE have a normal neonatal brain MRI, and those with injury have cerebral and BGT injury, 3) cord pH is associated with BGT injury; lower pH was seen with more severe BGT injury, 4) cooled PSE infants have less injury, 5) the neonatal MRI findings among both PSE and non-PSE infants were related with outcome at 18–22 months of age and 6) infants with a PSE have similar outcomes in infancy and childhood to those without a PSE.

The limitations of our study are the following; 1) this is a secondary analyses that has unavoidable limitations, 2) the study is under powered to explore some of the interesting questions regarding PSE events, 3) we are unable to distinguish between cord prolapse, knot, tear, rupture or compression, and 4) the MRI studies were performed over a wide range of ages which may contribute to some under-detection of injury. Our exploratory analyses suggest that future studies should be adequately powered to assess each PSE and outcome. We recognize that cord prolapse, rupture, tight nuchal cord, true knot and avulsed cord are clinically identifiable cord mishaps (unlike cord compression). These events will be captured separately in the current NICHD Neonatal Research RCT of whole body hypothermia for neonatal encephalopathy in premature infants at 33–35 weeks gestation (NCT01793129)

We conclude that PSE is associated with need for more resuscitation at birth and more BGT lesions in the neonatal MRI; outcome however was similar between PSE and no-PSE infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Additional NICHD NRN Trial members include:

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Table 1

MRI findings among study subjects by region and pattern of injury

MRI Results	With PSE n=84	Without PSE n=52	p-value
Normal	38 (45%)	22 (42%)	0.86
Abnormal	46 (55%)	30 (58%)	
Total hemispheric devastation			
Any	4 (5%)	4 (8%)	0.48
Cerebral Lesions---no. (%)	39 (46%)	26 (50%)	0.73
Any Frontal	31 (79%)	19 (73%)	0.56
Any Temporal	30 (77%)	16 (62%)	0.27
Any Parietal	30 (77%)	19 (73%)	0.77
Any Occipital	28 (72%)	15 (58%)	0.29
BGT Classification--no. (%) [‡]			0.03
Normal	46 (58%)	32 (65%)	
Minimal	4 (5%)	6 (12%)	
Moderate	17 (21%)	2 (4%)	
Severe	13 (16%)	9 (18%)	
PLIC Classification--no. (%) [‡]			0.70
Normal	45 (54%)	29 (57%)	
Equivocal	18 (22%)	8 (16%)	
Abnormal	20 (24%)	14 (27%)	
ALIC--no. (%) [‡]			0.58
Normal	45 (54%)	29 (57%)	
Equivocal	19 (23%)	8 (16%)	
Abnormal	19 (23%)	14 (27%)	
Watershed area [‡]			0.08
0 = no infarction	72 (87%)	40 (77%)	
1 = single focal infarction	0 (0%)	0 (0%)	
2 = anterior or posterior white matter	2 (2%)	0 (0%)	
3 = anterior, posterior watershed cortex and white matter	1 (1%)	2 (4%)	
4 = anterior and posterior watershed	2 (2%)	0 (0%)	
5 = more extensive cortical involvement beyond watershed zones	6 (7%)	10 (19%)	
Cerebellar injury (any cerebellar lesion)	3 (4%)	2 (4%)	1.00
Brain stem injury	3 (4%)	3 (6%)	0.67
Medulla	2 (67%)	1 (33%)	1.00
Pons	1 (33%)	1 (33%)	1.00

MRI Results	With PSE n=84	Without PSE n=52	p-value
Midbrain	2 (67%)	2 (67%)	1.00
Subarachnoid hemorrhage (extra-axial hemorrhage)	3 (4%)	0 (0%)	0.29
Ventricular dilation (moderate/marked)	6 (7%)	3 (6%)	1.0
Pattern of Injury			
NICHD NRN:			0.45
0	38 (45%)	22 (42%)	
1A	2 (2%)	4 (8%)	
1B	4 (5%)	0 (0%)	
2A	5 (6%)	3 (6%)	
2B	31 (37%)	19 (37%)	
3	4 (5%)	4 (8%)	

*BGT: 7 infants could not be classified, PLIC: 2 infants could not be classified, ALIC: 2 infants could not be classified, Watershed area: 1 infant could not be classified

Table 2

Relationship of PSE and neurodevelopmental outcome

At 18–22 months	With PSE n=83*	Without PSE n=51*	p-value
Death or moderate/severe disability	33 (40%)	19 (37%)	0.86
Death	11 (13%)	4 (8%)	0.41
Normal or mild disability	50 (69%)	32 (68%)	0.66
Moderate disability	2 (3%)	0 (0%)	
Severe disability	20 (28%)	15 (32%)	
Bayley MDI			0.65
85	36 (52%)	19 (43%)	
70–84	14 (20%)	10 (23%)	
<70	19 (28%)	15 (34%)	
Bayley PDI			0.59
85	43 (63%)	26 (59%)	
70–84	5 (7%)	6 (14%)	
<70	20 (29%)	12 (27%)	
Disabling CP (moderate-severe)	17 (24%)	11 (25%)	1.0
Type of CP (exclusive categories)			0.25
Spastic quadriplegia	15 (88%)	8 (73%)	
Hemiplegia	0 (0%)	2 (18%)	
Other	2 (12%)	1 (9%)	
Multiple impairments**	17 (24%)	11 (23%)	1.0
Blindness	8 (11%)	4 (10%)	1.0
Hearing impairment	7 (10%)	5 (11%)	0.76
Deafness	3 (4%)	3 (7%)	0.67
Seizures	13 (18%)	10 (23%)	0.63
Completely normal†	31 (39%)	16 (33%)	0.57
Outcomes at 6–7 years	N=79	N=45	
Death or IQ < 70	30 (38%)	18 (40%)	0.85
Death	14 (18%)	6 (13%)	0.62

* One infant in each group had missing follow-up evaluation.

** Multiple impairments includes two or more of the following: disabling CP, gross motor score level 3–5, MDI < 70, blindness, deafness.

† Completely normal is survival with MDI ≥ 85, PDI ≥ 85, no disabling CP, no blindness, and no hearing impairment.