The Relationship between Clinically Identifiable Intrapartum Sentinel Events and Short-Term Outcome after Therapeutic Hypothermia

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Objective To determine the impact of intrapartum sentinel events on short-term outcome post-hypothermia.
Study design Records of 77 infants of 36 weeks' gestation or more, who received therapeutic hypothermia, were reviewed. Some were delivered after a clinically identifiable intrapartum sentinel event (IISE). All survivors had brain magnetic resonance imaging (MRI) at 7 to 10 days of life. The primary outcome of neonatal death related to hypoxic-ischemic encephalopathy was compared in infants born with (n = 39) or without an IISE (n = 38). MRI abnormalities were also compared. Logistic regression analysis was used to determine the variables predicting the primary outcome.
Results The two groups had similar Apgar scores, initial blood pHs, and early neurologic examinations. Base deficit was more severe in the IISE group. Neonatal death and hypoxic-ischemic injury was shown on brain MRI with basal nuclei, cortical, and subcortical white matter lesions extending beyond the watershed areas in infants surviving beyond the neonatal period were more common in the IISE group (P = .014; OR 11.1; 95% CI 1.3-92.6; and P = .034; OR 4.1; 95% CI 1.1-14.9, respectively). Multivariate analysis identified IISE (P = .023; OR 12.2; 95% CI 1.4-105.8) to be independently associated with neonatal death.
Conclusions IISEs are associated with neonatal death and severe injury as shown in brain MRI, even after hypothermia. *(J Pediatr 2011;159:726-30)*.

Differences in the duration and severity of hypoxia-ischemia are associated with specific regional distribution of brain injury in term primates. Acute, near-total asphyxia results in injury to the basal ganglia and thalamus, whereas prolonged partial asphyxia leads to a pattern of injury involving the white matter (WM), with extension to the cortex when the injury is severe.[1,2] Similar asphyxial insults result in comparable patterns of injury in newborn infants because of similar regional vulnerabilities, and they are detectable by magnetic resonance imaging (MRI).[3] Intrapartum asphyxial insults are also reported to be associated with long-term neurodevelopmental outcomes that vary on the basis of their timing, severity, and duration.[4] It is not known whether this difference in outcome is altered by therapeutic hypothermia in infants with or without clinically identifiable intrapartum sentinel events (IISEs).

Because therapeutic hypothermia is associated with a consistent reduction in death rates and neurologic impairment in infants with hypoxic ischemic encephalopathy (HIE),[5] we hypothesized that there would be no difference in outcomes between infants treated with hypothermia after an IISE and those treated for generalized depression at birth but who had not experienced such an event. We designed this retrospective study to determine whether an IISE affects short-term outcome after therapeutic hypothermia. We compared the primary outcome of neonatal death related to HIE (with multiorgan dysfunction) and the secondary composite outcome of neonatal death (related to HIE, with multiorgan dysfunction) or the presence of MRI-identified brain abnormalities in infants with clinically IISEs and those without such events (non-IISEs).

Methods

The University of Michigan investigators participated in the Cool Cap trial[6] and now offer both selective head cooling (SHC) and whole-body cooling (WBC) using the same entry criteria as in the Cool Cap trial and the National Institute of Child Health and Human Development Neonatal Research Network trial.[7] WBC is now used more commonly than SHC.

We reviewed the medical records of 86 newborns of 36 weeks' gestation or more who were consecutively treated with therapeutic hypothermia between December 2003 and February 2009 by either SHC or WBC, according to the respective cooling

BGT	Basal ganglia and thalamus
HIE	Hypoxic ischemic encephalopathy
IISE	Identifiable intrapartum sentinel event
MRI	Magnetic resonance imaging
SHC	Selective head cooling
WBC	Whole body cooling
WM	White matter

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protocols.[6,7] Some of these infants were born after an acute IISE. These included placental abruption severe enough to prompt emergent cesarean delivery; cord accident (cord prolapse, cord avulsion, or bleeding vasa previa); ruptured uterus; maternal cardiorespiratory arrest necessitating emergent cesarean delivery; shoulder dystocia and any other difficult delivery (including difficult and prolonged breech extraction significant enough to explain birth depression according to the obstetrics team, in the absence of other obvious causes of antecedent intrapartum asphyxia); and unexpected out-of-hospital birth without the attendance of health care personnel and with history of asystole upon arrival of the medical attendants. All other cases, with or without maternal risk factors (e.g., pregnancy-induced hypertension, diabetes, tobacco or drug use, maternal fever, etc.) but without IISEs, constitute the non-IISE group.

Written informed consent was obtained from parents before the start of cooling, and this retrospective review was approved by the Institutional Review Board at the University of Michigan.

Data collection were concurrent with hypothermia and included details of the prenatal or intrapartum events, the immediate neonatal course (Apgar scores and details of resuscitation), and the subsequent neonatal course, including presence of moderate or severe encephalopathy; mode of hypothermia (SHC or WBC); and presence of seizures before commencement of hypothermia.

Because the point estimates of the neuroprotective effects of cooling are essentially identical in SHC and WBC trials,[8] the data concerning subjects receiving either SHC or WBC were merged for analysis.

All infants receiving therapeutic hypothermia also underwent neuroimaging, usually brain MRI, at 7 to 10 days of life. MRI was performed using a 1.5 T magnet with T1- and T2-weighted imaging sequences in both the coronal and axial planes. MRI scans were reviewed by neuroradiologists and pediatric neurologists during the initial admission so they could assess for the presence of abnormal signal intensities consistent with hypoxic-ischemic injury within the basal gangia and thalamus (BGT), internal capsule, subcortical WM or cortex. MRI of the brain was considered abnormal if any of these were seen. Scans were later reviewed independently and categorized (for the present study) by a neuroradiologist (J.B.) masked to the clinical histories, original MRI reports, and outcomes. The categorization of the brain injury was similar to the basal ganglia/watershed (BG/W) scoring system proposed by Barkovich et al, which was reported to be predictive of neuromotor and cognitive outcome at 12 months. Scans were read as normal or no injury; abnormal signal in the basal ganglia or thalamus; abnormal signal in the cortex, not extending beyond the watershed; abnormal signal in the cortex not extending beyond the watershed and basal nuclei; or abnormal signal in the cortex extending beyond the watershed areas and basal nuclei.[9] This categorization represents two basic categories of imaging patterns in asphyxiated infants: one includes primary injury to the deep gray matter nuclei; the other includes injury to the vascular boundary zones.[10]

The primary outcome of neonatal death related to HIE with worsening multiorgan dysfunction despite maximal treatment, and the secondary, short-term outcome of neonatal death or the presence of any abnormal signal intensities consistent with hypoxic-ischemic injury in the post-hypothermia MRI of the brain were compared in the two groups. This short-term composite outcome was selected because we believed that an IISE would have a greater impact on immediate neonatal outcomes than on long-term neurodevelopmental outcomes and because infants who died before undergoing brain MRI could be not otherwise classified.

Forward logistic regression analysis was also performed to determine which, if any, of the selected pre-hypothermia clinical and laboratory variables could predict the primary outcome. The variables selected for the forward logistic regression model to assess the severity of asphyxia included 5-minute Apgar scores of 0 to 3 or 4 to 6; 10-minute Apgar scores of 0 to 3 or 4 to 6; pH below 7 or below 6.7; base deficit above 18.5 mmol/L or base deficit above 22 mmol/L in cord blood or during the first hour of life; onset of clinical seizure activity before the start of hypothermia; abnormal early neurologic examination, including flaccidity, decerebrate posturing, absent spontaneous activity, and absent or weak suck and gag reflexes; mode of delivery; male sex; meconium staining of amniotic fluid; and presence or absence of an IISE. A P value below 0.05 was considered significant.

The selection of these pre-hypothermia variables, including pH and base deficit and the specific components of the neurologic examination, was based on previous reports.[11] We did not use the conventional Sarnat system; instead, we used specific components of the early neurologic examination to compare the severity of HIE in the two groups because parts of the early neurologic evaluation (flaccidity, decerebrate posturing, and absent spontaneous activity) are more predictive than Sarnat staging for death or severe disability in infants with HIE despite therapeutic hypothermia.[11]

Results

The short-term outcome measure was able to be evaluated in 77 of the 86 infants. Of them, 7 infants had only post-hypothermia computed tomographic scans of the brain and were excluded. Only 1 of these infants was born after an IISE (placental abruption), and all 7 survived beyond the neonatal period. There were 2 other infants—1 who underwent veno-arterial extracorporeal membrane oxygenation for severe persistent pulmonary hypertension during cooling (confounding the interpretation of the MRI scan) and 1 who was later diagnosed with congenital myotonic dystrophy—who were also excluded.

Of the 77 infants in the study, 39 were born after an IISE: 14 after abruptio placentae necessitating emergent delivery; 12 after cord accidents; 5 after shoulder dystocia or difficult breech extraction; 3 after uterine rupture; 2 after maternal cardiorespiratory arrest; 2 after having been delivered out of hospital (one unexpectedly in a bathtub and the other in an automobile); and 1, the second of twins, with severe fetal