Therapeutic Hypothermia in Neonatal Hypoxic Ischemic Encephalopathy: Electrographic Seizures and Magnetic Resonance Imaging Evidence of Injury

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Objective To evaluate the electrographic seizure burden in neonates with hypoxic ischemic encephalopathy (HIE) treated with or without therapeutic hypothermia and stratified results by severity of HIE and severity of injury as assessed by magnetic resonance imaging (MRI).

Study design Between 2007 and 2011, video-electroencephalography (EEG) monitoring was initiated in neonates with moderate to severe HIE. Seizure burden (in seconds) was calculated, and brain MRI scans were quantitatively scored. Data were analyzed by ANOVA, the Student *t* test, and the χ^2 test.

Results Sixty-nine neonates with moderate or severe HIE were prospectively enrolled, including 51 who received therapeutic hypothermia and 18 who did not. The mean duration of video-EEG monitoring was longer in the therapeutic hypothermia group (72 $\pm$ 34 hours vs 48 $\pm$ 34 hours; P = .01). The therapeutic hypothermia group had a lower electrographic seizure burden (log units) after controlling for injury, as assessed by MRI (2.9 $\pm$ 0.6 vs 6.2 $\pm$ 0.9; P = .003). A reduction in seizure burden was seen in neonates with moderate HIE (P = .0001), but not in those with severe HIE (P = .80). Among neonates with injury assessed by MRI, seizure burden was lower in those with mild (P = .0004) and moderate (P = .02) injury, but not in those with severe injury (P = .90).

Conclusion Therapeutic hypothermia was associated with reduced electrographic seizure burden in neonatal HIE. This effect was detected on video-EEG in infants with moderate HIE, but not in those with severe HIE. When stratified by injury as assessed by MRI, therapeutic hypothermia was associated with a reduced seizure burden in infants with mild and moderate injury, but not in those with severe injury. *(J Pediatr 2013;163:465-70)*.

Neonatal seizures are associated with an increased incidence of brain injury and long-term neurodevelopmental delay.[1,2] Between 20% and 50% of neonates with neonatal seizures experience later epilepsy.[3] Approximately 50%-75% of neonatal seizures at term are attributable to hypoxic ischemic encephalopathy (HIE).[4] Clinical assessment[5] and amplitude-integrated electroencephalography (aEEG)[6-8] might not accurately quantify seizure burden. Evaluation with a multichannel electroencephalography (EEG) video study remains the gold standard for accurate identification and quantification of seizures. Along with seizure monitoring by video-EEG in HIE, delineation of the nature and extent of cerebral injury is important to the clinical management and prognosis of neonates with HIE, and is best done with magnetic resonance imaging (MRI).[9] Seizures in neonates in the setting of hypoxia-ischemia are independently associated with brain injury and worse neurodevelopmental outcomes, and these trends are independent of the severity of brain injury as assessed by MRI.[2,5]

The use of moderate therapeutic hypothermia to treat neonates with HIE is increasing. A meta-analysis of 3 trials including 767 neonates showed that moderate therapeutic hypothermia in neonates with HIE was associated with consistently reduced rates of mortality and neurologic impairment at age 18 months.[8] Multiple pathways attenuating the secondary phase of energy failure mediate the improved outcomes after therapeutic hypothermia in HIE.[10] In a biphasic model of neuronal death after hypoxic-ischemic injury, the cascade of events during secondary energy failure was associated with seizures.[11] There is also evidence linking therapeutic hypothermia with reduced brain injury as assessed by MRI.[9] Data on the impact of therapeutic hypothermia on seizure burden in neonatal HIE are limited, however.

The present study evaluated the impact of therapeutic hypothermia on electrographic seizure burden in neonates with moderate to severe HIE, stratified by the severity of HIE on presentation as assessed by video-EEG and by the presence and severity of brain injury as assessed by MRI.

aEEG	Amplitude-integrated electroencephalography
EEG	Electroencephalography
HIE	Hypoxic ischemic encephalopathy
MRI	Magnetic resonance imaging

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Methods

Between 2007 and 2011, neonates born at ≥36 weeks gestational age with clinical evidence of moderate to severe HIE[12] with or without seizures, aged ≤24 hours, and managed with or without therapeutic hypothermia were prospectively enrolled for continuous video-EEG monitoring. This single-center study was conducted at St Louis Children's Hospital after approval from the Washington University Human Research Protection Office. Informed written consent was obtained from at least 1 parent for each neonate enrolled. Exclusion criteria included birth at <36 weeks gestational age, age >24 hours, presence of congenital anomalies of the central nervous system, moribund status with no planned escalation of care, and receipt of neuromuscular blockade.

At the start of the study, neonates born at ≥36 weeks gestational age who presented with moderate to severe HIE were eligible for video-EEG monitoring.[10] After the institution of therapeutic hypothermia in 2008, the eligibility criteria for therapeutic hypothermia were expanded to include all of the following: ≥36 weeks gestational age at birth, moderate to severe HIE[9] with or without seizures, and any of the following: 10-minute Apgar score <5, prolonged resuscitation at birth (eg, chest compressions and/or intubation or mask ventilation at 10 minutes), severe acidosis (pH < 7.1) on cord or neonate blood gas analysis within 60 minutes of birth, or base deficit (>12 mmol/L) on cord or neonate blood gas analysis within 60 minutes of birth. Infants were recruited into a study protocol, and eligibility criteria and management did not change over time.

The CritiCool and Pediatric CureWrap system (Mennen Medical Corp, Southampton, Pennsylvania) was used to provide servo-controlled hypothermia. Neonates in the therapeutic hypothermia group were cooled to a core (rectal) temperature of 33.5°C for 72 hours and then rewarmed gradually over 24 hours. All neonates underwent conventional multichannel video-EEG recordings using a 10-20 system of electrode placement. Scalp electrodes were placed at Fp1, Fp2, F3, F4, Fz, C3, C4, Cz, P3, P4, Pz, T7 (T3), T8 (T4), P7 (T5), P8 (T6), O1, and O2 locations to record EEG activity from frontal, central, parietal, temporal, and occipital areas.

The entire video-EEG recording from each neonate was independently reviewed by an epileptologist blinded to the clinical course. An electrographic seizure was defined as a sudden and repetitive, evolving stereotypic EEG waveform with a definite start and end lasting for at least 10 seconds on at least 1 channel.[13] Electrographic status epilepticus was defined as continuous[14] or cumulative[15] electrographically documented seizure activity lasting for at least one-half of each 1-hour period. Seizure burden was defined as total duration of electrographic seizures in seconds. Video-EEG monitoring was started as soon as feasible after admission to the neonatal intensive care unit and was continued for up to 4 days in the therapeutic hypothermia group and for up to 3 days in the no therapeutic hypothermia group.

All clinical and electrographic seizures were treated based on a standard antiseizure protocol that included specific indications for treatment and standard antiseizure medications. Phenobarbital 20 mg/kg was the first-line antiseizure medication, followed by a second dose if needed. Fosphenytoin 20 mg/kg was the second-line antiseizure agent, followed by midazolam if necessary. Timing and dose of all antiseizure medications administered were recorded.

Conventional (T1- and T2-weighted) and diffusion MRI of the brain performed between day of life 4 and 10 were reviewed. In neonates with injury detected on MRI, the severity of injury was classified as mild, moderate, or severe based on a standard quantitative scoring method[16] by 2 blinded independent reviewers experienced in interpreting neonatal brain MRI images.

Continuous variables are described using mean ± SD and median and IQR, and categorical variables are described using frequencies. Seizure burden data (in seconds) was log transformed to stabilize the variance. For comparison of log-transformed seizure burden in the 2 groups, ANOVA was applied to the log-transformed data. The χ^2 test was used for categorical variables. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina). All tests were 2-sided, and a P value <.05 was considered statistically significant.

Results

Continuous EEG and MRI data were available for 69 of 74 neonates with moderate to severe HIE, including 51 (74%) in the therapeutic hypothermia group and 18 (26%) in the no therapeutic hypothermia group (**Figure 1**). The majority of infants in the study cohort who did not undergo therapeutic hypothermia (11 of 18) were born before the institution of therapeutic hypothermia in 2008. The other 7 of these 18 infants were born after therapeutic hypothermia was clinically available, but were outside the 6-hour window of eligibility for this therapy.

Characteristics of neonates in the therapeutic hypothermia and no therapeutic hypothermia groups are shown in **Table I**. The therapeutic hypothermia and no therapeutic hypothermia groups were comparable in terms of gestational age, birth weight, sex distribution, inborn versus outborn status, 5-minute Apgar score, cord blood/first arterial blood gas pH, and age at the start of video-EEG monitoring. None of the neonates in either group had an axillary maximum temperature exceeding 37.6°C during the first 7 days of life.

The duration of video-EEG monitoring was longer in the therapeutic hypothermia group compared with the no therapeutic hypothermia group (72 ± 334 vs 48 ± 34 hours; $P = .01$) (**Table I**). Electrographic seizures were documented in 19 of the 51 neonates (37%) in the therapeutic hypothermia group and in 16 of 18 (88%) in the no therapeutic hypothermia group. Electrographic status epilepticus was detected in 5 of 19 neonates with seizures