EEG Monitoring Technique Influences the Management of Hypoxic-Ischemic Seizures in Neonates Undergoing Therapeutic Hypothermia

Saber Jan^{a, b} Frances J. Northington^{b, c} Charlamaine M. Parkinson^{b, c}
Carl E. Stafstrom^{b, d}

^a Johns Hopkins Bloomberg School of Public Health, ^b Neuroscience Intensive Care Nursery Program, The Johns Hopkins Hospital, and ^c Division of Neonatology, Department of Pediatrics, and ^d Division of Pediatric Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Keywords

Electroencephalography · Neonatal seizure · Amplitude-integrated electroencephalogram · Hypoxia-ischemia · Therapeutic hypothermia · Antiseizure drug

Abstract

Electroencephalogram (EEG) monitoring techniques for neonatal hypoxia-ischemia (HI) are evolving over time, and the specific type of EEG utilized could influence seizure diagnosis and management. We examined whether the type of EEG performed affected seizure treatment decisions (e.g., the choice and number of antiseizure drugs [ASDs]) in therapeutic hypothermia-treated neonates with HI from 2007 to 2015 in the Johns Hopkins Hospital Neonatal Intensive Care Unit. During this period, 3 different EEG monitoring protocols were utilized: Period 1 (2007–2009), single, brief conventional EEG (1 h duration) at a variable time during therapeutic hypothermia treatment, i.e., ordered when a seizure was suspected; Period 2 (2009–2013), single, brief conventional EEG followed by amplitude-integrated EEG for the duration of therapeutic hypothermia treatment and another brief

conventional EEG after rewarming; and Period 3 (2014–2015), continuous video-EEG (cEEG) for the duration of therapeutic hypothermia treatment (72 h) plus for an additional 12 h during and after rewarming. One hundred and sixty-two newborns were included in this retrospective cohort study. As a function of the type and duration of EEG monitoring, we assessed the risk (likelihood) of receiving no ASD, at least 1 ASD, or ≥ 2 ASDs. We found that the risk of a neonate being prescribed an ASD was 46% less during Period 3 (cEEG) than during Period 1 (brief conventional EEG only) (95% CI 6–69%, $p = 0.03$). After adjusting for initial EEG and MRI results, compared with Period 1, there was a 38% lower risk of receiving an ASD during Period 2 (95% CI: 9–58%, $p = 0.02$) and a 67% lower risk during Period 3 (95% CI: 23–86%, $p = 0.01$). The risk ratio of receiving ≥ 2 ASDs was not significantly different across the 3 periods. In conclusion, in addition to the higher sensitivity and specificity of continuous video-EEG monitoring, fewer infants are prescribed an ASD when undergoing continuous forms of EEG monitoring (aEEG or cEEG) than those receiving conventional EEG. We recommend that use of continuous video-EEG be considered whenever possible, both to treat seizures more specifically and to avoid over-treatment.

© 2017 S. Karger AG, Basel

Introduction

Therapeutic hypothermia (TH) is the standard of care for neonates with hypoxic-ischemic encephalopathy (HIE), with the presumption that hypothermia reduces metabolic demand and affords neuroprotection in the face of brain injury [1–3]. Seizures in the setting of neonatal HIE exacerbate the underlying HI-induced damage and TH reduces the total duration of seizures in neonates with HIE [4]. Electroencephalography is the primary tool for assessing the occurrence and duration of neonatal seizures, with the electroencephalography background being the best predictor of neonatal seizure occurrence [5].

Electroencephalogram (EEG) monitoring protocols differ among institutions for neonates with HIE who undergo TH, regarding the type of EEG, i.e., conventional versus amplitude-integrated EEG (aEEG) versus continuous video-EEG (cEEG). Conventional EEG, using the international 10–20 system of electrode placement, is considered the gold standard for detecting electroclinical or electrographic seizures, but the short duration (usually about 1 h) of routine EEG may miss clinical or electrographic seizures. Although aEEG is straightforward to apply, can be monitored by neonatologists or nurses, and can be used for multiple days, it has several limitations including low sensitivity and specificity for seizure detection and a limited ability to detect focal, low-amplitude, or short-duration seizures [6, 7]. In addition, aEEG interpretation varies according to the level of expertise of the bedside observer [8]. The American Clinical Neurophysiology Society (ACNS) guideline recommends that continuous EEG (cEEG) monitoring combined with synchronized video (cEEG) be used for high-risk patients, including those with HIE, to screen for seizure activity [9]. As a result, many institutions now utilize cEEG rather than aEEG as the standard of care in neonates at a high risk for seizures who are admitted to a neonatal intensive care unit (NICU).

There are no evidenced-based guidelines for initiating or switching antiseizure drugs (ASDs) for HI-related seizures [10, 11]. In 1 large study involving 31 children's hospitals in the USA, 62% of infants were treated initially with a single nonbenzodiazepine ASD and 16% were treated with ≥ 2 nonbenzodiazepine ASDs (an interhospital range of 48–76 and 6–35%, respectively) [12]. About 50% of neonatal seizures fail to respond to an initial ASD and 30% are refractory to the 1st- and 2nd-chosen agents [13]. The type of EEG monitoring protocol influences the clinical decision to initiate, adjust, discontinue, or switch ASDs [14].

Previous studies have assessed the impact of different types of EEG monitoring on clinical care measures such as the number of ASDs used in the management of neonatal seizures [15–17]. Ours is the first study to address this outcome solely in neonates with HI-related seizures that were all treated with TH. The aim of this study was to determine whether there was a difference in the number of ASDs used to manage HI-related seizures among neonates undergoing TH as a function of different EEG monitoring protocols as these evolved over the years 2007–2015. During that time interval, 3 different EEG monitoring techniques were utilized in the NICU at Johns Hopkins Hospital (JHH) while the TH protocol remained constant. We found that, with the continuous forms of EEG monitoring (aEEG or cEEG), fewer ASDs were prescribed than with a single brief conventional EEG, thus supporting the ACNS recommendation [9].

Methods

The goal of this study was to determine if there was any change in the prescribing practice of ASDs over time as a function of EEG type. This is a retrospective cohort study of all neonates admitted to the JHH NICU with HIE from 2007 to 2015 who were treated with TH. The study was approved by the Institutional Research Board at the JHH.

In the period 2007–2015, 162 newborns underwent TH and were divided into 3 categories according to their birth date. During those years, 3 different EEG monitoring protocols were used in the JHH NICU. During Period 1, from January 2007 to April 2009, infants ($n = 30$) underwent a single, brief conventional full-montage EEG (for approx. 1 h) performed at the request of the neonatology team at a variable time point during the TH treatment. Neither form of continuous EEG, aEEG or cEEG, was used and not all TH-treated infants received a conventional EEG. During Period 2, from May 2009 to December 2013, infants ($n = 104$) received a single, brief conventional EEG (for <1 h) during the first 24 h of TH; infants then received aEEG for the remainder of TH treatment and the rewarming period, followed by another single, brief conventional EEG within 24 h after the termination of TH. Period 2 coincided with the development of a Neuroscience Intensive Care Nursery (NICN) program at the JHH with protocolized guidelines for the use of TH including pediatric neurology consultation, neuroimaging (brain MRI scan), and the use of aEEG on each infant. During Period 3, from January 2014 to December 2015, cEEG replaced aEEG and was begun as soon as possible after infants ($n = 28$) were admitted to the NICU; it was continued throughout the 72 h of TH plus for an additional 12 h after the termination of TH (i.e., during and after rewarming).

The number of ASDs prescribed was analyzed as 2 binomial variables. The first outcome variable was the number of neonates who received at least 1 ASD compared with those who did not receive any ASD. The second outcome variable was the number of

Table 1. Demographic and baseline characteristics of the study population

	Period 1 (<i>n</i> = 30)	Period 2 (<i>n</i> = 104)	Period 3 (<i>n</i> = 28)	<i>p</i> value ^a	Total (<i>n</i> = 162)
Males	17 (56.7)	64 (61.5)	18 (64.3)	0.82	99 (61.1)
Gestational age, years	38.89 (±1.8)	39 (±1.6)	38.1 (±1.8)	0.49	38.8 (±1.7)
Birth weight, g	–	3,275.3 (±630)	3,152.4 (±477)	0.34	
Length of NICU stay, days	13 (7–16)	14 (10–26)	10 (7.5–14.5)	0.009 ^b	13 (9–24)
Cord pH	6.9 (±0.15)	6.9 (±0.17)	6.9 (±0.19)	0.49	6.9 (±0.17)
Days of intubation	4 (0.5–6)	2 (0.5–7)	2 (1–6.5)	0.67	3 (0.5–7)
Apgar score at 1 min	1 (0–3)	1 (1–2)	1 (1–1)	0.19	
Apgar score at 5 min	4 (±2.6)	4 (±2.2)	3 (±2.3)	0.63	
Apgar score at 10 min	5 (±2.6)	5 (±2.1)	4 (±2.7)	0.22	
Spontaneous vaginal delivery	5 (17.2)	15 (14.4)	2 (7.1)	0.56	22 (13.7)
Vaginal forceps or vacuum-assisted delivery	4 (13.8)	16 (15.4)	1 (3.6)	0.26	21 (13)
Elective cesarean section	5 (16.7)	18 (17.3)	5 (17.9)	0.99	28 (17.3)
Emergency cesarean section	16 (53.3)	55 (52.9)	14 (50)	0.96	85 (52.5)
Neonates who required ECMO	0 (0)	2 (2.1)	3 (11.5)	0.06	3 (3.3)
Abnormal MRI finding	7 (35)	43 (44.3)	13 (56.5)	0.36	63 (45)
Abnormal EEG during TH	15 (60)	76 (73.8)	11 (64.7)	0.35	102 (70.3)
Abnormal EEG during rewarming	8 (47.1)	58 (62.4)	12 (70.6)	0.35	78 (61.4)

Period 1: January 2007 to April 2009; Period 2: May 2009 to December 2013; Period 3: January 2014 to December 2015. Values are expressed as *n* (%), median (IQR), or mean (±SD). ECMO, extracorporeal membrane oxygenation.

^a For the test of the hypothesis of equality during the 3 time periods.

^b Period 1 vs. Period 2, *p* = 0.03; Period 1 vs. Period 3, *p* = 0.57; Period 2 vs. Period 3, *p* = 0.009.

neonates who received ≥2 ASDs compared with those who received 1 or no ASD.

The medical records of patients were reviewed systematically. Data collected included demographics such as gestational age, gender, birth weight, and race. Other data collected were: a history of fetal distress or asphyxia, umbilical cord pH, Apgar scores at 1, 5, 10, and 20 min, mode of delivery, umbilical cord or placental complications, time point and duration of passive and active cooling, the presence of any abnormalities on brief conventional EEG, aEEG, or cEEG, the date and results of brain MRI scans, the type and number of ASDs, the duration of NICU admission and whether the patient was discharged from the NICU on an ASD.

Data were analyzed using STATA statistical software v14.0 (STATA Inc., TX, USA). The χ^2 test was used to compare 2 × 2 categorical variables and the Fisher exact test was used to compare categorical variables if any value was <5. Analysis of variance (ANOVA) was used to compare the parametric mean values and the Kruskal-Wallis test to compare the nonparametric measures for the 3 time periods. Multivariable log binomial regression was used to estimate the risk ratio of selected outcomes. Crude and adjusted models were tested. The crude model was used to estimate the risk ratio without adjusting for any potential confounders. In the adjusted model, the initial EEG and MRI results were considered as potential confounders in estimating the risk ratio of selected outcomes. *p* < 0.05 was considered statistically significant.

Results

There were no significant differences in the demographics or most baseline characteristics of the neonates across the 3 groups (Table 1), except that the length of stay in the NICU was significantly longer for patients in Period 2 than in Periods 1 and 3 (*p* = 0.03 and *p* = 0.009, respectively). The number of neonates treated for suspected seizures and those with electrographically confirmed seizures is given in Table 2. With a single, brief conventional EEG, electrographic seizures were confirmed in 10% of neonates treated for suspected seizures (Period 1). In Period 2, we performed 2 brief conventional EEGs, at the onset of TH and after TH; 9.8% of the neonates treated for suspected seizures had electrographically proven seizures on the first EEG and 17.6% had them on the second EEG. In Period 3 (cEEG), 30% of the neonates with suspected seizures had electrographically confirmed seizures.

Data related to the association of different EEG monitoring protocols on the number of ASDs prescribed are presented in Table 3. The number of neonates who received only 1 ASD (in all of our cases, phenobarbital) was significantly higher in Period 1 than in Periods 2 and 3

Table 2. Neonates with electrographically proven seizures in the 3 time periods

	Period 1	Period 2 ^a	Period 3
Number of neonates with electrographically proven seizures	2	1st EEG: 5 2nd EEG: 9	3
Number of neonates treated for suspected seizures	20	51	10

^a The 1st EEG was obtained early, i.e., in the first few hours of TH treatment. The 2nd EEG was obtained during or after rewarming.

Table 3. Impact of the type of EEG on the number of ASDs prescribed

	Period 1 (n = 30)	Period 2 (n = 104)	Period 3 (n = 28)	p value ^a	Total (n = 162)
Neonates who received only 1 ASD	19 (63.3)	33 (31.7)	6 (21.4)	0.001 ^b	58 (35.8)
Neonates who received ≥2 ASDs	1 (3.3)	18 (17.8)	4 (14.3)	0.13	23 (14.5)
Neonates who received phenobarbital only	16 (80)	29 (59)	7 (70)	0.03 ^c	52 (56.8)
Neonates who were discharged or transferred on an ASD	6 (24)	27 (27.6)	3 (12.3)	0.35	36 (24.5)

Values are presented as n (%).
^a For the test of the hypothesis of equality during the 3 time periods.
^b Period 1 vs. Period 2, $p = 0.002$; Period 1 vs. Period 3, $p = 0.001$; Period 2 vs. Period 3, $p = 0.29$.
^c Period 1 vs. Period 2, $p = 0.01$; Period 1 vs. Period 3, $p = 0.03$; Period 2 vs. Period 3, $p = 0.68$.

($p = 0.001$ and 0.03 , respectively; Fig. 1). There was no significant difference between Periods 2 and 3 in terms of the number of infants who were prescribed 1 ($p = 0.29$) or ≥2 ASDs ($p = 0.68$). There was no significant difference across the 3 periods in the number of neonates who received ≥2 ASDs, or who were discharged or transferred from the NICU still on an ASD (Table 3).

The crude and adjusted risk ratios for receiving at least 1 ASD in Periods 2 and 3 compared with Period 1 are presented in Table 4. In the crude model (without adjusting for any potential confounders), the risk ratio of receiving at least 1 ASD was 26% less in Period 2 than in Period 1 (95% CI 0.01–47%, $p = 0.06$, not quite significant). The risk ratio of receiving at least 1 ASD was significantly (46%) less in Period 3 than in Period 1 (95% CI 6–69%, $p = 0.03$). After adjusting for initial EEG and MRI results (adjusted model), the number of neonates who received at least 1 ASD had a significantly lower risk ratio when comparing Period 2 with Period 1 (38% lower; 95% CI 9–58%, $p = 0.02$) and Period 3 with Period 1 (67% lower; 95% CI 23–86%, $p = 0.01$). There were no significant differences when comparing Periods 2 and 3 in either model.

The crude and adjusted risk ratios of receiving ≥2 ASDs in Periods 2 and 3 compared with Period 1 are pre-

Fig. 1. Percent of neonates undergoing TH who received ≥1 (left side) or ≥2 (right side) ASDs as a function of the EEG monitoring period. Significantly fewer neonates received an ASD during aEEG (Period 2) or cEEG (Period 3) compared to a single, brief conventional EEG (Period 1). * $p < 0.05$. See the text for details.

Table 4. Risk ratio of receiving at least 1 ASD

	Crude model risk ratio (95% CI)	<i>p</i> value	Adjusted model risk ratio ^a (95% CI)	<i>p</i> value
Period 1	ref.	–	ref.	–
Period 2	0.74 (0.53–1.01)	0.06	0.62 (0.42–0.91)	0.02
Period 3	0.54 (0.31–0.94)	0.03	0.33 (0.14–0.77)	0.01

^a Adjusted for initial EEG and initial MRI results.

Table 5. Risk ratio of receiving ≥2 ASDs

	Crude model risk ratio (95% CI)	<i>p</i> value	Adjusted model ^a risk ratio (95% CI)	<i>p</i> value
Period 1	ref.	–	ref.	–
Period 2	5.19 (0.72–37.31)	0.10	1.72 (0.29–10.36)	0.55
Period 3	4.29 (0.51–36.06)	0.18	1.34 (0.14–11.02)	0.79

^a Adjusted for initial EEG and initial MRI results.

sented in Table 5. In both the crude and adjusted models, there was no significant difference in risk ratios for receiving ≥2 ASDs across the 3 time periods.

A sensitivity analysis was performed to examine any change in the estimated risk ratio for both outcomes after adjusting for potential confounders. Using the crude model, the estimated risk ratio was not significantly different after adjusting for the following potential confounders: gender, gestational age, birth weight, length of NICU stay, cord pH, APGAR score at 10 min, the presence of nonreactive fetal heart rate, meconium-stained amniotic fluid, or preeclampsia/eclampsia, maternal vascular clotting, cord or placental complications, emergent cesarean section, chorioamnionitis, or edema on the initial head ultrasound.

Discussion

This is one of the first studies to examine the clinical association between the number of ASDs prescribed and the use of different EEG monitoring protocols in neonates undergoing TH, and the first in which the entire study population underwent TH. We demonstrate that the advent of the continuous forms of EEG monitoring (aEEG and cEEG) has resulted in significantly fewer ASDs being prescribed when compared to brief conventional EEG.

We found a statistically significant reduction of 46% in the risk ratio comparing neonates who received at least 1 ASD in Period 3 (cEEG) compared with Period 1 (brief conventional EEG), without adjusting for other confounders. This finding could be explained by the better sensitivity and specificity of cEEG for detecting epileptiform discharges and seizures than is possible with aEEG or conventional EEG, thereby leading to the exclusion of false-positive results, and consequently fewer ASDs being prescribed [6–8].

Since neonates often exhibit abnormal movements that are not associated with electrographic seizure activity, a reliance on clinical observation alone or in combination with a single, brief conventional EEG for seizure diagnosis (as in Period 1) can result in poor differentiation between seizures and nonseizure events [18]. As a result, neonates with abnormal movements that are not associated with ictal discharges may nevertheless be diagnosed with seizures and then unnecessarily treated with ASDs. The ability to correlate clinical seizures with continuously running aEEG that could be quickly reviewed or as abnormal electrical activity on cEEG in Periods 2 and 3 could have influenced the physicians to prescribe ASDs more cautiously.

In the adjusted model (adjusting for the initial EEG and MRI findings), there was a significant reduction in the risk of receiving ≥1 ASDs in Periods 2 (aEEG) and 3 (cEEG) compared with Period 1. Initial EEG and MRI results were used as indicators of HIE severity. Using data available in the NICN database, we categorized EEG and MRI results as normal or abnormal; this classifies both ictal and abnormal nonictal brain electrical activity in the same abnormal category. In addition, the designation of MRI results as “abnormal” covers a wide range of pathologies, from mild to severe, including such varied etiologies as ischemia or hemorrhage (rare). Comparing protocols using this indicator of disease severity during each period, our results showed that significantly fewer ASDs were used in Periods 2 and 3 compared with Period 1. In Period 1, with a single, brief conventional EEG, physicians were more reliant on clinical judgment as to the suspected etiology of an abnormal movement, possibly leading to more ASD usage. The use of ASDs declined significantly when continuous EEG monitoring techniques were employed in Periods 2 and 3.

The risk of receiving ≥2 ASDs was not significantly different when comparing Periods 2 and 3 with Period 1. The effect estimate became close to null and the 95% CI became narrower after adjusting for initial EEG and MRI results, but this was still not significant. Neonates who received ≥2 ASDs represented only 15% of the total sam-

ple size. Such a small subgroup could be related to the nonsignificant increment and the broad 95% CI of the risk ratio of receiving ≥ 2 ASDs in Periods 2 and 3 compared with Period 1. Additionally, this population was more severely affected. The decision to treat with ≥ 2 ASDs was always determined by the pediatric neurology consulting team based on the clinical situation. Moreover, the insignificant increment and broad 95% CI of the risk ratio could be explained by a shift in clinical practice over the 9 years of the study, leading to an early switch from 1st-line (typically, phenobarbital) to 2nd-line ASDs. Of note, the protocol and inclusion criteria for TH did not change over the study time period (2007–2015).

The risk of prescribing ASDs was significantly less after the implementation of continuous monitoring techniques (aEEG and cEEG). One study examined the change in clinical practice 3 years before and 3 years after the introduction of aEEG in an NICU [16]. There was no significant change in the number of neonates diagnosed with seizures after the introduction of aEEG. Another study similarly concluded that there was no significant change in the number of ASDs prescribed for neonatal seizures after the introduction of aEEG in an NICU compared with the use of serial conventional EEGs [17]. Wietstock et al. [15] reported a significant reduction in the cumulative dose of phenobarbital and no change in the number of ASDs used in neonates with HIE-related seizures before and after the implementation of a neonatal neurocritical care service, which included TH treatment, cEEG monitoring, seizure management guidelines, and educating physicians and nurses. None of these studies was limited to neonates undergoing TH as in our study, but rather included either all neonates with suspected seizures who were admitted to an NICU [15–17].

Some of the findings of the studies cited above would imply that the number of ASDs does not change as a function of the type of EEG monitoring but only when there is an overall programmatic change in the approach to the infant with seizures [16, 17]. These studies employed study designs different from ours, and we conclude that continuous EEG monitoring techniques are associated with a decrease in the number of ASDs prescribed.

It is quite likely that there was drift in our clinical practice because our study period covers the preinception, start-up and ongoing development of the Neuroscience Intensive Care Nursery at the JHH. One notable change during the period 2007–2015 was the increased collaboration between the neonatology and pediatric neurology treating teams. Late in Period 2, guidelines (not protocols) for suggested ASD use in neonatal seizures were de-

veloped. These guidelines did not address evidence needed for diagnosis of seizures, but were confined to suggestions as to which ASDs were to be considered as 1st-, 2nd- and 3rd-line treatments for seizures, and provided a suggested workup for the potential causes of seizures. Specifically, there was no requirement for electrographic evidence of seizures prior to treatment. The recommendations for the addition of a second agent for seizures also did not change significantly from common clinical practice, and this is borne out in the lack of difference in the use of ≥ 2 ASDs across the 3 time periods.

Reported incidences of neonatal seizures that are subclinical vary widely [19]; it is estimated that electrographic seizures account for the majority (up to 90%) of neonatal seizures, especially during TH [20, 21]. Therefore, it might have been expected that the higher sensitivity and specificity of recent cEEG protocols and more frequent EEG monitoring would result in a *higher* number of diagnosed seizures and *more* ASDs being prescribed. We did find that cEEG captured a higher percentage of electrographic seizures among neonates treated for suspected neonatal seizures, but that this was associated with *fewer* ASDs prescribed. Our findings can be explained by several factors. First, the use of tests with higher specificity for seizures (first aEEG, then cEEG) would exclude more false-positive results. Second, in a small study population such as ours, the number of diagnosed subclinical seizures might be very limited due to the low sample size. With cEEG in place, providers were likely more confident in their ability to detect seizures and thus more judicious in their use of ASDs.

The increased length of stay of infants in Period 2 compared to Periods 1 and 3 is interesting but remained unexplained in our study. It is not likely that the switch to aEEG and then to cEEG as the monitoring modality of choice explains this finding, especially considering that a significant reduction in ASD use is evident in Period 2 compared with Period 1.

Our study is limited in that it was conducted at a single institution and the sample size is somewhat small (162 neonates) with a preponderance of infants in Period 2 (104 neonates, representing 64% of the total sample). Such a distribution, which primarily reflects the longer duration of Period 2, disproportionately weights Period 2 in the analysis. As more patients are treated with cEEG, additional benefits may emerge. In the adjusted model, we could not adjust for the severity of HIE other than with clinical parameters found at birth, due to lack of availability of this information in the dataset. However, we adjusted for initial EEG and MRI results as approximate surrogates of HIE severity. The development of an NICN program at the

JHH during Periods 2 and 3, with protocolized guidelines for TH use, suggestions for ASD choice, a requisite pediatric neurology consultation, and neuroimaging and aEEG for each infant, likely introduced drift and thus played a role in the reduction of ASDs independently of the EEG monitoring modality. It was also necessary to analyze the total number of ASDs as categorical variables because the exact number was not documented in the dataset.

Conclusion

Our results emphasize that the type of EEG monitoring influences ASD-prescribing behavior for neonates undergoing TH. Optimal practice would address the goal of providing adequate seizure control while preventing unnecessary medications and their attendant side effects. In our study, fewer ASDs were prescribed for the infants who underwent aEEG and cEEG, highlighting the association between the type of EEG and the number of ASDs. We recommend that cEEG be used whenever possible, to

treat seizures more specifically and to avoid overtreatment. Further studies are needed to determine any consequences of the implementation of a neonatal neurosciences program during this time that included changing prior EEG protocols to cEEG monitoring, on many variables including the length of NICU stay, the number of subspecialty consultations, the number and utility of the imaging studies obtained, and seizure and developmental outcomes. Further study is also needed to estimate the cost-effectiveness of cEEG on neonates undergoing TH.

Acknowledgment

Dr. Northington was supported by NIH grants HD070996, HD086058, and HD074593, and a Covidien research grant.

Disclosure Statement

There were no conflicts of interest.

References

- Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG: Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev* 2013;1:CD003311.
- Harris MN, Carey WA, Ellsworth MA, Haas LR, Hartman TK, Lang TR, et al: Perceptions and practices of therapeutic hypothermia in American neonatal intensive care units. *Am J Perinatol* 2014;31:15–20.
- Wassink G, Gunn ER, Drury PP, Bennet L, Gunn AJ: The mechanisms and treatment of asphyxial encephalopathy. *Front Neurosci* 2014;8:40.
- Low E, Boylan GB, Mathieson SR, Murray DM, Korotchikova I, Stevenson NJ, et al: Cooling and seizure burden in term neonates: an observational study. *Arch Dis Child Fetal Neonatal Ed* 2012;97:F267–F272.
- Glass HC, Wusthoff CJ, Shellhaas RA, Tsuchida TN, Bonifacio SL, Cordeiro M, et al: Risk factors for EEG seizures in neonates treated with hypothermia: a multicenter cohort study. *Neurology* 2014;82:1239–1244.
- Shah DK, Mackay MT, Lavery S, Watson S, Harvey AS, Zempel J, et al: Accuracy of bedside electroencephalographic monitoring in comparison with simultaneous continuous conventional electroencephalography for seizure detection in term infants. *Pediatrics* 2008;121:1146–1154.
- Shellhaas RA, Soaita AI, Clancy RR: Sensitivity of amplitude-integrated electroencephalography for neonatal seizure detection. *Pediatrics* 2007;120:770–777.
- Rennie JM, Chorley G, Boylan GB, Pressler R, Nguyen Y, Hooper R: Non-expert use of the cerebral function monitor for neonatal seizure detection. *Arch Dis Child Fetal Neonatal Ed* 2004;89:F37–F40.
- Shellhaas RA, Chang T, Tsuchida T, Scher MS, Riviello JJ, Abend NS, et al: The American Clinical Neurophysiology Society's guideline on continuous electroencephalography monitoring in neonates. *J Clin Neurophysiol* 2011;28:611–617.
- Booth D, Evans DJ: Anticonvulsants for neonates with seizures. *Cochrane Database Syst Rev* 2004;4:CD004218.
- Slaughter LA, Patel AD, Slaughter JL: Pharmacological treatment of neonatal seizures: a systematic review. *J Child Neurol* 2013;28:351–364.
- Blume HK, Garrison MM, Christakis DA: Neonatal seizures: treatment and treatment variability in 31 United States pediatric hospitals. *J Child Neurol* 2009;24:148–154.
- Boylan GB, Rennie JM, Chorley G, Pressler RM, Fox GF, Farrer K, et al: Second-line anticonvulsant treatment of neonatal seizures: a video-EEG monitoring study. *Neurology* 2004;62:486–488.
- Kilbride RD, Costello DJ, Chiappa KH: How seizure detection by continuous electroencephalographic monitoring affects the prescribing of antiepileptic medications. *Arch Neurol* 2009;66:723–728.
- Wietstock SO, Bonifacio SL, McCulloch CE, Kuzniewicz MW, Glass HC: Neonatal neurocritical care service is associated with decreased administration of seizure medication. *J Child Neurol* 2015;30:1135–1141.
- Appendino JP, McNamara PJ, Keyzers M, Stephens D, Hahn CD: The impact of amplitude-integrated electroencephalography on NICU practice. *Can J Neurol Sci* 2012;39:355–360.
- Shellhaas RA, Barks AK: Impact of amplitude-integrated electroencephalograms on clinical care for neonates with seizures. *Pediatr Neurol* 2012;46:32–35.
- Murray DM, Boylan GB, Ali I, Ryan CA, Murphy BP, Connolly S: Defining the gap between electrographic seizure burden, clinical expression and staff recognition of neonatal seizures. *Arch Dis Child Fetal Neonatal Ed* 2008;93:F187–F191.
- Scher MS, Alvin J, Gaus L, Minnigh B, Painter MJ: Uncoupling of EEG-clinical neonatal seizures after antiepileptic drug use. *Pediatr Neurol* 2003;28:277–280.
- Nagarajan L, Ghosh S, Palumbo L: Ictal electroencephalograms in neonatal seizures: characteristics and associations. *Pediatr Neurol* 2011;45:11–16.
- Boylan GB, Kharoshankaya L, Wusthoff CJ: Seizures and hypothermia: importance of electroencephalographic monitoring and considerations for treatment. *Semin Fetal Neonatal Med* 2015;20:103–108.