Treating EEG Seizures in Hypoxic Ischemic Encephalopathy: A Randomized Controlled Trial

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abstract

BACKGROUND: The impact of treating electrographic seizures in hypoxic ischemic encephalopathy (HIE) is unknown.

METHODS: Neonates ≥36 weeks with moderate or severe HIE were randomly assigned to either treatment of electrographic seizures alone (ESG) or treatment of clinical seizures (CSG). Conventional EEG video was monitored in both groups for up to 96 hours. Cumulative electrographic seizure burden (SB) was calculated in seconds and converted to log units for analysis. MRI scans were scored for severity of brain injury. Infants underwent neurodevelopmental evaluation at 18 to 24 months. Statistical analyses were performed by using SAS 9.3 version (SAS Institute, Inc, Cary, NC).

RESULTS: Thirty-five of 69 neonates (51%) who were randomly assigned and included in the study developed seizures (15 in ESG and 20 in CSG). Excluding infants with status epilepticus, median SB (interquartile range) in seconds in ESG (n = 10) was lower than in CSG (n = 16) (449 [113–2070] vs 2226 [760–7654]; P = .02). ESG had fewer seizures with shorter time to treatment (P = .04). Twenty-four of 30 (80%) surviving infants with seizures underwent neurodevelopmental evaluation at 18 to 24 months. Increasing SB in the combined cohort was significantly associated with higher brain injury scores ($P < .03$) and lower performance scores across all 3 domains on BSID III (P = .03).

CONCLUSIONS: In neonates with HIE, EEG monitoring and treatment of electrographic seizures results in significant reduction in SB. SB is associated with more severe brain injury and significantly lower performance scores across all domains on BSID III.

WHAT'S KNOWN ON THIS SUBJECT: Continuous conventional EEG video is currently gold standard for identifying neonatal seizures and a substantial proportion of neonatal seizures are electrographic. Currently there is no direct evidence that EEG monitoring, seizure identification, or treatment impacts long-term outcomes.

WHAT THIS STUDY ADDS: In neonates with hypoxic ischemic encephalopathy, EEG monitoring and treatment of electrographic seizures results in significant reduction in seizure burden. Increasing seizure burden is associated with more severe brain injury and significantly lower performance scores on Bayley Scales of Infant Development III.

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Dr Srinivasakumar designed the study, developed the study protocol, conducted the study, recruited and randomly assigned study subjects, performed data collection and data analyses including scoring of MRI injury, interpreted data, performed literature search, drafted the initial manuscript, and revised the manuscript; Dr Zempel designed the study and developed the protocol, monitored the EEG data, identified seizure burden, contributed to data collection, analyses, and interpretation, and critically revised the manuscript; Drs Trivedi, Wallendorf, and Rao contributed to data analyses and interpretation; Ms Smith assisted in the design of the EEG protocol and coordinated and conducted the EEG studies; Dr Inder contributed to the study design and data analyses including scoring of MRI injury; Dr Mathur designed the study, developed the protocol, supervised the study protocol, contributed to data analyses and interpretation, and critically revised the manuscript; and all authors approved the final manuscript as submitted.

This trial has been registered at www.clinicaltrials.gov (identifier NCT01027715).

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Neonatal seizures (NSs) are the most common manifestations of neurologic disease in the neonatal period occurring in ~3.5/1000 live term births.[1] Of neonates with seizures, ~20% die in the neonatal period, 28% to 35% later exhibit significant neurodevelopmental delay, and 20% to 50% of survivors treated for clinical seizures have postneonatal epilepsy.[1] NSs are unique in many facets, including their pathophysiology, treatment, and outcome, and much debate focuses on whether intensive treatment of NSs is necessary. NSs can be difficult to identify clinically and are challenging to differentiate from a variety of normal, poorly coordinated, neonatal movements.[2]

Continuous conventional EEG (cEEG) video is currently the gold standard for identifying NSs, and a substantial proportion of NSs are subclinical, especially after administration of antiepileptic drugs (AEDs).[2–5] Because the clinical recognition of NSs is unreliable, NSs are often over or underestimated, resulting in inappropriate use of AEDs.[6,7] Standard treatment of NSs includes phenobarbital and fosphenytoin with or without benzodiazepines.[8,9] Animal data reveal that commonly used anticonvulsants may have deleterious effects on the developing brain.[4,10–12]

NSs are most commonly associated with perinatal hypoxic ischemic encephalopathy (HIE), accounting for more than 60% of early onset NS.[1,2] Although neurodevelopmental outcome in term infants with seizures is highly influenced by the underlying etiology, and a diagnostic MRI scan is essential to delineate underlying brain injury,[13] increasing evidence from animal models and human studies reveals that seizures in themselves may adversely impact the immature brain.[4,12,14–16] Thus, accurate estimation and precise treatment of the true SB requires continuous EEG monitoring with rapid feedback to the bedside medical team. Currently no direct evidence is available that neonatal EEG monitoring, seizure identification, or treatment of seizures impacts long-term clinical outcomes, and such effort requires considerable medical resources.

There is consensus regarding the importance of treatment and perhaps prevention of status epilepticus (SE).[17] Recent studies have attempted to correlate the seizures noted on amplitude-integrated EEG (aEEG) with outcome to determine if NSs are independently associated with a worse outcome.[16] A previous randomized trial[14] using aEEG revealed a trend toward a reduction in the duration of seizures when clinical and electrographic seizures were treated. Other studies have revealed that infants treated for clinical and electrographic seizures had a lower incidence of postneonatal epilepsy, compared with historical controls treated only for clinical seizures.[14,18–21] This study reveals the first randomized controlled trial (RCT) evaluating the impact of treatment of electrographic seizures using continuous cEEG video for monitoring and targeted treatment of electrographic seizures in HIE.

Our objective was to monitor and treat electrographic seizures in neonates ≥36 weeks with moderate to severe HIE.

Our hypothesis: in neonates with moderate to severe HIE, early EEG monitoring and targeted treatment of electrographic seizures results in a decrease in seizure burden (SB) compared with treatment of clinical seizures.

METHODS

Study Design

This was a single-center prospective RCT conducted from 2007 to 2011 with approval from the Washington University Human Research Protection Office.

Inclusion Criteria

Eligible neonates met all 3 criteria:

1. Were ≥36 weeks' gestation at delivery;
2. Admitted to the NICU within the first 24 hours of life; and
3. Either fulfilled clinical criteria for moderate to severe HIE (Eunice Kennedy Shriver National Institute of Child Health and Human Development criteria)[22] or had clinical seizures (suspected or confirmed).

Exclusion Criteria

1. Neonates <36 weeks' gestation
2. >24 hours of age (to exclude non-HIE causes of seizures)
3. Infants with congenital anomalies of the central nervous system
4. Moribund infants for whom no further aggressive treatment is planned
5. Infants who demonstrated electrographic SE at the beginning of the cEEG study (initial 1 hour cEEG) also were excluded, because immediate treatment with AEDs was clinically indicated

Informed consent was obtained from parents after eligibility of the infant was confirmed. Therapeutic hypothermia for HIE was clinically introduced into practice during the study and hence the study includes infants treated with and without hypothermia in both groups.

The study had 4 key components.

Randomization

Subject allocation was performed by study personnel using a sealed envelope-based randomization system. As mentioned earlier, neonates were randomly assigned to either the EEG seizure treatment group (ESG) or Clinical seizure treatment group (CSG) once informed written consent was obtained from the parents.

EEG Monitoring

All neonates underwent continuous cEEG video monitoring (Stellate Harmonie, Montreal, Canada) with Grass gold disc electrodes placed according to the international 10-20 system for up to 96 hours with minimum of 24 hours and by using electrode cables that also routed the EEG signal simultaneous from the C3, P3, C4, and P4 electrodes to the bedside aEEG BRM 3 monitor (Natus, Inc, San Carlos, CA).

ESG

Neonates in this group had the limited channel bedside aEEG monitor available to the treating clinicians. The automatic seizure detecting software (RecogniZe for the BrainZ BRM 3, Natus Inc, San Carlos, CA) alerted the bedside nurse/physician with a change in color of the display in the upper panel of the monitor. Seizures were defined as "rhythmic spike wave activity" lasting for >10 seconds. Clinicians evaluated if the event was a seizure by looking at the neonate (to ensure there was no obvious movement artifact) and the raw EEG trace. Emphasis was placed on identification and treatment of definite seizures. All seizures were rapidly confirmed on cEEG video by a study epileptologist (Dr Zempel) before institution of any intervention to ensure that only true seizure events were treated. Any EEG event, confirmed to be a seizure, with or without a clinical correlate lasting >30 seconds, or more than 2 confirmed events detected by the algorithm in a 24-hour period were thresholds to commence standardized AED treatment. Treatment was escalated for each subsequent event if any seizures persisted after 20 minutes after the completion of drug infusion. Treatment was dictated by the detailed treatment protocol below (Fig 1).

CSG

Neonates in this group had the cEEG video system recording but only had the system available to check impedance to ensure optimal sensor contact. No EEG (aEEG or the raw tracing) or seizure detection data were visible to the bedside caregivers. Seizure diagnosis and treatment was based solely on clinical observation and was based on the outlined treatment protocol (Fig 1). A 1-hour cEEG video report could be obtained at any time at the discretion of the clinical team. Neonates who developed electrographic SE, detected by the study epileptologist, in this group were unblinded and treated as in the ESG. Neonates in both study groups received standard medical care.

In both groups, the study epileptologist monitored the cEEG remotely for subclinical seizures or electrographic SE frequently. The frequency of monitoring varied from continuously to every 4 hours and depended on the EEG background and presence of seizures.

MRI was undertaken between 7 and 10 days of life in surviving infants as per standard clinical practice in the NICU.

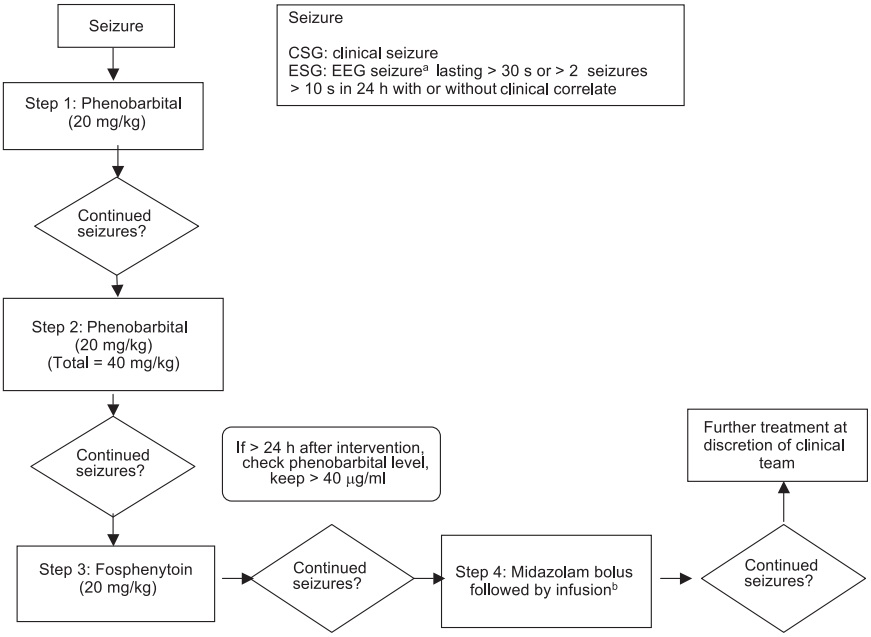

FIGURE 1

AED protocol. [a] EEG seizure defined as rhythmic repetitive spike wave activity lasting >10 seconds. [b] Midazolam was commenced with a bolus of 0.05 mg/kg, followed by a drip of 0.15 mg/kg per hour for 24 hours. The dose was decreased to 0.1 mg/kg per hour for 24 hours and then to 0.05 mg/kg per hour for 24 hours, before stopping.

Data Analysis

cEEG Analysis

All cEEG video recordings were analyzed off-line after the completion of enrollment. Seizure onset and duration was determined independently by an experienced epileptologist blinded to the subject (Dr Zempel). SB was defined as the duration of seizures (in seconds) in any electrode, focal, or diffuse. For each neonate, the total SB in seconds was calculated and log transformed to minimize the variance in the data. The primary outcome, cumulative SB, was compared between the 2 groups.

MRI Scoring

Severity of brain injury was assessed by using conventional T1- and T2-weighted spin echo sequences, with diffusion-weighted imaging and apparent diffusion coefficient maps. Injury was scored by a single reader (Dr Mathur) experienced in MRI scoring, and who was blinded to the group allocation, by using standardized methods described previously.[23]

Neurodevelopmental Follow-up

Eligible infants were followed up at 18 to 24 months' corrected age. Neurodevelopmental evaluation was performed by an independent, blinded developmental psychologist by using the Bayley Scales of Infant Development III (BSID III).[24]

Statistical Analyses

Before the study was started, a power analysis was performed by using a power ($1 - \beta$) of 0.85 and a significance level (α) of 0.05. We estimated that with a sample size of 50 neonates, we would have 85% power to detect a 50% reduction in SB at $P < .05$ level. Additional infants were recruited to maintain statistical power and account for the reduction in the seizure incidence noticed after initiation of therapeutic hypothermia and infants being excluded after randomization because of muscle relaxation for clinical management ($n = 72$). Infants in the CSG with SE detected after randomization were treated as in the ESG. Analysis of outcome data was by intention to treat.

Statistical analysis was performed by using SAS 9.3 version (SAS Institute, Inc, Cary, NC). Comparisons of baseline clinical and cEEG characteristics between groups were made with Fisher's exact test or χ^2 tests for categorical variables and with t tests and analysis of variance for logarithmically transformed continuous variables. Linear correlation analysis was used to test the relationship between SB and performance scores on BSID III. The level of significance was set at $P < .05$.

RESULTS

Seventy-two of the 91 neonates eligible by study criteria were enrolled during the study period (2007–2011). Three infants were excluded due to use of muscle relaxants during the monitoring period. Sixty-nine infants were randomly assigned into the study (ESG: $n = 35$, CSG: $n = 34$; Fig 2). All infants in the cohort had moderate–severe HIE as the primary etiology of seizures. Thirty-five neonates had seizures (15 in ESG and 20 in CSG). Nine neonates (5 in ESG and 4 in CSG) developed SE, and all of them were treated as in the ESG. No differences between the 2 groups with respect to baseline clinical characteristics were noted (Table 1). The total cumulative electrographic SB (log units) was significantly lower in the ESG compared with the CSG in those neonates without electrographic SE ($P = .02$; Table 2). This reduction in SB was observed in neonates with and without brain injury on MRI. In the ESG, 26/35 (74%) infants were cooled versus 24/34 (70%) in the CSG. The total number of seizures and time to treatment of seizures from onset were significantly lower in the ESG compared with CSG ($P = .04$; Table 2). There was a significant association between increasing SB and worse brain injury on MRI ($P < .03$; Figs 3 and 4). All neonates with electrographic SE in both groups had severe brain injury on MRI. Five infants died in the neonatal period (3 in ESG versus 2 in CSG). Intensive care support in these infants was withdrawn with parental consent and was due to clinical and hemodynamic instability in the setting of severe encephalopathy and brain injury on MRI and electrographic status unresponsive to treatment.

Between 2009 and 2013, 53/64 (83%) surviving infants (24/30 with seizures and 29/34 without seizures) in the cohort underwent neurodevelopmental testing with the BSID III at 18 to 24 months (with seizures: 8/12 in ESG versus 16/18 in CSG; without seizures: 18/20 in the ESG versus 11/14 in CSG). No significant differences in cognitive, motor, or language composite scores between the infants with seizures in the ESG and CSG groups were noted (ESG versus CSG with seizures [mean $\pm$ SD]: cognitive 89 $\pm$ 12 vs 89 $\pm$ 19; motor 93 $\pm$ 12 vs 89 $\pm$ 20; and language 90 $\pm$ 12 vs 89 $\pm$ 19; $P > .5$). Twenty-nine of 34 infants without seizures in the cohort underwent neurodevelopmental testing. Mean $\pm$ SD scores in this cohort were as follows: cognitive: 94 $\pm$ 14; motor: 95 $\pm$ 17; and language: 91 $\pm$ 19. These scores were not statistically different from infants in the ESG. Analysis of the whole cohort, however, revealed that increasing SB correlated significantly with lower performance scores across the cognitive, motor, and language domains on the BSID III ($P = .03$; Fig 3). Four infants in the cohort with seizures (4/30 survivors; 2 in ESG and 2 in CSG) developed postneonatal epilepsy.

DISCUSSION

In this single center, prospective, RCT utilizing cEEG video monitoring, treatment of EEG seizures in neonates with HIE results in a shorter time to treatment from seizure onset, a significant decrease in the cumulative electrographic SB, decrease in the number of seizures, and lower MRI injury scores when compared with treatment of clinical seizures alone. Infants who developed SE were excluded from this intergroup SB analysis because all of them were monitored and treated as in the ESG. In this study, treatment was initiated appropriately for clinically apparent seizure events, all of which had EEG correlates. Two infants already on AEDs in the CSG received an additional 10 mg/kg bolus of phenobarbital on the basis of clinical events without EEG correlate. However, subclinical and subtle seizures were substantially undertreated in the CSG.

No differences in the number of AEDs used or the phenobarbital levels were seen between ESG and CSG groups. It is possible that the earlier initiation of treatment in the ESG could influence the SB by earlier interruption of the seizure cascade.

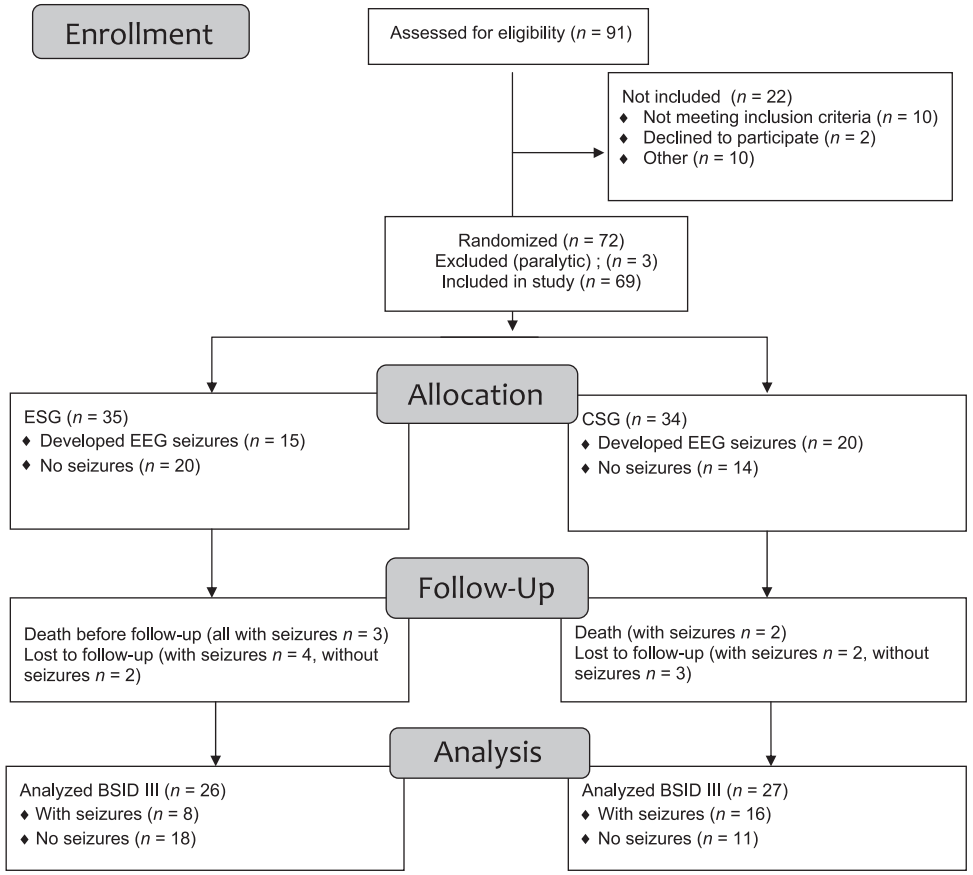

FIGURE 2
Consort flow diagram.

An overall association between electrographic SB and severity of brain injury on MRI was also present. All neonates with electrographic SE had severe brain injury on MRI.

In a recent multicenter RCT studying the effect of treating electrographic seizures detected with aEEG, van Rooij et al[14] showed a trend for a reduction in the duration of seizure patterns when clinical seizures and electrographic seizure patterns were treated. The van Rooij et al[14] study also revealed a significant association of seizure duration and severity of brain injury found on MRI scans, which was seen for infants who received treatment of clinical seizures only. These results were recently replicated in infants with HIE treated with therapeutic hypothermia.[25]

TABLE 1 Baseline Characteristics of the Cohort

Measure	ESG (With Seizures), *n* = 15	CSG (With Seizures), *n* = 20	*P*
Gestational age, mean ± SD, wk	38.3 ± 2	38.5 ± 2	.9
Birth weight, mean ± SD, g	3233 ± 585	3057 ± 602	.3
Gender, boy:girl, %	60:40	60:40	.7
5-min Apgar Score	4	4	NA
Cord/first pH, mean ± SD	7.05 ± 0.1	7.08 ± 0.2	.8
Inborn versus outborn, %	40:60	40:60	.5
Severity of HIE, moderate:severe, %	67:33	70:30	.7
Abnormality on brain MRI, %	66	85	.2
Therapeutic hypothermia, %	66	65	.8
Age at start of cEEG monitoring, mean ± SD, h	12.5 ± 9.5	13.3 ± 10.1	.3
Electrographic SE, %	33	20	.9
Duration of cEEG monitoring, mean ± SD, h	72.1 ± 37	69.5 ± 31	.7

NA, not applicable.

Multiple studies have revealed that prolonged seizures induce or worsen already-existing brain injury.[4,12,26] In human studies, it is difficult to measure the effect of seizures on neuronal injury and to distinguish this from the underlying pathogenesis of brain injury and possible effects of AED treatment. Available studies in neonates do suggest that seizures are likely to increase neuronal injury.[5,14,16,25,26] Understanding whether treatment of electrographic seizures impacts longer term outcome has been difficult because studies have included heterogeneous patient groups.

A major strength of this study is that it included a homogenous group of infants who met strict criteria for HIE. However, there were a few infants who were not treated with

TABLE 2 Comparison of Electrographic Seizure Characteristics Between the 2 Groups

Measure	ESG, n = 15	CSG, n = 20	P
SB, n = 35, mean ± SD, log units	7.4 ± 0.5	8.4 ± 0.4	.3
SB, median (interquartile range, first–third quartile), s	2214 (184–14 668)	4488 (844–11 923)	
SB, without SE; n = 26, mean ± SD, log units	6.0 ± 0.5	7.7 ± 0.4	.02*
SB, median (interquartile range), s	449 (113–2070)	2226 (760–7654)	
Number of EEG seizures, median	7	12	.04*
Severity of HIE, moderate:severe, %	80:20	90:10	.8
Time to treatment completion, mean ± SD, min	79 ± 35	170 ± 140	.04*
Total number of antiepileptic medications	1–3	1–3	NA
Total bolus dose of phenobarbital, mean ± SD, mg/kg	25 ± 15	30 ± 17	.3
Plasma phenobarbital level, mean ± SD, μg/mL	26 ± 16.5	31.5 ± 15	.4
Phenobarbital use before EEG monitoring, %	20	30	.8
Age at phenobarbital treatment, mean ± SD, h	14.5 ± 10	15.3 ± 8.5	.4

NA, not applicable; * P value significant.

therapeutic hypothermia in each group. Additionally, this study used cEEG video recording, the gold standard for monitoring seizures. Previous neonatal studies have used aEEG with its limitations of missing short and focal seizures.[27,28]

NSs have been reported to predispose patients to later problems with regard to cognition, behavior, and development of postneonatal epilepsy. Although there is potential harm of seizures in the immature brain, concern exists about possible adverse effects of anticonvulsant medications on the developing brain.[10]

This study demonstrated a significant reduction in SB with EEG monitoring and treatment in neonates with HIE who do not develop SE. Our data also revealed that increasing SB correlated significantly with worse MRI injury and adverse neurodevelopmental outcome at 18 to 24 months across domains. However, this study was not powered a priori to reveal an impact on neurodevelopmental outcome between the ESG and CSG. Such a study would need a cohort of 200 infants in each group to detect a 7.5-point (0.5 SD) difference between groups in the cognitive domain of the BSID III, with a power of 0.8 and α of 0.05. Our results support the American Clinical Neurophysiology Society guidelines that recommend EEG monitoring at least for 24 hours in infants with HIE,[17] and although this study was not sufficiently powered to reveal a difference in outcomes between groups, this study revealed a reduction in SB in the ESG.

Given the results of the current study and the recommendation for EEG monitoring in neonatal HIE by the American Clinical Neurophysiology Society,[17] early detection and treatment of EEG seizures may reduce cumulative SB. Confirming the impact of this approach on neurodevelopmental outcome will need a larger study. However, a larger multicenter, double-blinded clinical trial would be difficult to conduct because of ethical concerns. Although we recognize that another RCT may not be possible, 1 approach would be to perform a meta-analysis with other centers that have similar data. Another approach could be to set up a collaborative with institutions with similar clinical practices and follow-up and collect prospective data.

Results of this pragmatic trial that utilizes both a bedside monitoring tool (aEEG) and the gold standard of simultaneous cEEG-video should be generalizable to the majority of neonatal neurology/neonatology practice. Data from this study support the use of aEEG monitoring in situations where cEEG is not readily available. aEEG data alongside the raw EEG trace was able to detect 85% of the SB overall thus making it a reasonable option in NICUs where cEEG monitoring is not available.

CONCLUSIONS

We report the results of the first RCT of treatment of electrographic seizures using prolonged simultaneous limited channel aEEG and cEEG video monitoring. In this group of neonates with HIE, we were able to detect a significant reduction in the total cumulative electrographic

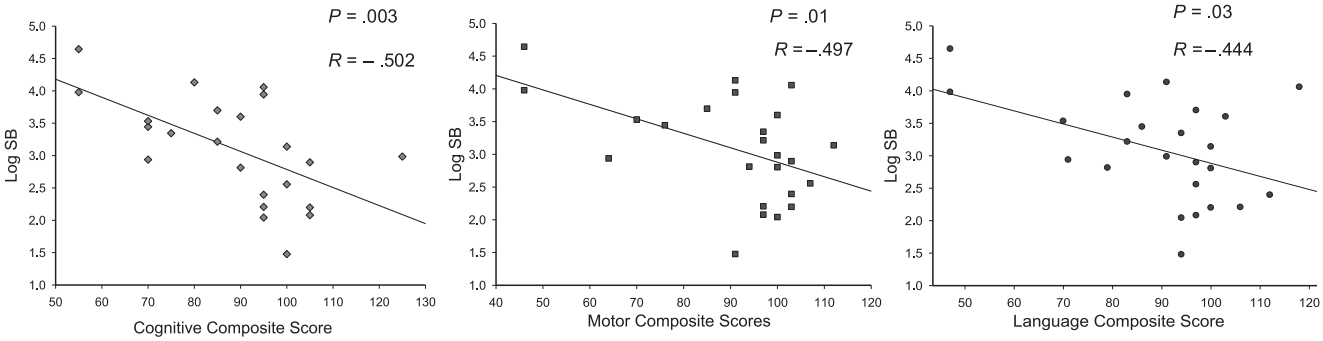

FIGURE 3
Correlation between electrographic SB and performance scores on BSID III. X-axis: Cognitive, motor, and language composite scores (BSID III); Y-axis: Log units of electrographic SB.

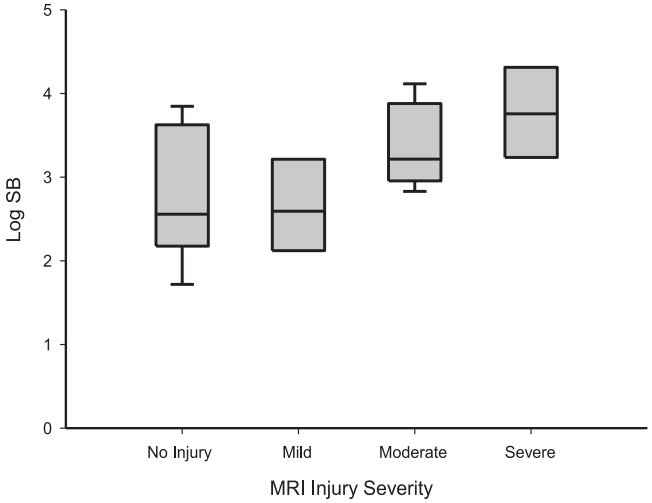

FIGURE 4

Overall trend of electrographic SB and severity of brain injury on MRI in the cohort. X-axis: Severity of brain injury on MRI; Y-axis: Log units of electrographic SB, $P < .03$ (no injury/mild versus moderate–severe).

SB with targeted treatment of electrographic seizures compared with treatment of clinical seizures alone. This reduction in SB was seen in neonates with and without brain injury on MRI. These findings, as well as the association of seizure duration and severity of brain injury on MRI reported in previous studies, may suggest that recognition and targeted treatment of electrographic seizures in neonates with HIE can reduce brain injury. In this study, we were able to show that overall, increasing SB correlated significantly with adverse neurodevelopmental outcome.

ACKNOWLEDGMENTS

We thank Anthony Barton who assisted with recruitment of subjects and data collection. We also appreciate the effort of the EEG technologists at St Louis Children's Hospital (Melanie Sewkarren, Sandra Boyd, Angela Johnson, Sarah Alt-Brockmeyer, Melissa Morris) and Michael Morrissey, PhD, for assistance with data management.

ABBREVIATIONS

AED: antiepileptic drug
aEEG: amplitude-integrated EEG
BSID III: Bayley Scales of Infant Development III
cEEG: conventional EEG
CSG: clinical seizure treatment group
ESG: EEG seizure treatment group
HIE: hypoxic ischemic encephalopathy
NS: neonatal seizure
RCT: randomized controlled trial
SB: seizure burden
SE: status epilepticus

www.pediatrics.org/cgi/doi/10.1542/peds.2014-3777

DOI: 10.1542/peds.2014-3777

Accepted for publication Aug 12, 2015

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Funded by the Thrasher Foundation.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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