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Seizure Control in Neonates Undergoing Screening vs Confirmatory EEG Monitoring

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Abstract

Objective

To determine whether screening continuous EEG monitoring (cEEG) is associated with greater odds of treatment success for neonatal seizures.

Methods

We included term neonates with acute symptomatic seizures enrolled in the Neonatal Seizure Registry (NSR), a prospective, multicenter cohort of neonates with seizures. We compared 2 cEEG approaches: (1) screening cEEG, initiated for indications of encephalopathy or paralysis without suspected clinical seizures; and (2) confirmatory cEEG, initiated for the indication of clinical events suspicious for seizures, either alone or in addition to other indications. The primary outcome was successful response to initial seizure treatment, defined as seizures resolved without recurrence within 30 minutes after initial loading dose of antiseizure medicine. Multivariable logistic regression analyses assessed the association between cEEG approach and successful seizure treatment.

Results

Among 514 neonates included, 161 (31%) had screening cEEG and 353 (69%) had confirmatory cEEG. Neonates with screening cEEG had a higher proportion of successful initial seizure treatment than neonates with confirmatory cEEG (39% vs 18%; $p < 0.0001$). After adjusting for covariates, there remained a greater odds ratio (OR) for successful initial seizure treatment in the screening vs confirmatory cEEG groups (adjusted OR 2.44, 95% confidence interval 1.45–4.11, $p = 0.0008$).

Conclusions

These findings provide evidence from a large, contemporary cohort of neonates that a screening cEEG approach may improve odds of successful treatment of acute seizures.

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Glossary

ASD = absolute standardized difference; **ASM** = antiseizure medication; **cEEG** = continuous EEG; **CI** = confidence interval; **HIE** = hypoxic-ischemic encephalopathy; **NICU** = neonatal intensive care unit; **NSR** = Neonatal Seizure Registry; **OR** = odds ratio.

Classification of Evidence

This study provides Class III evidence that for neonates a screening cEEG approach, compared to a confirmatory EEG approach, increases the probability of successful treatment of acute seizures.

Seizures in neonates are difficult to diagnose and often refractory to treatment. Up to two-thirds of neonates with acute symptomatic seizures have incomplete response to the initial loading dose of antiseizure medication (ASM).¹ Strategies to improve treatment of neonates with seizures include the use of continuous EEG monitoring (cEEG) to accurately diagnose seizures and assess response to treatment.² It is unknown whether preemptive use of cEEG to screen for seizures in high-risk neonates improves odds of treatment success, as compared to initiating cEEG to confirm the diagnosis of seizures only after clinically suspected seizures occur.

We hypothesized that utilization of a screening cEEG rather than a confirmatory cEEG approach would improve the likelihood of prompt and successful response to initial ASM treatment for neonates with acute symptomatic seizures.

Methods

The primary research question of this study was to provide Class III evidence for whether in neonates a screening cEEG approach rather than a confirmatory cEEG approach is associated with increased probability of successful treatment of acute seizures.

Study Design

We performed secondary analyses of data from the Neonatal Seizure Registry (NSR), a prospective registry of neonates with acute symptomatic seizures managed at 9 centers that adhere to the cEEG guidelines of the American Clinical Neurophysiology Society² from July 2013 through March 2018. The methods of the NSR have been reported previously.¹

For these analyses, data from 2 prospective cohorts were merged. NSR-I was a consecutive cohort of all neonates with seizures diagnosed clinically or with cEEG confirmation, enrolled under a waiver of consent from January 2013 to November 2015. NSR-II was a nonconsecutive cohort of neonates who survived acute symptomatic seizures diagnosed clinically or with cEEG confirmation enrolled with parental informed consent from July 2016 to March 2018. While all neonates with suspected seizures underwent cEEG as per American Clinical Neurophysiology Society guidelines, including continuing cEEG until no seizures had occurred for at

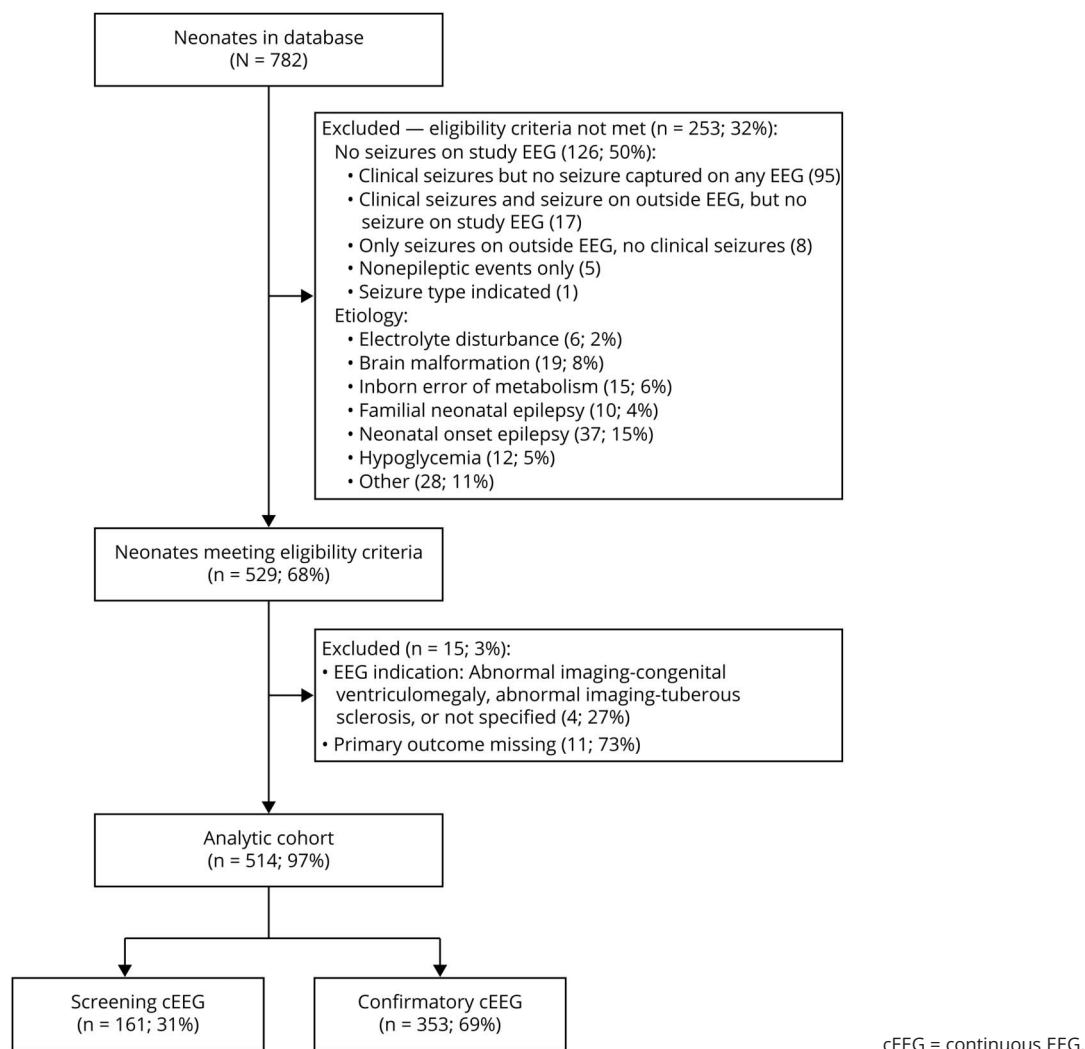
least 24 hours, and continuing cEEG for the duration of therapeutic hypothermia for infants treated for hypoxic-ischemic encephalopathy (HIE), the initiation and discontinuation times for cEEG were determined by treating clinicians. Similarly, seizure treatment regimens were at the discretion of the treating clinicians. Neonates from these NSR cohorts have been previously reported.^{1,3-5}

For these analyses, we included term neonates (born at ≥ 37 weeks gestational age) with seizure onset prior to 44 weeks postmenstrual age and acute symptomatic neonatal seizures due to an identified etiology, as determined by site investigator review of clinical documentation (figure 1). Acute symptomatic causes of neonatal seizures included HIE, ischemic stroke, intracranial hemorrhage, infection, and other acute brain injury as specified by the site investigator. Neonates were excluded if they had a transient cause of seizures (e.g., electrolyte abnormalities), had genetic or structural causes of neonatal epilepsy (rather than acute symptomatic seizures), or were missing data on either the cEEG approach used or the primary outcome. As the primary outcome for this analysis was seizure resolution as defined by EEG, we excluded NSR participants who never had seizures on cEEG at the study center (i.e., those with clinically diagnosed seizures that resolved prior to EEG, or those with seizures only reported on outside hospital EEG and not at the NSR study site cEEG). These neonates were included in a sensitivity analysis, as described below and in figure 2.

Definitions of Outcomes and Independent Variables

Our primary objective was to assess the association of cEEG approach with successful response to initial seizure treatment without seizure recurrence as confirmed on cEEG. Neonates were categorized as undergoing cEEG according to 1 of 2 monitoring approaches. A screening cEEG approach included neonates with cEEG ordered for sole indications of “encephalopathy” or “paralysis.” A confirmatory cEEG approach included neonates with cEEG ordered for indications of “clinical events suspicious for seizures” or “clinical events and encephalopathy,” either alone or in addition to other indications. The indication for cEEG was defined as the indication documented in the medical record. The primary outcome was successful response to initial treatment, defined as resolution

Figure 1 Participant Inclusion for Primary Analytic Cohort



of seizures on EEG no later than 30 minutes after administration of initial minimum loading dose of ASM (phenobarbital 20 mg/kg, phenytoin or fosphenytoin 15 mg/kg, or levetiracetam 40 mg/kg). Successful response to treatment required no relapse, either on EEG or by clinically diagnosed seizures, for the remainder of the neonatal intensive care unit (NICU) admission. The primary seizure etiology was categorized by the site investigator as HIE, ischemic stroke, intracranial hemorrhage, or other etiology. Multiple seizure etiologies were possible for a single patient.

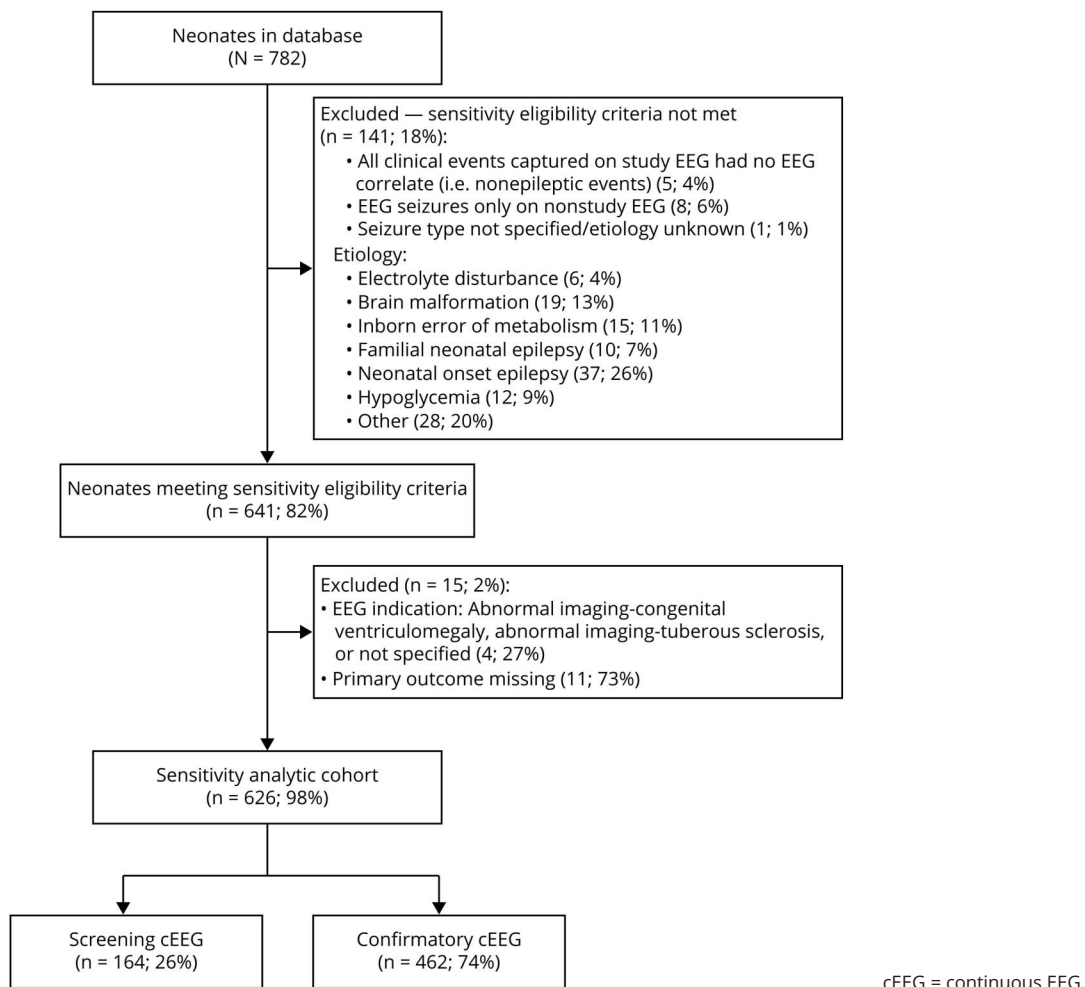
Statistical Analyses

Descriptive statistics characterized the cohort and compared cEEG groups by age, sex, race, ethnicity, birthweight, Apgar scores, and seizure etiology. The cEEG groups were described and compared for high seizure burden (defined as “frequent recurrent EEG seizures” or status epilepticus) and status epilepticus at any time during NICU admission; the registry data did not include details as to the timing of high seizure

burden or status epilepticus. Categorical variables were summarized using frequencies and percentages. Continuous variables were summarized using either mean with SD or median with interquartile range. Characteristics of the 2 cEEG groups were compared using absolute standardized difference (ASD), which was calculated as the difference in means or proportions divided by the standard error or multivariate Mahalanobis distance method. An imbalance between study groups was defined as ASD values greater than 0.2.⁶

The primary outcome of successful seizure treatment response was analyzed using bivariate and multivariable logistic regression analyses. Seizure severity has been associated with response to treatment; NSR data did not include detail regarding pretreatment seizure severity, but we adjusted for potential confounders previously identified as associated with seizure severity.¹ The following variables were included in the multivariable analysis as potential confounders related to seizure severity: Apgar score at 5 minutes, primary seizure

Figure 2 Participant Inclusion for Sensitivity Analytic Cohort



etiology category, presence/absence of multiple seizure etiologies, and whether the patient underwent therapeutic hypothermia.

Because HIE is a common clinical indication for cEEG, and thus of particular clinical interest, an exploratory analysis of the primary outcome was conducted restricting the analytic cohort to newborns who had a primary seizure etiology of HIE. In this analysis, the multivariable logistic regression model included Apgar score at 5 minutes and whether the patient underwent therapeutic hypothermia as potential confounders related to seizure severity.

Sensitivity analyses were performed to consider the potential effect of excluding neonates who never had seizures on study center cEEG (i.e., those with clinical events that resolved prior to EEG or those with clinical seizures and seizures reported on non–study site EEG but never on study EEG), and thus could not be assessed for the primary outcome of seizure resolution on cEEG. The documented indication for cEEG was used to classify these neonates into their cEEG approach group. Simulation studies were conducted to generate missing

outcome data by varying the assumption of treatment success (had EEG been available at the time of initial treatment). Treatment success rates simulated were 10%, 20%, 25% (the overall rate of treatment success in the primary analysis), 40% (the rate of treatment success observed in the screening cEEG group), 60%, 80%, and 100%. We also conducted simulations to determine the presumed treatment success rate at which there would be no difference between the 2 cEEG approach groups. Multivariable logistic regression was conducted using the same approach as used for the primary analysis to calculate the mean odds ratio (OR) and 95% confidence interval (CI) for 1,000 replications of each simulation study.

Unless otherwise specified, all statistical tests were interpreted at a 2-sided significance level of 0.05.

Power Analysis

We expected to include 534 infants in our analysis: 107 in the screening cEEG group and 427 in the confirmatory cEEG group. Based on prior work from the NSR, the overall rate of success with initial seizure treatment was estimated at 33%.¹ Using these sample sizes, we estimated over 80% power to

detect a difference of 15% in the successful seizure treatment response rate between the cEEG approach groups at a 2-sided α level of 0.05.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by institutional review boards at each center. Data from neonates in NSR were collected under an approved waiver of consent. Data from neonates in NSR-II were collected after written informed consent was obtained from guardians of all participants in this research. The NSR-II study was prospectively registered at ClinicalTrials.gov (NCT02789176).

Data Availability

Anonymized data from this study will be shared upon request of qualified investigators upon institutional review board approval after the end of the overall study.

Classification of Evidence

The study is rated Class III because of confounding by indication: screening cEEG was initiated for encephalopathy or paralysis without suspected clinical seizures, and confirmatory cEEG was initiated for clinical events suspicious for seizures.

Results

Characteristics of Patients in the cEEG Groups

Among 782 neonates in the dataset, 514 neonates were included in the primary analysis (figure 1). Among these neonates, 161 (31%) had screening cEEG and 353 (69%) had confirmatory cEEG. Among the 161 neonates with cEEG ordered for a screening indication, 10 developed clinically apparent seizures after cEEG was ordered but prior to initiation of cEEG. Similarly, of the 353 neonates with confirmatory cEEG ordered to evaluate events deemed suspicious enough to warrant cEEG for differential diagnosis, only 312 had clinical events of high enough suspicion that they were clinically diagnosed as seizures. Table 1 summarizes clinical and demographic characteristics. Neonates in the 2 cEEG groups differed in their primary seizure etiology (ASD 0.87): 75% in the screening cEEG group had HIE as their etiology vs 34% in the confirmatory cEEG group. Similarly, therapeutic hypothermia treatment differed (66% screening cEEG vs 15% confirmatory cEEG; ASD 1.2). Fifty-nine (12%) patients died during their neonatal admission, including 25 (16%) in the screening cEEG group and 34 (10%) in the confirmatory cEEG group.

Association of cEEG Approach With Treatment Success

Neonates in the screening cEEG group had a higher proportion of successful response to seizure treatment as compared to neonates in the confirmatory cEEG group (39% vs 18%; $p < 0.0001$) (table 2). Odds of successful response to seizure treatment remained greater in the screening cEEG group as compared to the confirmatory cEEG group after adjusting for covariates (adjusted OR 2.44, 95% CI 1.45–4.11; $p = 0.0008$). Similarly, among the subgroup of 241 neonates with HIE, the screening cEEG group had greater odds of

successful response to seizure treatment as compared to the confirmatory cEEG group after adjusting for covariates (adjusted OR 2.15, 95% CI 1.14–4.04; $p = 0.02$).

Sensitivity Analysis: Including Neonates Who Never Had Seizures on Study EEG

The primary analysis excluded 112 neonates with resolution of clinical events prior to study cEEG initiation, as this rendered us unable to measure the primary outcome of seizure resolution on EEG within 30 minutes of initial ASM loading dose (figure 1). Of these neonates, 3 (3%) were in the screening cEEG group and 109 (97%) were in the confirmatory cEEG group (figure 2). For the 3 neonates with clinical events resolved prior to cEEG initiation but assigned to the screening group, cEEG was ordered for the indication of screening, then clinical events began and resolved in the interval between the decision to order EEG and cEEG initiation.

Figure 3 shows the results of the analyses of simulated data under various assumptions of initial treatment response for the group with clinical events resolved prior to cEEG initiation. When the estimated treatment success rate for those with missing outcome data was 25% or 40%, the odds of seizure treatment success remained greater in the screening cEEG group as compared to the confirmatory cEEG group. Specifically, if the overall treatment success rate was assumed to be equal to that of the overall cohort from the primary analysis (25%), then neonates in the screening cEEG group continued to have greater odds of successful seizure treatment response after adjusting for covariates (adjusted OR 2.24, 95% CI 1.40–3.58). Only with assumed rates of successful response to initial treatment greater than 52% for those with missing data was there no difference between the 2 cEEG approach groups in their successful response to initial treatment (figure 3). EEG-based studies have shown neonatal seizure treatment success rates of 30%–50%^{1,7–9}; all simulations based on assumptions in this range supported greater odds of successful seizure treatment response in the screening cEEG group.

Discussion

Seizures are common among neonates with certain high-risk conditions, and they often lack distinct clinical signs.^{2,10,11} Accurate diagnosis of neonatal seizures relies on EEG confirmation. Screening cEEG allows detection of electrographic-only seizures and definitive diagnosis of clinically suspected seizures. Furthermore, in neonates, ASM administration can result in suppression of outward clinical signs while electrographic seizures persist (known as electroclinical “uncoupling”); cEEG is necessary to accurately assess response to ASM treatment. For this reason, some centers have developed pathways to employ cEEG for seizure detection among all neonates in high-risk groups, such as those with HIE or other conditions.¹² Similarly, the American Clinical Neurophysiology Society has published guidelines for clinical conditions in which cEEG is indicated due to a high risk of seizures.² The American Academy of Pediatrics has suggested that centers

Table 1 Demographic and Clinical Characteristics by Continuous EEG Monitoring (cEEG) Approach

	cEEG approach		Absolute standardized difference ^a
	Screening cEEG (n = 161)	Confirmatory cEEG (n = 353)	
Female sex	68 (42.2)	151 (42.8)	0.01
Race			0.29 ^a
White	73 (45.3)	199 (56.4)	
Black/African American	23 (14.3)	43 (12.2)	
Asian	16 (9.9)	22 (6.2)	
More than one race	3 (1.9)	12 (3.4)	
Other	23 (14.3)	33 (9.4)	
Unknown	23 (14.3)	44 (12.5)	
Ethnicity			0.14
Hispanic or Latino	30 (18.6)	51 (14.5)	
Not Hispanic or Latino	113 (70.2)	258 (73.1)	
Unknown/not reported	18 (11.2)	44 (12.5)	
Gestational age at birth, wk	38.4 ± 2.9	38.5 ± 3.4, n = 350	0.05
Birthweight, kg	3.1 ± 0.7, n = 160	3.2 ± 0.8, n = 345	0.13
Apgar score: 1 minute	2 (1–5), n = 154	5 (2–8), n = 327	0.68 ^a
Apgar score: 5 minutes	4 (2–7), n = 155	8 (5–9), n = 326	0.81 ^a
Apgar score: 10 minutes	5 (3–6), n = 106	7 (5–8), n = 117	0.46 ^a
Primary seizure etiology			0.87 ^a
Hypoxic-ischemic encephalopathy	118 (73.3)	123 (34.8)	
Hemorrhage	21 (13.0)	73 (20.7)	
Ischemic stroke	17 (10.6)	104 (29.5)	
Other	5 (3.1)	53 (15.0)	
Age at cEEG initiation, h	11.6 (8.2–59)	44.6 (20.6–147.6)	0.16
Duration of cEEG, h	87.0 (68.9–101.4)	61.7 (40.6–84.0)	0.62 ^a
Clinical seizures prior to cEEG	10 (6.2)	312 (88.4)	2.90 ^a
Phenobarbital given prior to cEEG	8 (5.0)	195 (55.2)	1.31 ^a
Therapeutic hypothermia	106 (66.3)	53 (15.0)	1.22 ^a
Initial medication used for loading			0.09
Phenobarbital	148 (91.9)	333 (94.3)	
Levetiracetam	9 (5.6)	15 (4.3)	
Phenytoin/fosphenytoin	2 (1.2)	2 (0.6)	
Other	0	1 (0.3)	
No loading dose given	2 (1.2)	2 (0.6)	
High seizure burden at any time during NICU admission	68 (42.2)	199 (56.4)	0.28 ^a
Status epilepticus at any time during NICU admission	32 (19.9)	74 (21.0)	0.03

Abbreviation: NICU = neonatal intensive care unit.

Data are presented as n (%), mean ± SD, or median (interquartile range).

^a An imbalance between study groups is defined as values greater than 0.20.

Table 2 Outcome by Continuous EEG (cEEG) Approach

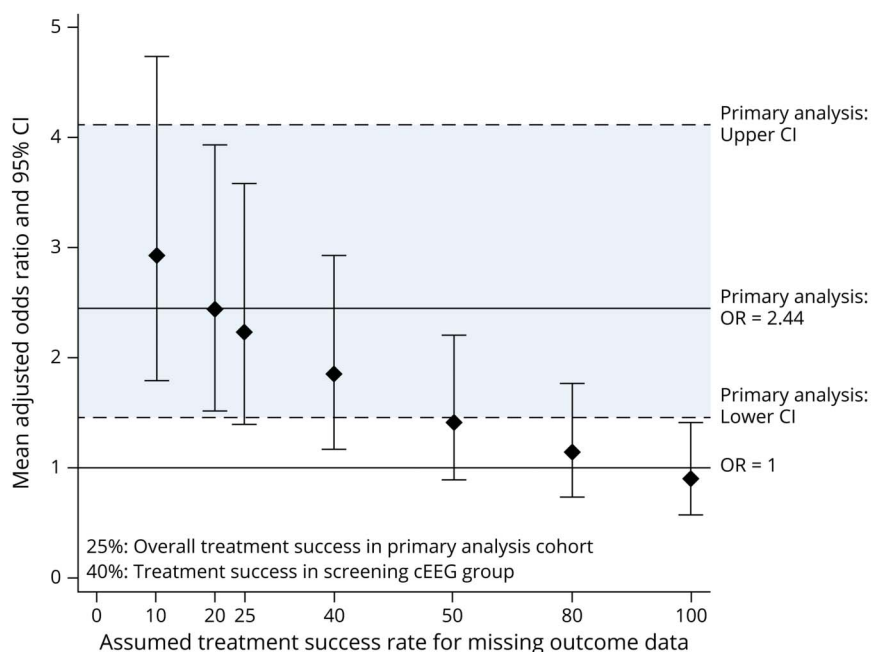
	Screening cEEG, n (%)	Confirmatory cEEG, n (%)	OR (95% CI); <i>p</i> value (unadjusted)	OR (95% CI); <i>p</i> value (adjusted ^a)
Primary analysis				
Neonates included	161 (31.3)	353 (68.7)		
Successful treatment response Odds of initial treatment success: screening cEEG vs confirmatory cEEG	63 (39.1)	65 (18.4)	2.85 (1.88–4.32); <i>p</i> < 0.0001	2.44 (1.45–4.11); <i>p</i> = 0.0008
Subgroup analysis: Hypoxic-ischemic encephalopathy seizure etiology				
Neonates included	118 (49)	123 (51)		
Successful treatment response Odds of initial treatment success: screening cEEG vs confirmatory cEEG	47 (39.8)	26 (21.1)	2.51 (1.42–4.43); <i>p</i> = 0.002	2.15 (1.14–4.04); <i>p</i> = 0.02

Abbreviations: CI = confidence interval; OR = odds ratio.

^a Multivariable analysis adjusted for Apgar score at 5 minutes, primary seizure etiology category, presence/absence of multiple seizure etiologies, and whether the patient underwent therapeutic hypothermia.

providing therapeutic hypothermia to neonates with HIE should also have the ability to provide cEEG or amplitude-integrated EEG monitoring for seizure detection.¹³ A recent survey of NICU practices in California found the majority of centers performed some degree of EEG monitoring among all neonates undergoing therapeutic hypothermia for HIE.¹⁴ The goal of using cEEG as a tool to screen for seizures among high-risk neonates is to facilitate earlier and more accurate diagnosis, and thereby more effective treatment, while avoiding ASM administration for seizure mimics.

At the same time, cEEG is resource-intensive, and may not be available for all high-risk neonates at all hospitals. Among neonates with HIE treated with hypothermia, fewer than half have seizures on EEG.¹⁵ Among groups of newborns with other risk factors, the incidence is even lower.¹⁶ For this reason, some centers have employed a strategy of initiating cEEG only when there is a clinical suspicion for seizure, such as an abnormal paroxysmal movement suspected to be seizure. This confirmatory cEEG strategy allows lower use of resources than screening all neonates at risk. It is unknown to

Figure 3 Simulation Results Modeling Varied Assumed Treatment Success Rates for Patients With Missing Outcome Data

Mean adjusted odds ratio: screening cEEG vs confirmatory cEEG

cEEG = continuous EEG; CI = confidence interval; OR = odds ratio.

what degree this approach misses high-risk neonates with seizures that do not have clinical manifestations or delays seizure diagnosis and treatment.

There is a paucity of evidence regarding the effect of cEEG strategy on short- and long-term outcomes. A randomized trial of screening vs confirmatory cEEG in neonates at risk for seizures is unlikely to occur, due both to a lack of equipoise at individual centers and the high expense of such a trial. In the absence of a randomized trial, other types of evidence must be sought to understand the effect of cEEG approaches on outcomes.

This study analyzed prospective, observational data from multiple centers to determine the association between cEEG monitoring approach and successful seizure treatment with the first loading dose of ASM. After adjusting for covariates, our results showed that neonates who underwent screening cEEG had more than 2 times greater odds of seizure treatment success as compared to those who underwent confirmatory cEEG. An analysis of only neonates with HIE yielded a similar conclusion: screening cEEG remained associated with more than 2 times greater odds of treatment success than confirmatory cEEG. These data suggest further study is warranted as to how utilization of a screening cEEG approach may facilitate improved successful seizure treatment response in neonates at high risk for seizures, and whether this ultimately affects long-term outcomes.

Strengths of this study include the large number of neonates included and prospective data collection. Because this is an observational study, it is important to recognize that our results showing an association do not prove causation. Our analysis only considered the overall association between cEEG approach and successful response to initial seizure treatment. We were not able to examine all potentially relevant intermediary steps, such as time to cEEG initiation, time to seizure recognition, and time to first ASM administration. However, studies of pediatric patients have found longer duration of seizure prior to treatment is associated with a more refractory course.^{17,18} This may be mediated at a cellular level by the internalization of inhibitory receptors as a result of prolonged seizure, among other mechanisms.¹⁹ Ongoing research is required to understand better any potential causal relationship between screening cEEG approach and increased success in seizure control. Similarly, there was no significant difference in the specific ASM used between groups, thus further studies are needed to determine whether monitoring approach is a factor in clinician choice of ASM, and how this might affect outcomes. NSR data did not include details on timing of seizure burden or quantification of seizure burden; we were not able to assess how pretreatment seizure burden affected seizure control in each group. Nor were we able to assess all potentially relevant outcome measures, such as reduction in seizure burden in the absence of seizure resolution or long-term outcomes. These are important avenues for future work; long-term neurodevelopmental follow-up is underway for neonates participating in the NSR.

An important limitation is that our primary outcome measure of successful response to initial treatment was defined by cEEG showing resolution of seizures within 30 minutes of first ASM administration. Thus, our primary analysis did not include neonates who never had seizures on cEEG. This necessarily excluded those neonates with clinically diagnosed seizures that resolved prior to initiation of cEEG. Whereas it is unknown whether all of these neonates had true electrographic seizures, each was considered to have seizures by clinical diagnosis upon review by the site investigator. It is likely that most had electro-clinical seizures at the time of diagnosis, and that these resolved at some point prior to cEEG initiation, although not necessarily within 30 minutes of first ASM administration. By excluding neonates who had apparent resolution prior to cEEG, the confirmatory cEEG approach group for the primary analysis may have included a higher proportion of neonates with more treatment-resistant seizures. To address this, we performed sensitivity analysis modeling how our results would change if the excluded neonates had been included; sensitivity analysis supported the findings of our primary analysis.

Similarly, we recognize that whether a neonate receives screening or confirmatory cEEG is not wholly at the discretion of the provider—for example, neonates may be transferred to referral centers only after clinical seizures are recognized. This is reflected in our own results, as 10 neonates had screening cEEG ordered prior to onset of clinical seizures, but then developed clinical seizures in the interval between the decision to order cEEG and initiation of cEEG recording. At the same time, it is possible to set a preferred strategy of screening or confirmatory cEEG for high-risk patients, such as those with HIE, through development of unit guidelines or institutional pathways. Thus, we find evidence to support the use of a screening cEEG approach as clinically relevant even though the option is not available for every patient. Finally, future research should investigate whether the benefit of improved seizure control may be seen with approaches that are less resource-intensive, such as screening cEEG for 24 hours with continued monitoring only for those identified to be at ongoing risk for seizures.

These findings provide evidence from a large, contemporary cohort of neonates that a screening cEEG strategy may improve rates of initial treatment success for acute symptomatic seizures. The use of cEEG to screen high-risk neonates for seizures before clinical seizures occur (screening cEEG) is associated with improved odds of seizure treatment success as compared to performing cEEG only after seizures are observed (confirmatory cEEG). This supports the clinical practice of screening cEEG for seizures in high-risk neonates.

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Appendix 1 Authors

Name	Location	Contribution
Courtney J. Wusthoff, MD, MS	Stanford University, Palo Alto, CA	Designed and conceptualized the study, analyzed the data, drafted the manuscript for intellectual content
Vandana Sundaram, MPH	Stanford University, Palo Alto, CA	Designed and performed the statistical analysis, drafted figures, revised the manuscript for intellectual content
Nicholas S. Abend, MD, MSCE	University of Pennsylvania, Philadelphia	Acquisition and interpretation of data, revised the manuscript for intellectual content
Shavonne L. Massey, MD MSCE	University of Pennsylvania, Philadelphia	Acquisition and interpretation of data, revised the manuscript for intellectual content

Appendix 1 (continued)

Name	Location	Contribution
Monica E. Lemmon, MD	Duke University, Durham, NC	Acquisition and interpretation of data, revised the manuscript for intellectual content
Cameron W. Thomas, MD, MS	University of Cincinnati, OH	Acquisition and interpretation of data, revised the manuscript for intellectual content
Charles E. McCulloch, PhD	University of California, San Francisco	Design of the statistical analysis, revised the manuscript for intellectual content
Taeun Chang, MD	George Washington University School of Medicine, Washington, DC	Acquisition and interpretation of data, revised the manuscript for intellectual content
Janet S. Soul, MDCM	Harvard Medical School, Boston, MA	Acquisition and interpretation of data, revised the manuscript for intellectual content
Catherine J. Chu, MD, MA, MMSc	Harvard Medical School, Boston, MA	Acquisition and interpretation of data, revised the manuscript for intellectual content
Elizabeth E. Rogers, MD	University of California, San Francisco	Acquisition and interpretation of data, revised the manuscript for intellectual content
Sonia L. Bonifacio, MD	Stanford University, Palo Alto, CA	Acquisition and interpretation of data, revised the manuscript for intellectual content
M. Roberta Cilio, MD, PhD	Université Catholique de Louvain, Brussels, Belgium	Acquisition and interpretation of data, revised the manuscript for intellectual content
Hannah C. Glass, MDCM	University of California, San Francisco	Design and conceptualization of study cohort, acquisition and interpretation of data, revised the manuscript for intellectual content
Renée Shellhaas, MD, MS	University of Michigan, Ann Arbor	Design and conceptualization of study cohort, acquisition and interpretation of data, revised the manuscript for intellectual content

Appendix 2 Coinvestigators

Name	Location	Role	Contribution
Adam L. Numis, MD	University of California, San Francisco	Site investigator	Contributed toward identification and enrollment of participants
Ronnie Guillet, MD, PhD	University of Rochester, NY	Coinvestigator	Provided input on NSR study processes
Linda S. Franck, RN, PhD	University of California, San Francisco	Coinvestigator	Provided input on NSR study processes

Continued

Appendix 2 (continued)

Name	Location	Role	Contribution
Marty Barnes	Austin, TX	Parent partner	Provided parental perspective toward NSR study processes
Tammy Tsuchida, MD	Children's National Hospital, Washington, DC	Coinvestigator	Contributed toward identification and enrollment of participants

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