Title

Seizures in Preterm Neonates: A Multicenter Observational Cohort Study.

Authors

Glass, Hannah
Shellhaas, Renée
Tsuchida, Tammy
et al.

Publication Date

2017-07-01

DOI

10.1016/j.pediatrneurol.2017.04.016

Peer reviewed

Published in final edited form as:

Pediatr Neurol. 2017 July ; 72: 19–24. doi:10.1016/j.pediatrneurol.2017.04.016.

Seizures in Preterm Neonates: A Multicenter Observational Cohort Study

Hannah C. Glass, MDCM, MAS[a,b,*], **Renée A. Shellhaas, MD, MS**[c], **Tammy N. Tsuchida, MD, PhD**[d], **Taeun Chang, MD**[d], **Courtney J. Wusthoff, MD**[e], **Catherine J. Chu, MD**[f], **M. Roberta Cilio, MD, PhD**[a], **Sonia L. Bonifacio, MD, MAS**[g], **Shavonne L. Massey, MD**[h], **Nicholas S. Abend, MD**[h], and **Janet S. Soul, MDCM**[i] **on behalf of On behalf of the Neonatal Seizure Registry study group**

[a]Departments of Neurology and Pediatrics, UCSF Benioff Children's Hospital, University of California San Francisco, San Francisco, California

[b]Department of Epidemiology & Biostatistics, University of California San Francisco, San Francisco, California

[c]Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, Michigan

[d]Department of Neurology, Children's National Health System, George Washington University School of Medicine, Washington, DC

[e]Departments of Neurology and Pediatrics, Stanford University, Palo Alto, California

[f]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

[g]Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University, Palo Alto, California

[h]Departments of Neurology and Pediatrics, The Children's Hospital of Philadelphia and The Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

[i]Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts

Abstract

BACKGROUND—The purpose of this study was to characterize seizures among preterm neonates enrolled in the Neonatal Seizure Registry, a prospective cohort of consecutive neonates with seizures at seven pediatric centers that follow the American Clinical Neurophysiology Society's neonatal electroencephalography monitoring guideline.

STUDY DESIGN—Of 611 enrolled neonates with seizures, 92 (15%) were born preterm. Seizure characteristics were evaluated by gestational age at birth for extremely preterm (<28 weeks, N =

*Communications should be addressed to: Dr. Glass; Departments of Neurology and Pediatrics; University of California San Francisco; 675 Nelson Rising Lane; Room 494; Box 0663; San Francisco, CA 94158. Hannah.Glass@ucsf.edu.

Conflicts of Interest: The authors have no disclosures or conflicts of interest.

18), very preterm (28 to <32 weeks, N = 18), and moderate to late preterm (32 to <37 weeks, N = 56) and compared with term neonates.

RESULTS—Hypoxic-ischemic encephalopathy (33%) and intracranial hemorrhage (27%) accounted for the etiology in more than half of preterm neonates. Hypothermia therapy was utilized in 15 moderate to late preterm subjects with encephalopathy. The presence of subclinical seizures, monotherapy treatment failure, and distribution of seizure burden (including status epilepticus) was similar in preterm and term neonates. However, exclusively subclinical seizures occurred more often in preterm than term neonates (24% vs 14%). Phenobarbital was the most common initial medication for all gestational age groups, and failure to respond to an initial loading dose was 63% in both preterm and term neonates. Mortality was similar among the three preterm gestational age groups; however, preterm mortality was more than twice that of term infants (35% vs 15%).

CONCLUSIONS—Subclinical seizures were more common and mortality was higher for preterm than term neonates. These data underscore the importance of electroencephalographic monitoring and the potential for improved management in preterm neonates.

Keywords

preterm; neonatal seizures; EEG; electroencephalograph; neurocritical care; neonatal encephalopathy; hypoxicischemic encephalopathy

Introduction

The risk of seizures is highest in the first year after birth and especially within the first month.[1] The risk of seizures appears to be inversely related to gestational age and birth weight: the reported incidence of seizures in very low birth weight infants (less than 1500 g at birth) is approximately 1.9% to 5.8% in population-based studies[2–4] and 3.9% to 48% in single center studies.[5–8] Lloyd et al.[9] summarized 120 preterm neonates (median gestational age 29 weeks, inter quartile range 27 to 30 weeks) who were monitored using continuous electroencephalography (cEEG) for approximately 72 hours after birth. They detected seizures in only six infants (5%), suggesting that the seizure frequency in an unselected population is at the lower range of what other groups have reported.

Population-based data largely rely on reporting from vital statistics and hospital discharge diagnoses, include neonates at both low and high acuity centers, and predominantly reflect a clinical diagnosis of seizures. In contrast, the single center studies largely report the experiences of tertiary care centers with a neurological focus and higher acuity and/or standardized neurophysiology monitoring. Therefore the differences in reported rates likely reflect both the populations studied and the method of ascertainment. Of note, the highest reported rates of seizure in preterm neonates come from centers that predominantly use amplitude-integrated electroencephalography (aEEG) for seizure detection, a technique that is subject to both false-negative and false-positive results.[10]

The primary objective of this study was to characterize seizures among preterm neonates in the Neonatal Seizure Registry, a prospective cohort of neonates with seizures managed at seven US pediatric centers that follow the American Clinical Neurophysiology Society

(ACNS) neonatal cEEG monitoring guideline.[11] We hypothesized that seizure etiology, response to treatment, and short-term outcome would differ by gestational age at birth.

Methods

This study was a prospective, observational cohort study of consecutive neonates with seizures treated at the seven sites of the Neonatal Seizure Registry. Each site has a level IV neonatal intensive care unit (NICU) and follows the ACNS guideline for cEEG.[11] The ACNS recommends monitoring neonates for differential diagnosis of paroxysmal events and for detection of electrographic seizures in selected high-risk populations. In neonates at risk for seizures, the ACNS guidelines recommend cEEG monitoring for a minimum of 24 hours and for 24 hours after the last electrographic seizure. In clinical practice, neonates with hypoxic-ischemic encephalopathy (HIE) who undergo therapeutic hypothermia at each of the study centers are monitored with cEEG until rewarming is complete.

All neonates with seizures diagnosed clinically and/or with EEG confirmation were enrolled from January 2013 through November 2015. Neonates with events that were determined *not* to be seizures based on clinical evaluation or EEG monitoring were not enrolled. Neonates with clinical events suspected to be seizures and treated as such with antiseizure medications were included if the clinical evaluation, event semiology, and/or outside hospital EEG supported the diagnosis of seizures, even if seizures were not identified on subsequent cEEG recordings at the study center. Indications for cEEG monitoring included differential diagnosis of clinical events concerning for seizure, encephalopathy, clinical events plus encephalopathy, or “other” indication. Details regarding seizure etiology, medical management, seizure burden, and treatment responses were recorded. The study site investigators determined primary seizure etiology based on a systematic review of the medical record. Seizure characteristics and short-term outcomes were compared within preterm gestational age groups (extremely preterm, gestational age less than 28 weeks; very preterm, gestational age 28 to less than 32 weeks; and moderate to late preterm, gestational age 32 to less than 37 weeks), and between preterm and term (gestational age 37 or more weeks) neonates. Abnormal examination was defined as any alteration in consciousness, tone, or reflexes.

For both term and preterm neonates, electrographic seizures were defined as a sudden, abnormal EEG event defined as a repetitive and evolving pattern with minimum amplitude of 2 μV and duration ≥10 seconds.[12] Seizure burden and characteristics were determined by video-EEG reports. A board-certified pediatric electroencephalographer with experience in neonatal neurophysiology reported the EEG at each site. Seizure exposure was defined as follows: no EEG seizures, isolated (fewer than seven) recorded seizures, many (seven or more) recorded seizures, frequent recurrent seizures (but not fulfilling criteria for status epilepticus), and status epilepticus (50% or more of any 60-minute EEG epoch comprising seizures). Treatment for seizures, including medication selection and duration of therapy, was at the discretion of the clinical team. No specific treatment guideline was provided to the sites as this was an observational study, although five of the seven sites had an institutional guideline, pathway, or suggested workflow for seizure management.

Descriptive statistics and results of *t* tests, ANOVA, Kruskall Wallis, Wilcoxon rank sum, and chi-square tests are presented. Analyses were performed both *within* preterm gestational age groups, as well as preterm compared with term neonates. Analyses were completed using Stata 14 (StataCorp, College Station, TX).

The local institutional review board for every site approved the study and granted a waiver of informed consent. Subjects from the Neonatal Seizure Registry were previously presented.[13,14]

Results

From January 2013 through November 2015, 611 consecutive neonates with seizures were enrolled into the Neonatal Seizure Registry. Fifteen percent (92 neonates) were born at gestational age less than 37 weeks as follows: N = 18 extremely preterm (gestational age less than 28 weeks), N = 18 very preterm (gestational age 28 to less than 32 weeks), and N = 56 moderate to late preterm (gestational age 32 to less than 37 weeks). Patient characteristics are presented in Table 1.

Seizure etiology

HIE was the most common seizure etiology among moderate to late preterm and term neonates, whereas intracranial hemorrhage was more common among extremely and very preterm neonates. Sixty percent of moderate to late preterm subjects with seizures caused by HIE were treated with therapeutic hypothermia at a median age of 36 (range $33^{1/7}$ to $36^{6/7}$) weeks. The 12 preterm survivors of HIE underwent cEEG monitoring for a median of 90 hours to include cooling and rewarming periods. Ischemic strokes and genetic epileptic encephalopathies were more commonly diagnosed in term neonates, whereas intracranial infections were a more common cause of seizures in preterm neonates ($P < 0.0005$). The proportion with an unknown etiology was similar across all gestational age groups (range 8% to 11% by gestational age group).

Monitoring and seizure characteristics

There were differences between term and preterm gestational age groups with regards to indication for monitoring. Extremely and very preterm neonates were more likely to have clinical events as the indication for monitoring, whereas moderate to late preterm and term neonates were more likely to have encephalopathy or encephalopathy plus clinical events as an indication for cEEG monitoring (Table 2). Among neonates born extremely preterm, abnormal imaging was the most common other reason for monitoring (40%).

Chronological age at first seizure was significantly older in the preterm than term neonates (median six days, interquartile range (IQR) 1, 21 days versus median 27 hours, IQR 11 hours, 83 hours, $P < 0.0005$ for first clinical seizure; and median ten days, IQR 38 hours, 34 days versus median 52 hours, IQR 23 hours, six days, $P < 0.0005$ for first EEG seizure). Median time from the onset of recording to identification of the first EEG seizure was similar by gestational age at birth (median two hours, IQR less than one hour, 16 hours for preterm, versus median 2 hours, IQR less than one hour, nine hours for term, $P = 0.3$). Total cEEG recording duration was also similar by birth gestational age (overall median 66, IQR

41, 96 hours). However, lower gestational age was strongly associated with later chronological age at the onset of cEEG recording ($P = 0.0001$), which was likely largely driven by later onset of first clinical seizure in extremely and very preterm newborns compared with term newborns.

There were high rates of EEG-confirmed seizures among extremely, very, and moderate to late preterm groups (100%, 72%, and 88%, respectively), although cEEG monitoring was initiated for reasons other than clinical events in 34%, 6%, and 41% of these preterm neonates (Table 2). The rate of EEG-confirmed seizures was similar for preterm and term neonates (87% vs 85%, $P = 0.7$).

The presence of subclinical seizures was similar across preterm gestational ages and also between term and preterm neonates ($P \geq 0.2$, Table 2). However, exclusively subclinical seizures were more common in preterm than term neonates (24% versus 14%, $P = 0.01$). The distribution of seizure burden was similar between preterm and term neonates, and specifically, preterm neonates were just as likely as terminfants to have documented status epilepticus (14% preterm versus 15% term, $P = 0.9$). In 15% of preterm neonates and 17% of term neonates, EEG at the study site did not confirm clinically suspected seizures ($P = 0.9$).

Seizure treatment

Phenobarbital was the most common initial loading medication for all gestational age groups (range 71% to 100% by gestational age at birth) and the most commonly used medication overall (range 82% to 100% of neonates receiving phenobarbital by gestational age, Table 3). Preterm neonates were less likely to receive phenobarbital before the onset of cEEG monitoring than term neonates (36% versus 48%, $P = 0.04$). Phenobarbital dosing was equivalent in preterm versus term neonates (with average initial loading dose at 19.4 mg/kg for term and 19.9 mg/kg for preterm, $P = 0.2$). Levetiracetam was the next most commonly prescribed medication, both as an initial loading dose (range 0% to 24% by gestational age) and overall (range 27% to 44% of neonates receiving levetiracetam by gestational age). Fosphenytoin was least likely to be used as an initial loading medication in all age groups (range 0% to 6% by gestational age with the high range prescribed to the extremely preterm) and overall (range 14% to 33% by gestational age). Fosphenytoin was more likely to be prescribed for term (32%) than preterm infants (18%, $P = 0.008$).

Overall, 63% of neonates had seizures that persisted after the initial loading dose of antiseizure medication and this was not different between preterm and term neonates ($P = 0.6$). There was also no significant difference when comparing medications: 64% had seizures that persisted after loading doses of phenobarbital, 58% for levetiracetam, and 100% for fosphenytoin ($P = 0.4$). Although response to the initial antiseizure medications was similar, preterm neonates received fewer medications during the inpatient admission than term neonates (median 1, IQR 1, 2 versus median 2, IQR 1, 3, $P = 0.003$, Table 3).

Short-term outcome

Preterm neonates with seizures were more than twice as likely to die during the hospital admission as term neonates with seizures (35% versus 15%, $P < 0.005$, Table 1). In-hospital

mortality was not significantly different among the three preterm age groups ($P = 0.9$). Mortality was higher when comparing preterm neonates to term neonates with a similar seizure etiology. Among neonates with a primary diagnosis of HIE, 14 of 30 (47%) preterm neonates versus 45 of 201 (22%) term neonates died ($P = 0.004$). Among neonates with a primary diagnosis of intracranial hemorrhage, seven of 25 (28%) preterm neonates versus five of 53 (9%) term neonates died ($P = 0.03$). However, when examining neonates with ischemic stroke or infection, there was no difference in mortality between preterm and term neonates.

Among survivors, preterm and term neonates with seizures were equally likely to have an abnormal neurological examination at the time of hospital discharge (50% versus 48%, $P = 0.8$, Table 1). There was no difference by gestational age in the likelihood of being prescribed antiseizure medications at the time of hospital discharge (67% for preterm versus 77% for term neonates, $P = 0.15$, Table 3).

Discussion

In this prospective multicenter study of preterm neonates with seizures who were monitored with continuous, conventional video EEG according to ACNS guidelines,[11] we show that seizure etiology was different and both likelihood of exclusively subclinical seizures and mortality were higher in preterm compared with term neonates, whereas seizure burden (including status epilepticus) and response to treatment was similar in all gestational age groups.

Intracranial hemorrhage was the most common seizure etiology in neonates born at less than 32 weeks' gestation, likely owing to the susceptibility to intraventricular hemorrhage in this age group and difficulty diagnosing and/or lack of routine monitoring for HIE (the most common cause in neonates at 32 or more weeks' gestation) in the very preterm. These findings are similar to the results of past studies.[6,15,16] Our findings that intracranial hemorrhage was the most common seizure etiology and that abnormal imaging was an important indication for monitoring among preterm neonates support ACNS recommendations for cEEG among neonates with acute high grade intracranial hemorrhage.[11]

There is no published evidence to guide treatment of seizures in preterm neonates. The few clinical trials that evaluate response to medication excluded preterm neonates.[17,18] In this study, phenobarbital was most commonly used as a first line medication in all age groups, and response to the initial loading dose was similar across age groups, with seizures persisting in more than 60% after a similar loading dose of antiseizure medication in all gestational age groups. Despite the similarly high incidence of seizures refractory to an initial load of antiseizure medication across age groups, term neonates were more likely to receive two or more medications. The reasons that preterm neonates were prescribed fewer medications in spite of similar rates of children with seizures persisting after the initial loading dose are not known. Physicians appear to make similar initial treatment choices for preterm neonates with seizures; those who have persistent seizures reflect an important

subpopulation that deserves additional investigation to help determine optimal medication selection and dosing strategy for effective treatment.

The timing of seizure identification was later in preterm than term neonates. Pisani et al.[16] similarly noted later onset in preterm neonates less than 29 weeks' gestation compared with older preterm neonates. The reason for later onset of seizures in preterm neonates is not known and may be related to several factors. First, unlike the term and late preterm neonates with HIE, there is not a systematic approach to initiating cEEG monitoring early in preterm neonates at risk for seizures in most centers. This factor may be related, in part, to frequent and significant cardiorespiratory illness being the main focus of management in the first days after birth and/or limited knowledge regarding the incidence of seizures in preterm neonates. Amplitude-integrated EEG may be more likely to be initiated early; however, the accuracy of aEEG for seizure identification is lower than that of EEG.[19] Second, term neonates most often have seizures because of HIE, and seizures in HIE typically begin within the first 24 hours after birth, whereas seizures resulting from common preterm etiologies like intraventricular hemorrhage or infection may occur later.

We found that 24% of preterm neonates had exclusively subclinical seizures (and 66% had at least one subclinical seizure). There are several reasons why preterm neonates have high rates of subclinical seizures. First, clinical manifestations of seizures are inherently subtle compared with normal movements in preterm neonates. Furthermore, observing seizures in preterm neonates (clinically or by video recording during EEG) may be difficult given that isolettes can cause glare on the recorded video and preterm neonates may be covered or swaddled for developmental care, which can obscure continuous/frequent clinical evaluation. Therefore it is possible that in our preterm neonates, clinical manifestations of seizures were missed. Second, the neurophysiology of seizures differs in that seizures tend to be shorter in duration and have a lower likelihood of propagation in the more immature preterm brain than in the term brain.[20] Finally, preterm neonates may be more likely to have electroclinical dissociation because of benzodiazepine given for sedation (often administered at doses inadequate to treat seizures). Janackova et al.[20] also reported a higher likelihood of subclinical seizures in preterm neonates. Altogether, these data support the importance of cEEG monitoring to identify seizures in preterm neonates.

Preterm neonates with seizures have a very high rate of adverse outcomes compared with term neonates with seizures.[21,22] In our cohort, risk factors for adverse outcome, such as status epilepticus and abnormal neurological examination, occurred at least as often in preterm as in term neonates with seizures, although mortality was higher in our preterm than term neonates. The Neonatal Seizure Registry was not designed to determine the reasons for differences in short-term outcome between preterm and term neonates, but our findings add to the literature showing that preterm neonates with seizures have a very high risk for adverse neurological outcome.

Although we report a large cohort from seven pediatric centers that follow the ACNS guidelines for monitoring in neonates with expert pediatric neurophysiologists and neonatal neurologists at each site to ensure quality of clinical and EEG data, our study has limitations. First, none of the centers had a standardized approach to cEEG monitoring specific to

preterm neonates, and none of the centers routinely monitored preterm infants for an indication of gestational age alone. Although the highest risk period for seizures in term neonates with encephalopathy is the first days after birth, the highest risk period for preterm neonates is not known. Therefore we are likely to have a biased sample of the sickest preterm neonates. Second, seizure characteristics were determined based on EEG reports and clinical charting. Each study center included a child neurologist and neurophysiologist with special interest in neonatal neurology, which strengthens clinical reporting, EEG data interpretation, and data collection for the study. Third, we did not collect detailed data such as the precise number, localization and duration of seizures (complete EEG data were not retained for detailed analysis at all sites), rationale for individual medication choices, or effect of medications on EEG seizures. Fourth, we did not collect detailed data about the timing of individual seizures. Finally, we included subjects with clinically suspected seizures that were not confirmed on EEG. Although we excluded subjects whose clinical events were shown *not* to be seizures and those for whom the suspicion that the events were seizures was low after a full evaluation, given that clinical diagnosis of seizures is not reliable, it is possible that some subjects had ictal events that did not have an electrographic correlate, such as brainstem release phenomena.

Conclusions

Preterm neonates accounted for 15% of 611 consecutive neonates with seizures at tertiary care pediatric centers that monitor at-risk infants with continuous, video EEG according to guidelines.[11] Exclusively subclinical seizures were more common and mortality was higher for preterm than term neonates with seizures. Management surveys indicate that preterm neonates with suspected seizures are less likely to undergo EEG monitoring than term neonates.[23] The high incidence of subclinical seizures, high rates of confirmed EEG seizures, and high likelihood of failure of the first antiseizure medication, as well as the high risk of poor outcome in preterm neonates with seizures support the need for increased efforts to identify electrographic seizures using cEEG and develop effective management of neonatal seizures. These data underscore the contribution of cEEG monitoring in preterm neonates and raise important knowledge gaps regarding the best approach to treatment for seizure in preterm neonates.

Acknowledgments

The Pediatric Epilepsy Research Foundation (Grant number: A120625) supported this study but did not participate in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. The authors would like to acknowledge Drs. Donna Ferriero, Faye Silverstein, and Kevin Staley for their contribution to the project and the research assistants at each study site.

References

1. Annegers JF, Hauser WA, Lee JR, Rocca WA. Incidence of acute symptomatic seizures in Rochester, Minnesota, 1935–1984. Epilepsia. 1995; 36:327–333. [PubMed: 7607110]
2. Saliba RM, Annegers JF, Waller DK, Tyson JE, Mizrahi EM. Incidence of neonatal seizures in Harris County, Texas, 1992–1994. Am J Epidemiol. 1999; 150:763–769. [PubMed: 10512430]
3. Kohelet D, Shochat R, Lusky A, Reichman B. Risk factors for neonatal seizures in very low birth weight infants: population-based survey. J Child Neurol. 2004; 19:123–128. [PubMed: 15072105]

4. Lanska MJ, Lanska DJ, Baumann RJ, Kryscio RJ. A population-based study of neonatal seizures in Fayette County, Kentucy. Neurology. 1995; 45:724–732. [PubMed: 7723962]
5. Scher MS, Aso K, Beggarly ME, Hamid MY, Steppe DA, Painter MJ. Electrographic seizures in preterm and full-term neonates: clinical correlates, associated brain lesions, and risk for neurologic sequelae. Pediatrics. 1993; 91:128–134. [PubMed: 8416475]
6. Sheth RD, Hobbs GR, Mullett M. Neonatal seizures: incidence, onset, and etiology by gestational age. J Perinatol. 1999; 19:40–43. [PubMed: 10685200]
7. Shah DK, Zempel J, Barton T, Lukas K, Inder TE. Electrographic seizures in preterm infants during the first week of life are associated with cerebral injury. Pediatr Res. 2010; 67:102–106. [PubMed: 19745782]
8. Vesoulis ZA, Inder TE, Woodward LJ, Buse B, Vavasseur C, Mathur AM. Early electrographic seizures, brain injury, and neurodevelopmental risk in the very preterm infant. Pediatr Res. 2014; 75:564–569. [PubMed: 24366515]
9. Lloyd, RO., O'Toole, JM., Pavlidis, E., Filan, PM., Boylan, GB. Electrographic seizures during the early postnatal period in preterm infants. J Pediatr. 2017. http://dx.doi.org/10.1016/j.jpeds.2017.03.004. [Epub ahead of print]
10. Evans E, Koh S, Lerner J, Sankar R, Garg M. Accuracy of amplitude integrated EEG in a neonatal cohort. Arch Dis Child Fetal Neonatal Ed. 2010; 95:F169–F173. [PubMed: 20444809]
11. Shellhaas RA, Chang T, Tsuchida T, et al. The American Clinical Neurophysiology Society's Guideline on continuous electroencephalography monitoring in neonates. J Clin Neurophysiol. 2011; 28:611–617. [PubMed: 22146359]
12. Tsuchida TN, Wusthoff CJ, Shellhaas RA, et al. American Clinical Neurophysiology Society standardized EEG terminology and categorization for the description of continuous EEG monitoring in neonates: report of the American Clinical Neurophysiology Society Critical Care Monitoring Committee. J Clin Neurophysiol. 2013; 30:161–173. [PubMed: 23545767]
13. Glass HC, Shellhaas RA, Wusthoff CJ, et al. Contemporary profile of seizures in neonates: a prospective cohort study. J Pediatr. 2016; 174:98–103.e1. [PubMed: 27106855]
14. Shellhaas R, Chang T, Wusthoff C, et al. Treatment duration after acute symptomatic seizures in neonates: a multicenter cohort study. J Pediatr. 2017; 181:298–301.e1. [PubMed: 27829512]
15. Scher MS. Neonatal seizures and brain damage. Pediatr Neurol. 2003; 29:381–390. [PubMed: 14684233]
16. Pisani F, Facini C, Pelosi A, Mazzotta S, Spagnoli C, Pavlidis E. Neonatal seizures in preterm newborns: a predictive model for outcome. Eur J Paediatr Neurol. 2016; 20:243–251. [PubMed: 26777334]
17. Painter MJ, Scher MS, Stein AD, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med. 1999; 341:485–489. [PubMed: 10441604]
18. Pressler RM, Boylan GB, Marlow N, et al. Bumetanide for the treatment of seizures in newborn babies with hypoxic ischaemic encephalopathy (NEMO): an open-label, dose finding, and feasibility phase 1/2 trial. Lancet Neurol. 2015; 14:469–477. [PubMed: 25765333]
19. Glass HC, Wusthoff CJ, Shellhaas RA. Amplitude-integrated electroencephalography: the child neurologist's perspective. J Child Neurol. 2013; 28:1342–1350. [PubMed: 23690296]
20. Janackova S, Boyd S, Yozawitz E, et al. Electroencephalographic characteristics of epileptic seizures in preterm neonates. Clin Neurophysiol. 2016; 127:2721–2727. [PubMed: 27417043]
21. Pisani F, Spagnoli C. Neonatal seizures: a review of outcomes and outcome predictors. Neuropediatrics. 2016; 47:12–19. [PubMed: 26587762]
22. Pavlidis E, Spagnoli C, Pelosi A, Mazzotta S, Pisani F. Neonatal status epilepticus: differences between preterm and term newborns. Eur J Paediatr Neurol. 2015; 19:314–319. [PubMed: 25613545]
23. Glass HC, Kan J, Bonifacio SL, Ferriero DM. Neonatal seizures: treatment practices among term and preterm infants. Pediatr Neurol. 2012; 46:111–115. [PubMed: 22264706]

TABLE 1

Clinical Characteristics of 611 Infants With Seizures in the Neonatal Period

Clinical Characteristics	Preterm N = 92	Extremely Preterm (<28 weeks) N = 18	Very Preterm (28 to <32 weeks) N = 18	Moderate/Late Preterm (32 to <37 weeks) N = 56	*P* Value (Comparing Preterm Categories)	Term N = 519	*P* Value (Preterm Versus Term)
Male	48 (52%)	10 (56%)	7 (39%)	31 (55%)	0.5	289 (56%)	0.5
Death	32 (35%)	7 (39%)	6 (33%)	19 (33%)	0.9	78 (15%)	<0.0005
Abnormal examination at discharge *	30 (50%)	4 (36%)	6 (50%)	20 (54%)	0.6	213 (48%)	0.8

Data are presented as N (%) or mean (interquartile range).

* Among 501 survivors.

TABLE 2

Indication for Monitoring and Seizure Characteristics of 611 Neonates Monitored by Continuous Video-EEG

Indications for Monitoring and Seizure Characteristics	Preterm N = 92	Extremely Preterm (<28 weeks) N = 18	Very Preterm (28 to <32 weeks) N = 18	Moderate/Late Preterm (32 to <37 weeks) N = 56	*P* Value (Comparing Preterm categories)	Term N = 519	*P* Value (Preterm Versus Term)
Indication for monitoring							
Clinical events	54 (59%)	12 (67%)	15 (83%)	27 (48%)		322 (62%)	
Encephalopathy	20 (22%)	2 (11%)	0	18 (32%)		95 (18%)	
Events + encephalopathy	8 (9%)	0	2 (11%)	6 (11%)	0.046	84 (16%)	0.001
Other	10 (11%)	4 (23%)	1 (6%)	5 (9%)		18 (3%)	
Seizure characteristics							
Any subclinical seizures	61 (66%)	12 (67%)	9 (50%)	40 (71%)	0.2	331 (64%)	0.6
Only subclinical seizure	22 (24%)	5 (28%)	2 (11%)	15 (27%)	0.4	72 (14%)	0.01
EEG seizures *					0.04		0.9
No EEG seizures captured at the study site	14 (15%)	0	7 (39%)	7 (13%)		88 (17%)	
Rare EEG seizures (<7)	23 (25%)	4 (22%)	1 (6%)	18 (32%)		127 (25%)	
Many EEG seizures (>7)	11 (12%)	3 (17%)	2 (11%)	6 (11%)		83 (16%)	
Frequent recurrent	28 (30%)	6 (33%)	6 (33%)	16 (29%)		141 (27%)	
Status epilepticus	13 (14%)	5 (28%)	2 (11%)	6 (11%)		78 (15%)	
Initial loading antiseizure medication †					0.01		0.1
Phenobarbital	74 (88%)	12 (71%)	18 (100%)	44 (90%)		466 (94%)	
Levetiracetam	9 (11%)	4 (24%)	0	5 (10%)		24 (5%)	
Fosphenytoin	1 (1%)	1 (6%)	0	0		3 (< 1%)	
Medications prescribed during the admission							
Number of medications used	1 (1, 2)	1.5 (1, 3)	1 (1, 3)	1 (1, 2)	0.4	2 (1, 3)	0.003
Seizures refractory to initial load	54 (63%)	13 (76%)	11 (61%)	30 (60%)	0.6	319 (63%)	0.6
Discharged home on antiseizure medications ‡	31/46 (67%)	4/6 (67%)	6/10 (60%)	21/30 (70%)	0.8	294/382 (77%)	0.15

Data are presented as N (%) or mean (interquartile range).

* As documented at the study hospital among 606 subjects with documentation adequate to quantify seizure burden.

† Among 580 neonates who received a loading dose of antiseizure medication.

[‡] Among 428 neonates discharged to home.

TABLE 3

Seizure Management for 611 Neonates

Seizure Management	Preterm N = 92	Extremely Preterm (<28 weeks) N = 18	Very Preterm (28 to <32 weeks) N = 18	Moderate/Late Preterm (32 to <37 weeks) N = 56	*P* Value (Comparing Preterm Categories)	Term N = 519	*P* Value (Preterm Versus Term)
Initial loading antiseizure medication *					0.01		0.1
Phenobarbital	74 (88%)	12 (71%)	18 (100%)	44 (90%)		466 (94%)	
Levetiracetam	9 (11%)	4 (24%)	0	5 (10%)		24 (5%)	
Fosphenytoin	1 (1%)	1 (6%)	0	0		3 (< 1%)	
Number of medications used	1 (1, 2)	1.5 (1, 3)	1 (1, 3)	1 (1, 2)	0.4	2 (1, 3)	0.003
Seizures refractory to initial load	54 (63%)	13 (76%)	11 (61%)	30 (60%)	0.6	319 (63%)	0.6
Discharged home on antiseizure medications †	31/46 (67%)	4/6 (67%)	6/10 (60%)	21/30 (70%)	0.8	294/382 (77%)	0.15

* Among 580 neonates who received a loading dose of anti-seizure medication.

† Among 428 neonates discharged to home.