UCSF
UC San Francisco Previously Published Works

Title

Treatment Duration After Acute Symptomatic Seizures in Neonates: A Multicenter Cohort Study.

Permalink

https://escholarship.org/uc/item/7h58m613

Authors

Shellhaas, Renée
Chang, Taeun
Wusthoff, Courtney
et al.

Publication Date

2017-02-01

DOI

10.1016/j.jpeds.2016.10.039

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

J Pediatr. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:

J Pediatr. 2017 February ; 181: 298–301.e1. doi:10.1016/j.jpeds.2016.10.039.

Treatment Duration After Acute Symptomatic Seizures in Neonates: A Multicenter Cohort Study

Renée A. Shellhaas, MD, MS[1], **Taeun Chang, MD**[2], **Courtney J. Wusthoff, MD, MS**[3], **Janet S. Soul, MD**[4], **Shavonne L. Massey, MD**[5], **Catherine J. Chu, MD, MS**[6], **M. Roberta Cilio, MD, PhD**[7], **Sonia L. Bonifacio, MD, MS**[3], **Nicholas S. Abend, MD, MSCE**[5], **Tammy N. Tsuchida, MD, PhD**[2], and **Hannah C. Glass, MDCM, MS**[7,8,*] **on behalf of the Neonatal Seizure Registry Study Group**

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

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

[3]Departments of Neurology and Pediatrics, Stanford University, Palo Alto, CA

[4]Department of Neurology, Boston Children's Hospital, Boston, MA

[5]Departments of Neurology and Pediatrics, The Perelman School of Medicine, The Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA

[6]Department of Neurology, Massachusetts General Hospital, Boston, MA

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

[8]Department of Epidemiology and Biostatistics; University of California San Francisco, San Francisco, CA

Abstract

We aimed to define determinants of duration of treatment for acute symptomatic neonatal seizures in a contemporary multicenter observational cohort study. After adjustment for potential confounders, only study site and seizure etiology remained significantly associated with the chance of continuing antiseizure medication after discharge to home.

Despite the wide-ranging impacts of seizures in the newborn, many knowledge gaps persist, and the optimal treatment strategy is unknown. In animal models, both seizures and their treatment with phenobarbital and phenytoin can cause abnormal brain development.[1] Treating clinicians are left to make decisions regarding medication, dosage, and duration without the benefit of practice guidelines. Published reports that examine management strategies for seizures in neonates have been limited by single center study designs, reliance

Reprint requests: Renée A. Shellhaas, MD, MS, Pediatric Neurology, C.S. Mott Children's Hospital, Room 12-733, 1540 E. Hospital Dr, Ann Arbor, MI 48109-4279. shellhaa@med.umich.edu.

*List of additional Neonatal Seizure Registry Study Group members is available at www.jpeds.com (Appendix).

The authors declare no conflicts of interest.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

on clinical (vs electroencephalographic) seizure detection, limited distinction between neonatal onset epilepsies vs acute symptomatic seizures, and the use of survey data.[2–5] Survey data suggest that although the initial management of neonatal seizures is similar between centers, subsequent antiseizure medication choices and duration of treatment are extremely variable.[2–6]

We aimed to evaluate contemporary treatment practices related to prescription of antiseizure medications at the time of discharge to home for newborns with acute symptomatic seizures. We hypothesized that there would be substantial treatment variability across tertiary care centers because there is little evidence to guide prescribing practices for seizure medications in this patient population.

Methods

This was a prospective, observational cohort study of consecutive newborns with seizures treated at the 7 sites of the Neonatal Seizure Registry. Each site has a level IV neonatal intensive care unit and follows the American Clinical Neurophysiology Society guidelines for continuous video-electroencephalogram ([EEG] cEEG) monitoring.[7] The local institutional review board for every site approved the study and granted a waiver of informed consent.

All newborns with seizures diagnosed clinically or with EEG confirmation were enrolled from January 2013 through November 2015. Neonates with events that were determined by EEG not to be seizures were not enrolled. The demographic and etiologic data for a subset of 427 newborns in this cohort were reported separately[8]; the present analyses include the management details of the full Registry cohort (n = 611). Indications for cEEG monitoring included differential diagnosis of abnormal paroxysmal events, screening for seizures in high-risk patients (eg, hypoxic ischemic encephalopathy), and the assessment of background abnormalities or seizures in newborns with acute encephalopathy.

Details regarding seizure etiology, medical management, and treatment were abstracted from medical records and recorded prospectively. Treatment for neonatal seizures, including medication selection and duration of therapy, was at the discretion of each neonate's clinical team. No specific treatment algorithm or guideline was provided to the study sites, and sites did not all have an institutional standard neonatal seizure treatment pathway.

Potential confounders and covariables for treatment duration included study site, seizure etiology, electrographic confirmation of neonatal seizures, presence of status epilepticus, seizures that were refractory to the initial loading dose of antiseizure medication, and abnormal neurologic examination at the time of discharge (defined as documented abnormality in consciousness, tone, and/or reflexes). Analyses of treatment duration excluded the following infants: those who did not survive the neonatal admission, who were discharged from the neonatal intensive care unit to palliative care or hospice, or who were transferred from a study site to another hospital.

Descriptive statistics and results of ANOVA and χ^2 tests are presented. Variables that were significant at a level of $P \leq 0.1$ in univariable analyses were included in the multivariable

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

models. Backward stepwise regression was employed to reach the final multivariable model. Analyses were completed using Stata 12 (StataCorp, College Station, Texas).

Results

From January 2013 through November 2015, the 7 study sites enrolled 611 consecutive newborns with seizures in the Neonatal Seizure Registry (male: n = 337, 55%; >37 weeks gestation, n = 519, 85%) (Table I). Among these, 458 (75%) had acute symptomatic seizures, of whom 373 (81%) survived, and 317 (69%) were discharged to home from the study center. Demographic and clinical characteristics of the study cohort are presented in Table I.

Initial treatment strategies were similar between sites. The site at which the patient was treated was a strong predictor of medication continuation at the time of hospital discharge to home.

Antiseizure medications were continued at the time of hospital discharge for 73% of survivors of acute symptomatic seizures (range 4%–91% across sites, $P < .0005$, χ^2). Site 1 was the most likely to discontinue antiseizure medication before discharge. Even when that site was excluded, there was significant variability across sites' prescription of medications at discharge ($P = .003$, χ^2).

Phenobarbital was the most commonly prescribed medication among those discharged home; 63% of survivors were receiving phenobarbital at the time of discharge (range by site 10%–88%, $P < .0005$, χ^2). Levetiracetam was prescribed to 24% at the time of discharge (range by site 6%–44%, $P < .0005$, χ^2). Phenytoin was prescribed to <1% of survivors at discharge (range by site 0%–2%, $P = .8$, χ^2).

Discharge to home on medication was also strongly associated with seizure etiology ($P < .0005$, χ^2). Among 82 survivors of hypoxic-ischemic encephalopathy treated with therapeutic hypothermia, 47 (57%) were discharged to home on medications (range by site 0%–88%, $P < .0005$, χ^2). Among 92 survivors of ischemic stroke, 72 (78%) were discharged to home on medications (range by site 0%–100%, $P < .0005$, χ^2).

Among 56 survivors of intracranial hemorrhage, 46 (82%) were discharged to home on medications (range by site 0%–100%, $P = .01$, χ^2).

In univariable analyses, among survivors of acute symptomatic seizures who were discharged home, additional clinical factors associated with continuing medication upon discharge were EEG-confirmed seizures, status epilepticus, seizures refractory to the initial loading dose of medication, and abnormal neurologic examination at the time of hospital discharge (Table II). After adjustment for each of these variables, as well as seizure etiology and study site, only study site and seizure etiology remained significantly associated with the chance of continuing medication at the time of discharge to home.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Discussion

In this prospective multicenter study of consecutive newborns with seizures who were monitored with cEEG according to American Clinical Neurophysiology Society guidelines, the decision regarding whether or not to send a newborn with acute symptomatic seizures home on antiseizure medications was significantly associated with the hospital to which the infant was admitted, even after adjusting for important potential confounders such as seizure burden and seizure etiology. At some centers, few to no patients with acute symptomatic neonatal seizures were prescribed antiseizure medications at the time of discharge home, whereas at other sites, almost all newborns were prescribed antiseizure medications upon hospital discharge. This finding is in keeping with physician survey results, in which respondents offered different opinions regarding appropriate duration of medication administration for the same clinical vignette.[5]

For any major health condition, understanding the correct treatment choice and the ideal length of treatment is critical. Phenobarbital, the most commonly prescribed first line antiseizure medication for neonatal seizures, is often maintained for several months because of clinicians' and parents' concern that early discontinuation of medicine may result in seizure recurrence.[5]

However, continued exposure to phenobarbital is sedating, which may prolong the time it takes for a newborn to establish oral feeding, and this medicine may have deleterious long-term effects on the developing brain.[9–11] Preliminary evidence suggests that early discontinuation of medication is not harmful,[5,9,12] but the optimal duration of therapy remains unknown.

Whether phenobarbital should remain the first line medication for neonatal seizures and how long to treat a newborn with antiseizure medications remain open questions, and lead to significant practice variability.[5] This variability is clearly reflected in these data from the Neonatal Seizure Registry, in which fewer than one-half of the sites have local treatment pathways and those local guidelines differ from one another. There is a clear need for scientific evidence to serve as the foundation not only for hospital-specific treatment pathways but also for nationally recognized treatment guidelines.

The Neonatal Seizure Registry is not designed to gather long-term outcome data. Therefore, we are unable to comment on the potential implications of early vs later discontinuation of medication for acute symptomatic neonatal seizures. However, a major strength of this study is that we evaluated actual clinical practice for a very large consecutive cohort of newborns with seizures, as opposed to surveying clinicians about their preferred treatment approaches. These real-world contemporary data highlight the need for careful evaluation of the potential long-term benefits and consequences of different treatment strategies for newborns with seizures.

Whereas neonates with early onset epilepsy typically require long-term antiseizure medications, the ideal duration of antiseizure therapy for newborns with acute symptomatic seizures is not known. The rationale for continued antiseizure medication is to prevent seizure recurrence. Yet, the risk of postneonatal epilepsy in the first several years of life is

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

less than 25% for neonates with acute symptomatic seizures and postneonatal epilepsies (particularly West Syndrome) do not necessarily respond to the medications prescribed in the neonatal period.[13–15]

Although some sites in our study discontinued antiseizure medications in most or all neonates with acute symptomatic seizures before sending the infant home, the majority of neonates were discharged home on antiseizure medications, including those with a low seizure burden or even those without confirmed electrographic seizures on study center cEEG recordings. Our results highlight the pressing need for rigorous study regarding optimal treatment duration for neonates with acute symptomatic seizures.

Acknowledgments

Supported by the Pediatric Epilepsy Research Foundation. R.S. receives support from the National Institutes of Health (NIH; R21HD083409), the American Sleep Medicine Foundation, Patient-Centered Outcomes Research Institute (2015C2-1507-31187), and the Pediatric Epilepsy Research Foundation; serves as a consultant for the Epilepsy Study Consortium; and receives honoraria from UpToDate. T.C. receives support from the Pediatric Epilepsy Research Foundation, the Thrasher Foundation, and the Cerebral Palsy International Research Foundation. J.S. receives support from NIH (R01 HD076258 and R01 NS066929) and Boston Children's Hospital Intellectual and Developmental Disabilities Research Center. C.C. receives research support from NIH (K23 NS092923) and the Pediatric Epilepsy Research Foundation. S.B. receives support from NIH. N.A. receives support from NIH (K23 NS076550) and the Pediatric Epilepsy Research Foundation. T.T. receives support from the Epilepsy Foundation, Citizens United for Research in Epilepsy, and NIH. H.G. receives support from NIH (K23 NS66137), the Cerebral Palsy Alliance (PG2314), Patient-Centered Outcomes Research Institute, and the Pediatric Epilepsy Research Foundation.

We thank the research assistants at the study sites for their valuable contributions to this work: Manogna Manne (funded by PERF and Patient-Centered Outcomes Research Institute); Stephanie Rau (funded by PERF, Patient-Centered Outcomes Research Institute, and National Institutes of Health); Jessica Landers (funded by PERF, Patient-Centered Outcomes Research Institute, and Boston Children's Hospital Translational Research Program Grant); Kari Harris (funded by PERF and Epilepsy Foundation); Emily Thorn (funded by PERF); and Catherine Clark (funded by PERF).

Glossary

cEEG	Continuous video-EEG
EEG	Electroencephalogram
PERF	Pediatric Epilepsy Research Foundation

References

1. Holmes GL. The Long-term effects of neonatal seizures. Clin Perinatol. 2009; 36:901–914. [PubMed: 19944841]
2. Bartha AI, Shen J, Katz KH, Mischel RE, Yap KR, Ivacko JA, et al. Neonatal seizures: multicenter variability in current treatment practices. Pediatr Neurol. 2007; 37:85–90. [PubMed: 17675022]
3. Blume HK, Garrison MM, Christakis DA. Neonatal seizures: treatment and treatment variability in 31 United States pediatric hospitals. J Child Neurol. 2009; 24:148–154. [PubMed: 19182150]
4. Glass HC, Kan J, Bonifacio SL, Ferriero DM. Neonatal seizures: treatment practices among term and preterm infants. Pediatr Neurol. 2012; 26:111–115.
5. Guillet R, Kwon JM. Prophylactic phenobarbital administration after resolution of neonatal seizures: survey of current practice. Pediatrics. 2008; 122:731–735. [PubMed: 18829795]
6. Bassan H, Bental Y, Shany E, Berger I, Froom P, Levi L, et al. Neonatal seizures: dilemmas in workup and management. Pediatr Neurol. 2008; 38:415–421. [PubMed: 18486824]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

7. Shellhaas RA, Chang T, Tsuchida T, Scher MS, Riviello JJ, Abend NS, et al. The American clinical neurophysiology society's guideline on continuous electroencephalography monitoring in neonates. J Clin Neurophysiol. 2011; 28:611–617. [PubMed: 22146359]
8. Glass HC, Shellhaas RA, Wusthoff CJ, Chang T, Abend NS, Chu CJ, et al. Contemporary profile of seizures in neonates: a prospective cohort study. J Pediatr. 2016; 174:98–103. [PubMed: 27106855]
9. Farwell JR, Lee YJ, Hirtz DG, Sulzbacher SI, Ellenberg JH, Nelson KB. Phenobarbital for febrile seizures—effects on intelligence and on seizure recurrence. N Engl J Med. 1990; 322:364–369. [PubMed: 2242106]
10. Sulzbacher S, Farwell JR, Temkin N, Lu AS, Hirtz DG. Late cognitive effects of early treatment with phenobarbital. Clin Pediatr (Phila). 1999; 38:387–394. [PubMed: 10416094]
11. Kaushal S, Tamer Z, Opoku F, Forcelli PA. Anticonvulsant drug-induced cell death in the developing white matter of the rodent brain. Epilepsia. 2016; 57:727–734. [PubMed: 27012547]
12. Guillet R, Kwon J. Seizure recurrence and developmental disabilities after neonatal seizures: outcomes are unrelated to use of phenobarbital prophylaxis. J Child Neurol. 2007; 22:389–395. [PubMed: 17621516]
13. Wusthoff CJ, Kessler SK, Vossough A, Ichord R, Zelonis S, Halperin A, et al. Risk of later seizure after perinatal arterial ischemic stroke: a prospective cohort study. Pediatrics. 2011; 127:e1550–e1557. [PubMed: 21576305]
14. Grunt S, Mazenauer L, Buerki SE, Boltshauser E, Mori AC, Datta AN, et al. Incidence and outcomes of symptomatic neonatal arterial ischemic stroke. Pediatrics. 2015; 135:e1220–e1228. [PubMed: 25896840]
15. Pisani F, Orsini M, Braibanti S, Copioli C, Sisti L, Turco EC. Development of epilepsy in newborns with moderate hypoxic-ischemic encephalopathy and neonatal seizures. Brain Dev. 2009; 31:64–68. [PubMed: 18490125]

Appendix

Additional Neonatal Seizure Registry Study Group members include:

Ann Marie Bergin, MB, ScM, MRCP (UK), Boston Children's Hospital and Harvard Medical School, Boston, MA; Dennis Dlugos, MD, MSCE, Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine, Philadelphia, PA; Donna M. Ferriero, MD, MS, University of California- San Francisco, Benioff Children's Hospital and University of California San Francisco School of Medicine, San Francisco, CA; Faye Silverstein, MD, University of Michigan, Ann Arbor, MI; Kevin Staley, MD, Massachusetts General Hospital and Harvard Medical School, Boston, MA.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table I

Clinical characteristics of 611 consecutive newborns with seizures at the 7 Neonatal Seizure Registry sites

Clinical characteristics	Overall n = 611	Site 1 n = 68	Site 2 n = 113	Site 3 n = 34	Site 4 n = 80	Site 5 n = 121	Site 6 n = 65	Site 7 n = 130	*P* value
Male sex	337 (55%)	39 (57%)	63 (56%)	21 (62%)	47 (59%)	59 (49%)	33 (51%)	75 (58%)	.7 *
Term (>37 wk gestation)	519 (85%)	58 (85%)	95 (84%)	33 (97%)	64 (80%)	103 (85%)	54 (83%)	112 (86%)	.4 *
EEG monitoring, h	66 (41, 99)	55 (25, 87)	66 (41, 107)	64 (40, 96)	63 (39, 102)	64 (37, 91)	86 (56, 106)	66 (41, 96)	.03 †
Primary seizure etiology									.04 *
Hypoxic-ischemic encephalopathy	231 (38%)	20 (29%)	46 (41%)	10 (29%)	29 (36%)	41 (34%)	31 (48%)	54 (41%)	
Ischemic stroke	101 (17%)	10 (15%)	16 (14%)	13 (38%)	14 (18%)	18 (15%)	6 (9%)	24 (18%)	
Intracranial haemorrhage	78 (13%)	7 (10%)	13 (12%)	1 (3%)	10 (13%)	17 (14%)	11 (17%)	19 (15%)	
Epilepsy ‡	80 (13%)	15 (22%)	17 (15%)	2 (6%)	11 (14%)	17 (14%)	7 (11%)	11 (8%)	
Deceased	110 (18%)	19 (28%)	20 (18%)	2 (6%)	17 (21%)	22 (18%)	14 (22%)	16 (12%)	.06 *
Length of stay among survivors (d)	15 (10, 30)	11 (7, 20)	20 (10, 33)	10.5 (8, 14.5)	16 (11, 41)	10 (14, 35)	21 (14, 35)	13 (9, 34)	.05 †
Discharge to home on antiseizure medication									
All subjects	428 (76%)	12 (27%)	76 (90%)	27 (90%)	49 (89%)	61 (71%)	39 (83%)	61 (74%)	<.0005 *
Acute symptomatic etiology (n = 318)	233 (73%)	1 (4%)	57 (89%)	21 (91%)	32 (89%)	39 (65%)	33 (84%)	50 (71%)	<.0005 *

Data are presented as N(%) or median (IQR).

* χ^2.

† ANOVA.

‡ Neonatal epilepsy includes epileptic encephalopathy, brain malformation, and benign familial neonatal epilepsy.

J Pediatr. Author manuscript; available in PMC 2018 February 01.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

J Pediatr. Author manuscript; available in PMC 2018 February 01.

Table II

Variables associated with medications continuation at the time of discharge to home among the 317 survivors of acute symptomatic seizures

			Univariable analyses*			Multivariable analyses†		
	n	Discharged with AED	RR	95% CI	*P*	OR	95% CI	*P*
EEG confirmed seizures								
Yes	266	206 (77%)	1.5	(1.2–2.0)	.0001	2.3	(0.97–5.4)	.06
No	51	26 (51%)						
Status epilepticus								
Yes	48	42 (88%)	1.2	(1.1–1.4)	.015	2.1	(0.6–7.3)	.2
No	269	190 (71%)						
Seizures refractory to initial loading dose								
Yes	196	160 (82%)	1.3	(1.1–1.5)	.0003	1.6	(0.8–3.2)	.2
No/unknown	115	71 (62%)						
Abnormal examination at discharge								
Yes	150	123 (82%)	1.3	(1.1–1.4)	.0008	2.0	(0.99–4.1)	.053
No	167	109 (67%)						

AED, antiepileptic drug; *RR*, relative risk.

*χ^2.

†Wald *P* value adjusted for each of the risk factors plus site, and etiology, which remain highly significant ($P < .0005$).