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

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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. *(J Pediatr 2017;181:298-301).*

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 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.

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

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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 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.

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

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).
*χ2.
†ANOVA.
‡Neonatal epilepsy includes epileptic encephalopathy, brain malformation, and benign familial neonatal epilepsy.