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Neonatal Seizures: Treatment Practices Among Term and Preterm

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Abstract

Neonatal seizures are common clinical conditions in both term and preterm neonates, yet there are no clinical management guidelines to direct care. We surveyed 193 international neurologists and neonatologists to assess management practices seizures in preterm and term neonates among neurologists, neonatologists, and specialists in neonatal neurology or neonatal neurocritical care. We found high reported rates of electroencephalogram (EEG) and amplitude-integrated EEG (aEEG) monitoring for detection of neonatal seizures, prevalent use of older anticonvulsant agents, and high rates of neuroimaging. Overall, responses were similar for term and preterm neonates, however term neonates were more likely to be more heavily investigated, with higher use of EEG and aEEG monitoring of at-risk neonates and higher use of MRI. Continuous monitoring and brain imaging in the setting of neonatal seizures are now standard of care in many centers, though management practices vary widely. Early recognition and management of neonatal seizures and possible underlying injury may lead to increased opportunities for stopping seizures, protecting the brain, and improving developmental outcomes in at risk neonates. There is urgent need for collaboration among neonatologists and neurologists to address the gaps in knowledge regarding management of neonatal seizures in term and preterm neonates.

Keywords

Infant; neonate; Seizures; Electroencephalography; Magnetic resonance imaging

Introduction

The risk of seizures, particularly acute symptomatic seizures, is highest in the first year of life (1). This elevated seizure risk likely reflects both developmental stage-specific mechanisms that lead to relative excitability in the neonatal brain (2), and the high risk for brain injury in the perinatal period. In term neonates, seizures occur in approximately 1-3.5 per 1,000 live births, and the reported rate is even higher among children born preterm (3-6)

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(7-9). Clinical and electrographic neonatal seizures frequently reflect serious underlying brain injury; clinical seizures are often one of the first signs of neurologic dysfunction and acutely encephalopathic neonates frequently have electrographic seizures without clinical signs(10).

In the past decades, several factors have influenced a burgeoning interest in optimizing management of neonatal seizures with a focus on reducing seizure burden. First, electrographic seizures are becoming easier to detect in this population. Advances in technology permit continuous brain monitoring with digital recording and storage for remote, real time recognition of seizures. In addition, simplified electroencephalogram trending (for example, amplitude-integrated EEG, aEEG) permits bedside seizure detection by practitioners with limited training. Second, evidence from animal studies suggests that seizures may alter brain development and lead to long-term deficits in learning, memory and behavior (11-14). Third, observational and randomized studies suggest that rapid, protocol-driven therapy leads to reduced seizure burden (15, 16).

Although there is no definitive evidence that minimizing seizure burden improves childhood neurodevelopment, many experts are moving toward early and aggressive seizure therapy. However, some clinicians maintain concern that the potential neurotoxic risks of commonly used seizure medications (17) may outweigh any benefit of treating seizures. Despite the recognition that timely diagnosis and management of neonatal seizures is critical, little evidence guides investigation and treatment. As such, management practices vary widely (18).

The objective of this study was to assess management practices for seizures in preterm and term neonates among neurologists, neonatologists, and specialists in neonatal neurology or neonatal neurocritical care.

Methods

Study Design

A multidisciplinary group of neonatologists and neurologists developed an English, Web-based questionnaire using a commercial survey tool (http://www.surveymonkey.com). Questions were developed by the authors and tested among a local group of physicians from diverse disciplines. University of California, San Francisco Institutional Review Board approval was obtained to use anonymous physician response data.

The anonymous Web-based questionnaire was distributed between July 1, 2010 and August 31, 2010 via email to colleagues in neonatology and child neurology in the US, UK, Europe, and Canada; participants of the 2010 *Brain Monitoring and Neuroprotection in the Neonate Conference*; and an online child neurology listserv (http://www-personal.umich.edu/~leber/c-n/e-mailUM.html). Participation was voluntary. Respondents were also requested to forward the questionnaire to colleagues involved in decision making of critically ill neonates. The likely known number of people with access to the survey is 400-500. A single person who answered only demographic data but did not answer any of the survey was excluded from the study.

Study Questionnaire

The Web-based questionnaire included 23 multiple-choice questions addressing seizure management practices in preterm and term infants. The questionnaire was divided into 4 sections: 1) demographics, including questions on specialty training, practice setting, and experience; 2) diagnosis of seizures and EEG monitoring (including multiple choice questions on modality (clinical observation alone, aEEG without EEG, EEG, aEEG or

EEG), EEG duration (≤60 minutes, 24 hours, until the child has been seizure-free for 24 hours) or EEG not available), and monitoring of high risk populations (using aEEG, EEG, both aEEG and EEG or no monitoring); 3) medical therapy (participants asked to name first-, second-, third-, and fourth-line medications from among a list of commonly used agents), and recommendations for treatment of electrographic seizures without clinical correlate; and 4) imaging using head ultrasound or magnetic resonance imaging based on a 5-point Likert scale. Respondents were asked to answer similar questions for both preterm and term neonates.

Statistical Analysis

Survey results are presented in actual numbers and percentages. Categorical responses were compared using contingency tables. The chi-square test or Fisher exact test was used to examine the difference between 2 proportions with the statistical significance set at 0.05.

Results

Respondent Characteristics

In total, 193 physicians responded to the questionnaire. Most participants answered all of the questions (median overall: 94% complete, range overall: 92-97% complete). Demographic and practice characteristics are shown in Table 1. More than half of respondents were neurologists (55.9%), one quarter were neonatologists (24.9%), and the remaining physicians self-identified as neonatal neurologists and/or specialists in neonatal neurocritical care (19.2%). The majority of respondents worked in a hospital with Level IIIC intensive care nursery (ICN, 80.4%), in a university or academic setting (88.0%) located in the United States (75.6%). In terms of number of practice years, the largest proportion of respondents had been practicing >20 years (30.9%), though >40% had been practicing for <10 years or were still in training.

Diagnosis of seizures and EEG monitoring

Participants were asked which modality they used to diagnose seizures in term newborns (response options: “clinical observation alone,” “aEEG without EEG,” “EEG,” “aEEG or EEG,” Table 2). EEG was the most commonly used modality (58%), although 33% used either aEEG or EEG, and almost 8% accepted clinical observation alone for diagnosis of seizures. There was no apparent difference in modality choice for preterm versus term neonates (Table 2). However, for both preterm and term, neurologists were more likely to favor EEG diagnosis (>65%), whereas neonatologists and neonatal neurologists/neonatal critical care specialists were equally likely to use aEEG or EEG to make a diagnosis of seizures (44-50% for both EEG and aEEG or EEG, $p<0.05$). Participants were asked about the duration of monitoring in newborns with suspected seizures (response options: “≤60 minutes,” “24 hours,” “seizure-free for 24 hours,” or “no EEG available,” Table 2). The most common practice was to monitor until the patient was seizure-free for 24 hours, or for 24 hours duration (combined >65%), however one third monitor for only up to 60 minutes. There was no apparent difference in the duration of monitoring for preterm versus term neonates (Table 2). Neonatal neurologists/neonatal neurocritical care specialists were more likely to favor a longer duration of monitoring: >60% favored 24 hours seizure-free monitoring, as compared to approximately 50% of neurologists and 30% of neonatologists.

Monitoring in at risk newborns

Participants were asked whether they monitor neonates at risk for seizures (response options: “yes, with aEEG,” “yes, with EEG,” “yes, with both aEEG and EEG,” “no,” Table 2). At-risk conditions included birth asphyxia, extra corporeal life support and cardiac arrest

in term newborns. For preterm newborns, the conditions included low gestational age, intraventricular hemorrhage, birth asphyxia and cardiac arrest. More than half of respondents monitor with aEEG, EEG, or both. Monitoring is more common for term newborns than for preterm newborns, although the difference was not significant (P=0.07).

Seizure treatment

Participants were asked to rank use of common anticonvulsants for treatment of neonatal seizures (response options: “lorazepam,” “phenobarbital,” “phenytoin/fosphenytoin,” “levetiracetam,” “midazolam,” “lidocaine” and “topiramate,” Table 3). Phenobarbital was the most-widely used first-line medication (>70%) with phenytoin as second-line (>40%). Levetiracetam was the most commonly used third-line agent (19%). There was no apparent difference in medication choice for preterm versus term neonates, or across clinician specialties.

Participants were asked whether they recommended treating electrographic seizures without clinical correlate (response options: “always,” “usually,” “about half the time,” “seldom,” “never”). More than 75% endorsed treating “always” or “usually.” There was no apparent difference for term versus preterm neonates, or across clinician specialties.

Imaging neonates with seizures

Participants were asked how often, at their center, head ultrasound (HUS) or magnetic resonance imaging (MRI) was used to image newborns with seizures (response options: “always,” “usually,” “about half the time,” “seldom,” “never” Table 4). Both modalities were commonly used in both term and preterm infants, with >75% responding “always” or “usually.” However, preterm newborns appear more likely to receive head ultrasound as compared with term neonates (95% vs 78% responding “always” or “usually”, $P<0.05$), and less likely to receive magnetic resonance imaging (MRI, 76% vs 93% responding “always” or “usually”, $p<0.05$). Neonatologists are more likely to favor head ultrasound, whereas neurologists and neonatal neurologists are more likely to recommend MRI.

Discussion

In this international survey of 193 neonatologists and neurologists, participants reported a wide variety of practices with respect to type and duration of monitoring, medication use, and imaging modality. In general, there were high reported rates of monitoring for detection of neonatal seizures, prevalent use of older anticonvulsant agents such as phenobarbital and phenytoin/fosphenytoin, and high rates of neuroimaging. Overall, responses were similar for term and preterm neonates, however term neonates were more likely to be more heavily investigated, with higher use of monitoring of at-risk neonates and higher use of MRI.

Widespread use of both EEG and aEEG monitoring is evident from the results of this survey, especially in the setting of suspected clinical seizures, where >90% of respondents endorsed monitoring. However, almost 10% of participants accepted clinical detection of seizures, although there is very good evidence showing that discrimination of neonatal seizures by clinical observation alone is very poor (19). Furthermore, duration of monitoring was limited to ≤60 minutes for 30% of participants and approximately 40% do not monitor at-risk neonates, especially preterm neonates, suggesting that monitoring may be inadequate in many cases. There is increasing recognition that critically ill children have seizures that go unrecognized unless they are routinely monitored (15, 20). Conventional video-EEG is the gold standard for electrographic seizure detection in neonates with spells (21), although aEEG is easier to interpret and is often more readily available (22). aEEG is less sensitive than conventional video-EEG, especially when seizures are brief, low amplitude, or distal to

the recording site, and when users lack experience or do not use the raw EEG trace in their interpretation (23-25). Neurologist preference for EEG may be related to its higher accuracy as compared to aEEG, or to lack of training in interpretation of aEEG. Nonetheless, many newborns have seizures that are evident on aEEG, and there is growing support for its use, especially in centers where availability of prolonged conventional EEG monitoring is limited (26). There is no good evidence to guide duration of monitoring for neonates at high risk for, or with suspected seizures, however expert opinion supports monitoring during the period of critical illness, and especially while the patient is encephalopathic. Neonates monitored following cardiac surgery had seizure onset at a mean of 21 hours post-operative (range 10-36 hours)(27), whereas age at onset was variable in neonates treated with therapeutic hypothermia (mean 9 hours, range 6 – 97 hours in one study and median 12-18 hours, range 10-62 hours in another)(28, 29). Neonatal seizures typically resolve abruptly within 24-72 hours, and experts have recommended monitoring for a 24-hour period following apparent resolution of seizures. However, in one recent study, seizures recurred after a 24-hour seizure-free period in one third of patients (29), which suggests that even 24-hours may not be adequate in some patients.

The approach to seizure therapy was similar for preterm and term neonates and across specialties. Phenobarbital and phenytoin/fosphenytoin remain in widespread use despite limited efficacy and potential neurotoxicity (17, 30). Newer agents, such as levetiracetam and topiramate, are often used for refractory seizures, although efficacy, side effect profiles, and pharmacokinetic data are limited. Widespread use of levetiracetam in spite of limited evidence may be related to its ease of use, safety profile in older children, as well as lack of sedating effects and EEG depression. A very high proportion of respondents endorsed treatment of seizures without electrographic correlate (>75% treat “always” or “usually”). Though there is still some controversy regarding the utility of treating seizures that have no clear clinical correlate, most experts advocate treatment of all electrographic seizures based the fact that bedside providers may miss subtle clinical signs or the encephalopathy as a sign of seizures, and also based on animal data showing that both clinical and subclinical seizures are associated with brain injury (31).

Respondents reported widespread use of imaging for neonates with seizures (>85%). However, preterm neonates appear less likely than term neonates to receive MRI. When compared with HUS, MRI has much higher resolution for parenchymal injury (32-35), and, as such, is more likely to detect injury associated with seizures in both preterm and term neonates. In one small study of preterm neonates with seizures, MRI provided information that could be useful to guide management or parent counseling (36). Transport and imaging using MRI is safe for preterm neonates, though it requires expertise both in neonatal transport and MR interpretation (37).

Although this survey captures a large, diverse group of physicians who specialize in caring for neonates, it is not without limitations. First, the survey was distributed through online groups, and so it is not possible to know precisely how many people received access to the survey, but failed to complete it. Second, participants were asked to choose from among a limited number of set answers, which may not accurately reflect their practice. Finally, this was a voluntary survey, so the physicians who chose to respond may also be those who are most conscious about issues regarding neonatal seizures and results may not represent Child Neurologists or Neonatologists at large.

The field of neonatal neurocritical is advancing rapidly, and there is increasing focus on optimizing care to improve developmental outcomes. Continuous monitoring and brain imaging in the setting of neonatal seizures are now standard of care in many centers, and these technologies are being used to guide management, diagnosis and prognosis.

Management practices vary widely, which likely reflects lack of evidence and consensus-based guidelines, as well as differences in training among neonatologists and neurologists. Early recognition and management of neonatal seizures and the underlying injury may lead to increased opportunities for stopping seizures, protecting the brain and improving developmental outcomes in at risk neonates.

There is urgent need for collaboration among neonatologists and neurologists both at the bedside in the intensive care nursery, and to design and conduct clinical studies and trials to address the gaps in knowledge regarding management of neonatal seizures in term and preterm neonates.

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Table 1

Demographic characteristics among 193 neurologists and neonatologists responding to an online questionnaire.

	n (%)
Specialty	
Neurology	108 (55.9)
Neonatology	48 (24.9)
Neonatal Neurology/Neonatal Neurocritical Care	37 (19.2)
ICN Level	
I	1 (0.5)
II	5 (2.6)
IIIA	4 (2.1)
IIIB	28 (14.5)
IIIC	155 (80.3)
Practice Setting	
University/Academic	168 (87.0)
Private Practice	13 (6.7)
Private Solo Practice	7 (3.6)
HMO	3 (1.6)
Other	2 (1.0)
Practice Location	
USA	145 (75.1)
Continental Europe	20 (10.4)
Canada	10 (5.2)
UK	5 (2.6)
Other	13 (6.7)
Practice Experience, yrs	
Resident/Fellow	15 (7.8)
<5	37 (19.2)
5-10	29 (15.0)
11-15	31 (16.0)
16-20	22 (11.4)
>20	59 (30.6)

ICN intensive care nursery

Table 2

Monitoring for preterm and term neonates with seizures, or at risk for seizures.

	Preterm	Term	P-value
	n (%)	n (%)	
Method of seizure diagnosis			
Clinical observation only	(6.9) 13	14 (7.7)	1
aEEG without EEG	2 (1.1)	2 (1.1)	
EEG	109 (58.0)	106 (58.2)	
aEEG or EEG	64 (34.0)	60 (33.0)	
Duration of monitoring			
≤60 minutes	57 (30.5)	56 (30.8)	0.9
24 hours	35 (18.7)	30 (16.5)	
Seizure-free for 24 hrs	87 (46.5)	89 (48.9)	
no EEG	8 (4.3)	7 (3.8)	
Monitoring At-Risk Newborns			
Yes, with aEEG	41 (21.9)	44 (24.2)	0.07
Yes, with EEG	32 (17.1)	43 (23.6)	
Yes, with both	27 (14.5)	34 (18.7)	
No	87 (46.5)	61 (33.5)	

EEG electroencephalogram; **aEEG** amplitude-integrated electroencephalogram

Table 3

Anticonvulsant choice for preterm and term neonates.

	Preterm			Term		
	1st	2nd	3rd	1st	2nd	3rd
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Phenobarbitol	135 (72.2)	49 (26.2)	2 (1.1)	120 (70.9)	49 (27.2)	3 (1.7)
Lorazepam	41 (21.9)	26 (13.9)	23 (13.1)	42 (23.1)	19 (10.6)	26 (14.9)
Phenytoin	4 (2.1)	76 (40.6)	62 (35.2)	4 (2.2)	77 (42.8)	61 (34.9)
Levetiracetam	2 (1.1)	17 (9.1)	37 (21.0)	2 (1.1)	16 (8.9)	33 (18.9)
Midazolam	5 (2.7)	14 (7.5)	29 (16.5)	5 (2.7)	17 (9.4)	28 (16.0)
Topiramate	0 (0.0)	1 (0.5)	12 (6.8)	0 (0.0)	0 (0.0)	11 (6.3)
Lidocaine	0 (0.0)	4 (2.1)	7 (4.0)	0 (0.0)	2 (1.1)	11 (6.3)
Other	0 (0.0)	0 (0.0)	4 (2.3)	0 (0.0)	0 (0.0)	2 (1.1)

Table 4

Brain imaging for preterm and term neonates with seizures.

Head Ultrasound			
	Preterm	**Term**	**P-value**
	n (%)	**n (%)**	
Always	147 (79.9)	86 (48.3)	P<0.0005
Usually	28 (15.2)	53 (29.8)	
~1/2 the time	7 (3.8)	21 (11.8)	
Seldom	2 (1.1)	18 (10.1)	
Never	0 (0.0)	0 (0.0)	
MRI			
Always	65 (35.0)	97 (53.6)	P<0.0005
Usually	77 (41.4)	72 (39.8)	
~1/2 the time	29 (15.6)	7 (3.9)	
Seldom	14 (7.5)	4 (2.2)	
Never	1 (0.5)	1 (0.6)	