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Impact of amplitude-integrated EEG on the clinical care for neonates with seizures

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Abstract

Amplitude-integrated EEG (aEEG) was introduced relatively recently into neonatal intensive care in the U.S.A. We aimed to evaluate whether aEEG has changed clinical care for neonates with seizures. All 202 neonates treated for seizures at our hospital from 2002 to 2007 were included in this study. Neonates monitored with aEEG (n=67) were compared to a contemporary control group of neonates who were not monitored, despite aEEG availability (n=57), and a historical control group of neonates treated for seizures before aEEG was introduced in our NICU (n=78). 82% of those treated with phenobarbital (137/167) continued treatment after discharge, with no difference among the groups. Adjusted for gestational age and length of stay, there was also no difference among groups in the number of neuroimaging studies or number of anticonvulsants per patient. Fewer patients in the aEEG group, compared to contemporary controls (n=16/67 vs. 29/57, p=0.001) or historical controls (n=38/78, p=0.002), were diagnosed clinically with seizures without electrographic confirmation. We conclude that introducing aEEG did not increase neuroimaging tests, nor did it alter anticonvulsant use. However, diagnostic precision for neonatal seizures improved after aEEG introduction, as fewer neonates were treated for seizures based solely on clinical findings, without electrographic confirmation.

Keywords

neonatal seizures; electroencephalography; amplitude-integrated EEG; aEEG; EEG; hypoxic ischemic encephalopathy; phenobarbital

Introduction

Amplitude-integrated EEG (aEEG) is a one- or two-channel EEG monitoring device that has been introduced into clinical care in neonatal intensive care units (NICUs) in the USA relatively recently. In some protocols, aEEG is used to determine eligibility for therapeutic

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hypothermia in neonates with hypoxic ischemic encephalopathy (HIE)[1, 2], and the aEEG background is predictive of neurodevelopmental outcome among neonates with HIE.[3–5] One advantage of aEEG is that it allows for expedient monitoring of cerebral activity. Its electrodes are relatively easy to place, and the results can be interpreted at the bedside by neonatologists.

Although primarily intended as a device for trending the EEG background, aEEG monitoring has also been used as a tool for detection of neonatal seizures. Neonatal seizures are a recognized risk factor for adverse neurodevelopmental outcome.[6] Many neonatal seizures can be subtle in their clinical manifestations, or completely subclinical, making them difficult to detect.[7] In such cases, EEG monitoring devices are integral to the diagnosis and quantification of neonatal seizures. However, because neonatal seizures are typically very brief (60% lasting less than 90 seconds)[8], they can be difficult to distinguish in a time-compressed aEEG tracing. Due to the limited number of electrodes applied in aEEG monitoring, seizures may also go undetected if their spatial distribution is restricted and different from the aEEG electrodes. Factors such as these contribute to aEEG's limited sensitivity for neonatal seizure detection.[8–10] Despite this, the specificity appears more reliable, with few false positive records reported in systematic studies.[8, 10]

Although there is a substantial body of research on the value of aEEG as a monitoring device, there is currently a lack of information about the effect that aEEG has on the overall clinical care provided to neonates with seizures. This study aims to determine the effect of introducing this new technology to the clinical care of neonates with seizures in our NICU.

Study Design and Methods

This study was approved by our university's Institutional Review Board. We identified all neonates treated for seizures or suspected seizures in our NICU from 2002–2007. These 202 patients were divided into three groups. Newborn infants who were monitored by aEEG during their hospitalization in the neonatal period (N=67), were compared to two different control groups. The contemporary control group (N=57) consisted of all neonates treated for seizures after the introduction of aEEG into our NICU, but who did not receive aEEG monitoring despite its availability, based on the treating clinician's discretion. The historical control group (N=78) consisted of all patients treated for seizures in our NICU during the two years prior to the consistent clinical availability of aEEG.

The patients' medical records were reviewed systematically. Data collected included demographics such as gestational age, birth weight and birth hospital, admission and discharge diagnoses, and seizure etiology. If seizures were diagnosed, we determined if the diagnosis was made with or without electrographic confirmation, and by which method(s) (e.g. aEEG, routine-length conventional EEG, or extended video-EEG monitoring). Information regarding the clinical care received during the hospital stay was also collected and quantified, based on documentation in the electronic medical record. This included the number of routine EEGs, prolonged video-EEG monitoring studies, and amplitude-integrated EEG's, number of neuroimaging studies (cranial ultrasound, computed tomography, and magnetic resonance imaging), anticonvulsant treatment regimen (number of anticonvulsants and whether or not the patient was discharged on phenobarbital), duration of hospital stay, and latency from first suspicion of seizures until the diagnosis was confirmed or refuted.

Conventional routine-length (30-to-60-minutes) and video-EEG monitoring utilized the International 10–20 System of electrode placement, modified for neonates, and always had concurrent video recording. aEEG monitoring was either single-channel, recorded from

biparietal electrodes, or dual channel, recorded from bilateral central-parietal derivations. When utilized, aEEG traces were reviewed periodically by the clinical neonatology team, independent from the clinical neurophysiology (neurology) service. For this study, EEG and aEEG results were extracted from clinical notes and formal reports, rather than from review of the actual tracings, so the precise duration of aEEG recordings were not uniformly available.

The three groups were compared using chi-squared tests, T-tests, and generalized linear modeling techniques, in order to determine if there were significant differences among the groups that corresponded to the introduction of aEEG. Multivariate generalized linear modeling techniques were employed where appropriate, to adjust results for gestational age and length of stay (SAS 9.1.2 software; SAS Institute, Cary, NC).

Results

The demographic profile of the three groups is shown in Table 1. There was no significant difference in the distribution of gender among the groups. The historical control group had significantly higher average birth weight than both the aEEG and contemporary control groups (p=0.014, p=0.0002), but there was no difference between the latter two groups (p=0.17). Correspondingly, gestational age was higher in historical compared to contemporary controls (p=0.0002), but not the aEEG subjects (p=0.058). There was no significant difference in gestational age between the aEEG and contemporary control groups (p=0.054). More patients from the aEEG group were transported to our NICU from referring hospitals than the contemporary or historical controls (p=0.05, p=0.017).

Analysis of seizure etiologies showed that more patients in the aEEG group were diagnosed with HIE than in the contemporary (N=30 vs. 6, p<0.0001) or historical control groups (30 vs. 13, p=0.002). However, there were no other significant differences in distribution of etiologies among the groups.

Data related to the impact of aEEG on clinical care are presented in Table 2. The time to diagnosis was defined as the number of days from the first documented suspicion of seizures to the confirmation or rejection of the seizure diagnosis. Subjects whose seizures were suspected prior to transfer from a referring institution (n=53) were excluded from this portion of the analysis, since diagnostic techniques for those hospitals could not be assessed. For the remaining 149 subjects, there was no significant difference among the groups in time to diagnosis (p<0.05 for all comparisons, without change in result when adjusted for gestational age).

Since the aEEG group had significantly more patients with HIE than the contemporary controls, and aEEG was part of the treatment protocol for those with HIE who were treated with therapeutic hypothermia, we divided our analysis into patients with a diagnosis of HIE and those without. Among patients with HIE, the time to seizure diagnosis was marginally shorter in the aEEG group compared with contemporary controls (mean 1.2 ± S.D. 1.6 days vs. 6.2 ± 12.8 days, p=0.05; median 0.5 days for both groups). When one clear outlier was removed from the analysis (a subject in the contemporary control group with time to diagnosis greater than 1.5 times the interquartile range), this difference did not persist. For patients without HIE, there was no significant difference in time to diagnosis among groups (p>0.05 for all comparisons).

Adjusted for gestational age and length of stay in our hospital, there was no significant difference in the number of neuroimaging studies (head ultrasound, CT, and MRI) that individual patients received. There was also no overall difference in the number of anticonvulsant medications prescribed per patient. Among all patients in our study who

received phenobarbital during their hospitalization, 82% (137/167) were continued on this medication after discharge. There was no difference among groups in the percent of patients discharged on phenobarbital.

Seizure diagnoses were divided into two categories: electrographic and clinical (diagnosis without electrographic confirmation). Electrographic confirmation was made by any combination of seizure(s) detected by aEEG, routine conventional EEG, or video-EEG monitoring. Among patients who received aEEG monitoring, a significantly lower percentage of the seizure diagnoses were made clinically, without electrographic confirmation, compared to those in the contemporary control group (23.9% vs. 50.9%, p= 0.002) or historical control group (48.7%, p= 0.001).

Discussion

To our knowledge, this is the first published analysis of the impact of introducing aEEG on the clinical care of neonates with seizures or suspected seizures. We demonstrate that the introduction of aEEG did not change some aspects of clinical care, such as anticonvulsant drug treatment and the number of neuroimaging studies performed. However, we did find that fewer patients were diagnosed clinically with seizures, without electrographic confirmation, following the introduction of aEEG into our NICU.

One concern that has been raised in regard to the introduction of aEEG is that, while it may aid in the electrographic detection of seizures, the consequence of seizures on overall neurodevelopment is unknown.[11] Evidence from animal models suggests that seizures cause or exacerbate neuronal injury, but this is more difficult to prove in humans[12–14]. If treatment were changed based on the increased detection of seizures, there is a theoretical risk that increased use of anticonvulsants of only modest efficacy could be more harmful to the patients than the seizures themselves.[15–18] In light of these concerns, it is reassuring that there were no changes in anticonvulsant use associated with the introduction of aEEG into our NICU.

Adding another method of seizure detection to clinical care in the NICU has the potential to lead to increased resource utilization, and therefore increased cost of care. However, based on the present study, this does not appear to be the case. Antiepileptic treatment was unaffected, but more importantly to cost of care, the number of costly neuroimaging studies remained unchanged (adjusted for gestational age) after the introduction of aEEG. Because many of our patients are transferred from other hospitals, and are transferred back to the referring institution once the acute medical conditions are addressed, we were unable to assess the impact of aEEG on overall length of stay. Data regarding nursing ratios and impact of aEEG monitoring on nursing care were not available. These are important measures of resource utilization and should be addressed in future studies.

Newborns are known to have many abnormal movements that have no associated electrographic abnormalities.[7, 19] Therefore, diagnosis of neonatal seizures based on clinical observation alone, without EEG confirmation, results in poor seizure detection and inadequate differentiation between seizure and non-seizure events.[7, 20] As a result, patients with abnormal, but non-seizure, events may be diagnosed with seizures and treated unnecessarily with anticonvulsant medications. One of the most reassuring findings of our study is that, after the introduction of aEEG into our NICU, fewer patients were diagnosed with seizures based on a clinical diagnosis alone (without electrographic confirmation of seizures). This could be indicative of a positive change in practice, resulting in fewer patients being treated with anticonvulsants based on a potentially inaccurate clinical diagnosis of seizures.

A previous preliminary report suggested that the introduction of aEEG was not associated with any change in the number of seizure diagnoses made among neonates referred to a tertiary-care NICU.[21] While Appendino *et al.* considered all patients admitted to the NICU, we considered only patients with seizures or suspected seizures. Additionally, we broke seizure diagnoses into two categories (clinical and electrographic), while Appendino *et al.* did not. Because of these differences in study design, the results are difficult to compare.

A recognized limitation of this study is that it analyzes data from a single treatment center. Despite this, we had a large sample size (N=202), and among those patients for whom the birth hospital was known 72.5% (145/200) were born at another hospital and transferred to our center, similar to other large academic NICUs. Another limitation of this study is that it is retrospective. It could be argued that any differences between groups are due to changes in clinical practice over time, rather than the introduction of aEEG. We addressed this potential problem by having both a contemporary and a historical control group. We looked for changes specific to the aEEG group, rather than changes to both the aEEG group and the contemporary control group, and there were very few differences between the contemporary and historical controls. Additionally, there were no new evidence-based practice changes introduced during the study time-frame (2002 through 2007).

Finally, use of aEEG monitoring was determined by the attending neonatologist, rather than a strictly defined protocol (except in the case of HIE patients being considered for therapeutic hypothermia). This reflects clinical practice variation, but introduces the potential for confounding of the approach to neonatal seizure management between those who were in the aEEG group, compared to the contemporary controls. The lack of significant differences in anticonvulsant or diagnostic test use between these two groups suggests that significant bias was not present.

Conclusions

In this first published analysis of the impact of incorporating aEEG into NICU care on the clinical care of neonates with seizures, we found that introduction of this tool in our NICU was not associated with a change in antiepileptic drug treatment, or in the number of neuroimaging studies that patients received. We also found that the number of patients treated for seizures on the basis of a clinical diagnosis alone, without electrographic confirmation, was significantly lower among patients monitored by aEEG compared to those who did not receive aEEG monitoring. Since neonatal seizures are difficult to accurately identify clinically, this is an important change which decreases the risk of neonates receiving unnecessary treatment. Future studies should assess the impact of electroencephalopgraphic monitoring, with aEEG and/or conventional video-EEG monitoring, on resource utilization and short- and long-term outcomes among high risk neonates.

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Table 1

Demographic profile of study subjects

	aEEG (Group 1)	Contemporary Control (Group 2)	Historical Control (Group 3)
Number of Study Patients	67	57	78
Gender (N, %)			
Female	27 (40.3%)	28 (49.1%)	27 (34.6%)
Male	40 (59.7%)	29 (50.9%)	51 (65.4%)
Gestational Age (weeks±S.D*)	38.4±3.0	37.4±4.0	39.4±1.6†
Birth Weight (grams±S.D*)	3156±774	2969±878	3469±604‡
Birth Hospital (N, %)			
Inborn	11 (16.4%)	18 (31.6%)	26 (34.2%)
Outborn	56 (83.6%)§	39 (68.4%)	50 (65.8%)
Types of EEG studies||			
aEEG	67	0	0
Routine-length conventional EEG	60	53	75
Video EEG monitoring	21	19	18
Seizure Etiology (N)			
Hypoxic Ischemic Encephalopathy	30¶	6	13
Infection	6	4	3
Stroke	3	4	10
Hyponatremia	0	1	3
Hypocalcemia	1	2	1
Intracranial Hemorrhage	10	17	16
Genetic Syndrome	0	4	2
Congenital Cerebral Malformation	3	4	6
Unknown	5	8	12
Other	8	8	7
Non-Seizure Diagnosis#	12	10	12

*S.D. = standard deviation

†Group 3 vs. group 2, p=0.0002;

‡Group 3 vs. group 1, p=0.014; group 3 vs. group 2, p=0.0002

§Group 1 vs. group 2, p=0.05; group 1 vs. group 3, p=0.017

||Individual subjects could have had more than one type of EEG.

¶Group 1 vs. group 2, p<0.0001; group 1 vs. group 3, p=0.002

#Infants in this group had identified diagnoses other than seizures which explained their paroxysmal clinical events (e.g. benign neonatal sleep myoclonus, jitteriness, and apnea).

Table 2

The impact of aEEG on clinical care for neonates with suspected seizures

	aEEG (Group 1)	Contemporary Control (Group 2)	Historical Control (Group 3)
Number of Anticonvulsants (median, range)	1, 0–5	1, 0–3	1, 0–5
Number of Neuroimaging Studies	3.8±5.0	3.8±4.4	2.9±2.7
Time to Diagnosis (days±S.D.)[*]			
With hypoxic-ischemic encephalopathy	1.2±1.6[†]	6.2±12.8	0.5±0.7
Without hypoxic-ischemic encephalopathy	1.6±2.2	2.2±7.8	1.5±1.9
Seizure Diagnoses:			
Clinical Only	25	35	49
Electrographic Only	3	2	4
Both Clinical and Electrographic	37	17	23
Clinical Diagnosis Without Electrographic Confirmation	16/67 (23.9%)[‡]	29/57 (50.9%)	38/78 (48.7%)

[*] Time to diagnosis was defined as the number of days from the first documented suspicion of seizures to the confirmation or exclusion of the diagnosis. Subjects whose seizures were diagnosed at a referring institution, prior to transfer to our hospital, were excluded from this analysis. Data are presented as days ± standard deviation.

[†] Group 1 vs. group 2, p=0.05 derived from generalized linear models (p=NS when 1 outlier was removed from the data set).

[‡] Group 1 vs. group 2, p=0.002; group 1 vs. group 3, p=0.001 derived from generalized linear models.