A Pilot Study of Continuous Limited-Channel aEEG in Term Infants with Encephalopathy

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Objective To evaluate the accuracy, feasibility, and impact of limited-channel amplitude integrated electroencephalogram (aEEG) monitoring in encephalopathic infants.

Study design Encephalopathic infants were placed on limited-channel aEEG with a software-based seizure event detector for 72 hours. A 12-hour epoch of conventional EEG-video (cEEG) was simultaneously collected. Infants were randomly assigned to monitoring that was blinded or visible to the clinical team. If a seizure detection event occurred in the visible group, the clinical team interpreted whether the event was a seizure, based on review of the limited-channel aEEG. EEG data were reviewed independently offline.

Results In more than 68 hours per infant of limited-channel aEEG monitoring, 1116 seizures occurred (>90% clinically silent), with 615 detected by the seizure event detector (55%). Detection improved with increasing duration of seizures (73% >30 seconds, 87% >60 seconds). Bedside physicians were able to accurately use this algorithm to differentiate true seizures from false-positives. The visible group had a 52% reduction in seizure burden ($P = .114$) compared with the blinded group.

Conclusions Monitoring for seizures with limited-channel aEEG can be accurately interpreted, compares favorably with cEEG, and is associated with a trend toward reduced seizure burden. *(J Pediatr 2009;154:835-41)*

Seizures are more prevalent during the neonatal period than at any other time in life, with an incidence of 1 to 3.5 per 1000 live births.[1,2] Term infants with seizures have very poor outcomes, with 20% dying in the neonatal period and survivors having a 28% to 35% risk for severe neurodevelopmental disability and 20% to 50% risk for epilepsy.[3-7] This condition poses additional challenges due to limitations in accurate clinical diagnosis. More than half of electrographic (EEG) seizures in newborn infants have no clinical correlate, and the majority of those with clinical correlates are missed at the bedside.[8,9] Recognition of the presence and extent of seizure burden in these high-risk infants may be critical, as there is growing evidence that seizures in the newborn may be harmful.[10-13]

Conventional EEG (cEEG) with greater than 10 electrodes and concurrent video recording is the gold standard for the detection of seizures. However, cEEG is labor intensive to both set up and interpret, and the interpretation is rarely available in real time. As an alternative, many NICU centers have adopted amplitude integrated EEG (aEEG) with the goal of identifying and more aggressively treating electrographic seizures. Although some have questioned the accuracy of aEEG alone in detecting seizures, combining the unprocessed signal of limited-channel EEG to the aEEG has the potential to detect close to 80% of seizures detected by cEEG.[14-18]

The aim of this study was to evaluate the feasibility and impact of continuous bedside limited-channel aEEG monitoring in the NICU setting. Our hypothesis was that such monitoring could be accurately utilized by NICU clinicians and that the treatment of EEG seizures using these devices would improve outcomes.

METHODS

In this prospective, randomized pilot trial, families of infants ≥36 weeks' gestation admitted to St Louis Children's Hospital between the dates of March 2007 to March 2008 who met any of the following criteria were approached: (1) Neonatal encephalopathy

BE	Base excess	cEEG	Conventional electroencephalogram
EEG	Electroencephalogram	HIE	Hypoxic ischemic encephalopathy
aEEG	Amplitude-integrated electroencephalogram		

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(defined by modified Sarnat I-III) including suspected or confirmed clinical seizure event; (2) pH ≤7 or base excess (BE) ≥12 by cord gas or within 1 hour of life; (3) Apgar ≤5 at 5 minutes of life; and (4) severe clinical course requiring muscle relaxation for >4 hours.

Any infant suspected of having a congenital abnormality of the central nervous system was excluded. The ethics committee at St Louis Children's Hospital and the HRPO of Washington University approved this study. Written informed parental consent was obtained for all patients. There were no limitations for enrollment from the time of birth and infants could be either inborn or transported from an outside facility.

Once enrolled, patients were randomly assigned by sealed envelope into 1 of 2 different groups; either a blinded seizure group (blinded) or a monitored seizure group (visible). The infants were placed on limited-channel aEEG (BRM 3, BrainZ Instruments, Auckland, New Zealand) for a goal of at least 72 hours. Patients treated with hypothermia were monitored through rewarming. For the purposes of this study, limited-channel aEEG refers to the combined information collected from both the unprocessed EEG signal collected from limited EEG channels (2 channels placed bilaterally over the central-parietal regions of C3-P3 and C4-P4 using hydrogel electrodes) and the condensed-amplitude integrated EEG (aEEG) processed from these 2 channels. Simultaneous conventional EEG with video (cEEG) was collected, if clinically feasible, for up to 12 hours using a split lead set up, usually within the first 24 hours of limited-channel aEEG monitoring. Conventional EEG with video was done (Stellate; Montreal, Quebec, Canada) with 17 standard gold disk electrodes using the 10-20 international system. Electrodes were placed at the following locations: FP1, FP2, F3, Fz, F4, T7, C4, CZ, C3, T8, P7, P3, Pz, P4, P8, O1, O2, along with 1 ground electrode, 1 chin EMG electrode, bilateral eye electrodes, 1 respiratory electrode, and 1 standard electrocardiographic electrode. The C3, P3, C4, P4 electrodes were also used for the limited-channel aEEG monitoring through split leads with limited-channel aEEG and cEEG traces being recorded simultaneously. Patients had MRI imaging between 7 and 10 days of life if clinically stable.

In the blinded group, limited-channel EEG was recorded but blinded to the clinical team with only the electrode impedance values visible to ensure adequate data collection. Nurses annotated all care-giving activities such as feeding or patting on the monitor along with suspected clinical seizure events. Blinded patients were treated for their seizures based only on clinical observation and a 1-hour cEEG without video as standard practice in our NICU.

In the visible group, data from the limited-channel aEEG monitor was available for interpretation by the clinical team. Each limited-channel aEEG monitor was equipped with seizure detection software (RecogniZe, BrainZ Instruments, Ltd) to alert bedside caregivers to potential electrographic seizures.[19] This detector was tested previously with retrospective cEEG data without video with favorable results but had not been evaluated prospectively with a limited-channel aEEG device. When activated, the seizure detection software placed a gold bar over the segment of suspected EEG seizure (Figure 1). Nurses were instructed to notify a physician (fellow or attending level) if the seizure detection software triggered a seizure detection event. In addition, nurses were asked to mark all care events, feeds, and suspected clinical seizure events by annotating on the limited-channel aEEG monitor. When notified of a seizure detection event, physicians evaluated the infant, the limited-channel unprocessed EEG signal, and the aEEG tracing and then decided whether or not the seizure detection event was in fact a true seizure event. These evaluations along with the subsequent clinical decision were documented at the bedside on standardized study recording sheets. Physicians received informal training prior to and during the study on EEG interpretation with the limited-channel aEEG monitors. Clinical decisions about the timing and nature of pharmacological therapy for seizures were left to the discretion of the clinical team. The routine antiseizure medication regimen was phenobarbital as a first-line treatment (up to 40 mg/kg), followed by fosphenytoin (20 mg phenytoin equivalents/kg) and then a benzodiazepine (midazolam 0.1 mg/kg bolus followed by a continuous infusion).

Seizures were defined as EEG waveforms, which evolve in frequency, amplitude, or morphology occurring in either cerebral hemisphere for ≥10 seconds. Seizure duration was recorded in seconds, based on the limited-channel aEEG data to estimate the total seizure burden for a given patient (the summation of all the seizures in seconds). A cessation in seizure activity of >10 seconds qualified a subsequent epileptic event as a distinctly new seizure for both cEEG and limited-channel aEEG. Limited-channel aEEG data were retrospectively and independently reviewed by both a blinded epileptologist and an unblinded experienced limited-channel EEG reader. Any disputed seizures were resolved between the two readers. In the event that no agreement could be reached, a third experienced reader was used to resolve the differences. cEEG data were interpreted by a separate blinded epileptologist. Clinical data such as Apgar scores, length of time to full oral feeds, time to discharge, number and dose of antiseizure medications, and discharge medications were recorded. MRIs were read by a blinded reader who scored the images on injury to the cortex, white matter, deep nuclear gray matter, and brainstem. Images were then assigned a global score based on overall degree of injury (1 = normal, 5 = severe global injury). For classification purposes, hypoxic ischemic encephalopathy was defined as 2 of the following 3 in the presence of a known perinatal event (cord accidents, nonreassuring fetal heart tracings, placental abruption, etc): evidence of acidosis (pH <7 or BE >12), need for respiratory support shortly after birth, or an Apgar score at 5 minutes of ≤5.

Statistical Analysis

All data processing was done on SPSS version 16.0 (SPSS Inc, Chicago, Illinois). Comparisons between groups