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Original Article

Implementation of a Neurocritical Care Program: Improved Seizure Detection and Decreased Antiseizure Medication at Discharge in Neonates With Hypoxic-Ischemic Encephalopathy

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ABSTRACT

BACKGROUND: We report the impact of implementing continuous video electroencephalography monitoring for neonates with hypoxic-ischemic encephalopathy via a protocol in the context of neonatal neuro-critical care program. **METHODS:** Neonates with hypoxic-ischemic encephalopathy were studied retrospectively two years before and after implementing continuous video electroencephalography for 72 hours as a care protocol. Before continuous video electroencephalography, a 60-minute routine electroencephalography was performed at the discretion of the provider. Primary outcome: electrographic seizure detection; secondary outcome: use of maintenance antiseizure medications, discharge antiseizure medications, and cumulative burden for each antiseizure medication defined as total mg/kg during hospital stay. **RESULTS:** A total of 157 patients with a median gestation of 40 weeks were analyzed; 103 (66%) underwent therapeutic hypothermia. Baseline and clinical characteristics including disease severity and cooling were similar. Before continuous video-electroencephalography ($n = 86$), 44 (51.2%) had clinical seizures, of those 35 had available routine electroencephalography; 12 of 35 (34%) had electrographic seizures. None of the infants without clinical seizures showed electrographic seizures. After continuous video-electroencephalography ($n = 71$), 34 (47.9%) had clinical seizures, of those 18 (53%) had electrographic seizures; five of 37 (14%) of infants with no clinical seizures had electrographic seizures. The introduction of continuous video-electroencephalography significantly increased electrographic seizure detection ($P = 0.016$). Although there was no significant difference in the initiation and maintenance use of antiseizure medications after continuous video-electroencephalography, fewer infants were discharged on any antiseizure medication ($P = 0.008$). Also, the mean phenobarbital burden reduced ($P = 0.04$), without increase in other antiseizure medications use or burden. **CONCLUSION:** Use of continuous video-electroencephalography as part of the neonatal neuro-critical care program was associated with improved electrographic seizure detection, decreased phenobarbital burden, and antiseizure medication use at discharge.

Keywords: neonatal neurocritical care, continuous video-EEG, neonatal seizures, hypoxic-ischemic encephalopathy, antiepileptic drugs therapeutic hypothermia

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Introduction

Hypoxic-ischemic encephalopathy (HIE) remains a major cause of seizures in neonates.[1] Even after therapeutic hypothermia became the standard of care in HIE, the incidence of neonatal seizures is unchanged and they are mostly subclinical, although the overall seizure burden has

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reduced.[2] Neonatal seizures can easily be underdiagnosed or misdiagnosed clinically.[3] Seizures should be recognized as they may be associated with independent worsening of neurodevelopmental outcome, regardless of the primary neurological insult from hypoxia and ischemia.[4-6] Also, misdiagnosis of paroxysmal events in neonates as seizures will lead to overuse of antiseizure medications (ASMs), which in turn may alter normal brain development and potentially induce apoptosis of the developing brain.[7-9] Electrophysiological studies help to understand the cortical electrical activity and thus identify seizures.

Initially, electroencephalography (EEG) was done routinely in neonates with seizures to assess cerebral injury and for prognostication; later amplitude-integrated EEG (aEEG) became increasingly used in the neonatal intensive care units (NICUs) for seizure monitoring.[10] It was shown that seizures were missed with aEEG monitoring if they were brief (less than 30 seconds), low amplitude, and frequently recurring.[11] Continuous video-EEG (cvEEG) monitoring that provides full, standard EEG electrode coverage and video correlations is recommended as the gold standard for monitoring neonatal seizures; this monitoring should be available in intensive care units caring for neonates with HIE.[12-14]

An updated systematic review and meta-analysis involving more than 40,000 patients suggested that the mortality and neurological recovery were better when brain-injured patients were cared for in neurointensive care units.[15] This finding was attributed to the expertise gained from experience of caring for more such patients, adherence to protocols, and multimodal neuromonitoring.[15] This success has led to the development of neonatal neurocritical care programs, which help in giving brain-focused care and thereby preventing secondary brain injury, with multidisciplinary inputs.[16,17] EEG monitoring for detection of neonatal seizures is an essential part of neurocritical care programs.

The Department of Pediatrics (Sections of Neonatology and Pediatric Neurology) in Southern Alberta began a neonatal neuro-critical care (NNCC) program in August 2013. We hypothesized that routine video-electroencephalographic monitoring of neonates with HIE during therapeutic hypothermia and shortly after rewarming in the context of protocolized management by NNCC program will help in timely detection of seizures (clinical and electrographic) and appropriate treatment with ASM. The intent was to better detect and treat seizures when evident on cvEEG and, at the same time, minimize subjecting the injured brain to the potentially neurotoxic effects of ASMs.

The primary objective of our study was to detect the impact of cvEEG in the context of NNCC versus routine EEG (rEEG) on seizure detection in neonates with HIE. The secondary objective was to identify the impact of cvEEG on seizure treatment in terms of ASM burden and use of ASMs as maintenance and at discharge, in comparison to rEEG. ASM burden for each drug was the cumulative dose of ASM, calculated as the total mg/kg used during the hospital stay.

Patients and Methods

CvEEG monitoring was introduced as standard of care in our NICUs as part of NNCC initiative in August 2013. A multidisciplinary neurocritical care team was formed which included members from the following specialties: pediatrics, clinical electrophysiology, pediatric neurology, neuroradiology, and neonatology with expertise in neonatal neurology. The same pediatric neurology team covered all the NICUs in the Calgary region.

Three different models of NNCC were considered: (1) a dedicated physical space for neonatal neurointensive care patients at the outborn center, which was not feasible because of variability in the admission rate of such neonates over the year; (2) a neurocritical care team directly managing neonates requiring neurointensive care, which had logistic difficulties in terms of manpower and resources; and (3) a consultation model in which neurocritical care team was consulted by the NICU house staff. The latter was easily adopted into the NICU, by developing and updating neonatal neurology protocols and guidelines and proper handling and inservicing of the house staff and nurses on cvEEG monitoring. A neonatologist with special interest in neonatal neurology was available round the clock for troubleshooting the issues arising in the NICU from cvEEG lead application, impedance checking, operating the Natus software, identifying EEG background, and suspecting seizures. In addition, once a designated neurocritical core team was available, the interservice collaboration and communication became very efficient. With the help of the centralized server, the core team members accessed both live and recorded cvEEG within the hospital, between the level 3 NICUs and remotely.

The studies were interpreted by a board-certified pediatric clinical neurophysiologist during working hours, and the clinical care team was updated in a timely fashion on the occurrence of seizures, thereby facilitating decision-making on the appropriate use of ASMs. After 5 PM, the on-call pediatric neurologist was consulted. In the event of a seizure, the first-line ASM used was phenobarbital to a maximum of 60 mg/kg/day; this was followed by fosphenytoin at 20 mg/kg/day and midazolam infusions. Maintenance phenobarbital was started at a dose of 5 mg/kg/day after a total bolus dose of 40 mg/kg/day. During the period in which this study was conducted, levetiracetam was increasingly used. The discharge ASM, when required, was phenobarbital or levetiracetam.

This study was a retrospective cohort study done on all neonates with HIE admitted to the NICUs of Calgary from August 2011 to October 2015. HIE was graded using a modified Sarnat scoring system.[18] A consensus-driven local guideline, as elaborated later, was used for initiation of the therapeutic hypothermia protocol, which is the standard of care for neonates with moderate to severe HIE.

Infants at $\geq$35-week gestation and third percentile birth weight or more who satisfied criteria A and B within six hours of birth were eligible for cooling.

1) Criteria A: at least one of the following within one hour of birth:
   i) Apgar score $\leq$5 at ten minutes
   ii) Ongoing resuscitation, including positive pressure ventilation, required at ten minutes
   iii) Cord pH or postnatal arterial blood gas pH less than 7.0 within one hour of birth
   iv) Base deficit of $\geq$16 on cord gas or postnatal arterial blood gas within one hour of birth

2) Criteria B: evidence of acute moderate to severe encephalopathy as per the modified Sarnat scoring system

Infants with major congenital anomalies, congenital infections, chromosomal anomalies, known congenital neuromuscular disease, severe growth restriction, and severe uncontrolled bleeding were excluded from cooling. Eligible infants underwent whole-body therapeutic hypothermia with a target core temperature between 33°C and 34°C, maintained for 72 hours; then, the infants were rewarmed gradually at the rate of 0.5°C every hour, until they reached 36.5°C over 12 hours.

Traditionally, neonates with HIE had a rEEG consisting of 60 minutes of EEG recording usually within the first 12 hours of age, and subsequent EEGs were requested at the discretion of the provider. As per the protocol developed by the NNCC program, cvEEG was commenced as soon as possible after admission by the NICU bedside staff for a total of 72 hours during the entire duration of therapeutic hypothermia and rewarming.