



## EDITORIAL

# Amplitude integrated electroencephalogram (aEEG): has it found its niche in neonatal intensive care unit? ☆, ☆☆

## Eletronecefalograma de Amplitude Integrada (aEEG): será que ele encontrou seu nicho na Unidade de Terapia Intensiva Neonatal?

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There has been an important change in newborn intensive care for infants with encephalopathy assumed to be of a hypoxic-ischemic origin. Prior to 2005, a brain specific therapy was not available and management was limited to intensive supportive care. The latter consisted of correction of physiologic derangements in blood pressure, acid-base, and minerals/electrolytes, treatment of seizures, and support of organ dysfunction, while waiting for the return of cerebral function. The demonstration that therapeutic hypothermia reduced death or disability in infants  $\geq$  36 weeks gestation with perinatal hypoxia-ischemia has changed the approach towards infants with encephalopathy immediately after birth. A critical characteristic of the therapy was that it needed to be initiated within 6 hours of birth based on elegant laboratory studies using fetal sheep; the latter confirmed a relatively short therapeutic window of approximately 6 hours after a hypoxic-ischemic event.<sup>1</sup> Given this time frame, identification of infants at high risk of death or disability was of paramount importance. The goal was to avoid using a new therapy with an uncertain

safety profile among infants who inherently were at low risk of an adverse outcome from hypoxia-ischemia. Initiation of clinical trials of therapeutic hypothermia, starting in 1999 with the CoolCap trial,<sup>2</sup> pushed the amplitude integrated electroencephalogram (aEEG) to the forefront of diagnostic tools to facilitate identification of appropriate study candidates. The article by Toso et al.,<sup>3</sup> entitled “Clinical utility of early amplitude integrated EEG monitoring in term newborns at risk of neurological injury”, provides an appropriate description of how one center has moved from using the aEEG for investigative purposes into real world clinical application. This article raises the issue of whether aEEG has found its place among the diagnostic tools used within neonatal intensive care units.

Eligibility for many clinical trials in newborn intensive care consists of discreet, categorical, readily defined inclusion criteria such as birth weight, gestational age, or type/level of ventilator support. In contrast, inclusion criteria for newborn neuroprotection trials typically are tiered, whereby infants must demonstrate some evidence of impaired placental gas exchange (either biochemically and/or clinically), followed by clinical evidence of moderate or severe encephalopathy using a neurological examination. Categorizing neurological findings after birth is a complex task, given transitional physiology, maternal medications/anesthesia, evolving neurological abnormalities (either toward improvement or deterioration), and non-hypoxic-ischemic etiologies for encephalopathy. Given these considerations and the subjectivity of neurological

DOI of original article:

<http://dx.doi.org/10.1016/j.jpmed.2013.07.004>

☆ Please cite this article as: Laptook A. Amplitude integrated electroencephalogram (aEEG): has it found its niche in neonatal intensive care unit? J Pediatr (Rio J). 2014;90:102–4.

☆☆ See paper by Toso PA et al. in pages 143–8.

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examinations, some clinical trials desired a more objective measure of cerebral dysfunction. The aEEG appears to have found a niche by demonstrating the electrical background activity of the brain, which is highly correlated with the background pattern of conventional, full montage EEG recordings. Abnormalities found on aEEG early in life have strong predictive indices for abnormal outcome at 1 year of age. For example, Toet et al. studied 72 term infants with evidence of perinatal hypoxia-ischemia with a single channel aEEG recorded at 3 and 6 hours following birth. The recording was classified by pattern recognition as continuous normal voltage, discontinuous normal voltage, burst suppression, continuous low voltage, or flat trace.<sup>4</sup> Follow-up at more than 1 year of age was accomplished in 93% of the cohort. The ability to predict a normal outcome after a normal tracing was high. The sensitivity and specificity of abnormal patterns (burst suppression, continuous low voltage, and flat trace) for predicting poor outcomes were 85% and 77%, respectively, at 3 hours of age, and was 91% and 86%, respectively, at 6 hours of age. A meta-analysis of eight cohort studies reported the predictive indices of aEEG for death or disability among term infants with HIE: sensitivity was 91%, specificity was 88%, positive likelihood ratio was 10.1, and the negative likelihood ratio was 0.09.<sup>5</sup> In the era of therapeutic hypothermia, one study reported that the positive predictive value of the aEEG obtained within 6 hours of birth for predicting abnormal outcome at 18 months was 84% in infants with perinatal hypoxia-ischemia; moderate hypothermia reduced such predictive values due the neuroprotection associated with the therapy.<sup>6</sup>

As encouraging as these early aEEG studies were, not all clinical trials of therapeutic hypothermia have used the aEEG to identify eligible patients. In the Cochrane meta-analysis, only three of the six major clinical trials of therapeutic hypothermia for perinatal hypoxia-ischemia used aEEG for patient eligibility.<sup>7</sup> Trials that did not use the aEEG limited their inclusion criteria to biochemical and/or clinical indicators of impaired placental gas exchange and the presence of moderate or severe encephalopathy.<sup>8-10</sup> Whether trials that used aEEG for eligibility enrolled infants with a different level of severity of encephalopathy (which a brief neurological examination may not detect) remains unclear. In contrast to the cohort studies above, the analysis of 314 aEEG recordings from the TOBY randomized trial of hypothermia<sup>11</sup> indicated that the positive predictive value of an abnormal aEEG for adverse outcome at 18 months of age (death or disability) was lower than that reported in cohort studies (0.59 and 0.51 for non-cooled and cooled infants by voltage recognition, respectively). These results suggest that higher predictive indices reported from observational, non-randomized trials that included historical controls and sub-groups from randomized trials may be subject to selection bias. The results from the TOBY trial are in agreement with the report from the NICHD Neonatal Research Network of 108 infants, which included 46 infants from the NICHD whole body cooling trial<sup>6</sup> and 62 infants who were enrolled after the trial.<sup>12</sup> The positive predictive value for an adverse outcome at 18 months (death or disability) was 0.56, and did not differ whether the aEEG was acquired at < 6 hours of age or between 6 and 9 hours of age. Similar to the results of the TOBY trial and the report from Thorsen et al.,<sup>6</sup> the

positive predictive value of aEEG was reduced by hypothermia therapy, reflecting the neuroprotection afforded by this treatment.

Where does this leave a clinician regarding the use of aEEG for deciding whether therapeutic hypothermia should be initiated? In the absence of a biomarker with high positive and negative predictive indices for outcome at 18 months of age, aEEG is still a very valuable tool, but it should be used in conjunction with a neurological examination for infants with evidence of acute impairment of gas exchange. It may be of greatest use in infants who have some features of encephalopathy, when the examination borders between mild and moderate severity. This is especially important for clinicians who lack experience with neurological examination, since it can be challenging in critically ill infants. In the presence of unequivocal moderate or severe encephalopathy, the presence of a "normal" aEEG should not preclude initiation of therapeutic hypothermia, given a suboptimal negative predictive value of the aEEG.<sup>13</sup>

Other applications of aEEG have emerged since it was first evaluated as a tool to identify infants for neuroprotection. It is technically easy to maintain aEEG recordings during the duration of therapeutic hypothermia; this has facilitated examining the recovery of aEEG background pattern as another potential prognostic marker. These studies indicate that the natural history of the aEEG pattern after a putative perinatal event can be quite diverse. An earlier return to normal of the background pattern has been associated with a better outcome at 24 months, especially if this occurs in the first 24 hours after birth;<sup>14</sup> some authors have concluded that the recovery time to a normal background is the best predictor of poor outcome in early childhood.<sup>6</sup> Other reports indicate that the presence, time of return, and quality of sleep-wake cycles reflect the severity of the perinatal hypoxic-ischemic event.<sup>15</sup> Furthermore, the time of return of sleep-wake cycle activity has predictive value for neurodevelopment. In a consecutive series of 171 term infants born between 1992 and 2002, each increase in hour from birth to the return of sleep-wake cycles was associated with a 0.96 decrease in the odds of a good outcome at 12 to 66 months of age (95% confidence interval, 0.94-0.98).<sup>15</sup> Smaller cohorts have suggested similar conclusions.<sup>16</sup> The beneficial effects of hypothermia on the neurodevelopmental outcome is thought to explain why the time to return of sleep-wake cycles is a better predictor of early childhood outcome for infants treated with hypothermia compared to those kept normothermic.<sup>6</sup> Notably, all of these reports are retrospective, cohort studies. An important observational cohort study entitled "Prediction of outcome in hypoxic-ischemic encephalopathy using amplitude integrated EEG" is being performed as a secondary study to the NICHD Neonatal Research Network trial "Optimizing cooling strategies at < 6 hours of age for neonatal hypoxic-ischemic encephalopathy" (ClinicalTrials.gov: NCT01192776). This secondary study is designed to test the ability of an aEEG acquired beyond 6 hours of age to predict death or disability at 18-22 months in term infants with encephalopathy in the setting of a randomized trial.

Interest in the use of aEEG has been extended to other areas of newborn intensive care. Detection of seizures is of great interest among clinicians given the diverse phenotypes

of neonatal seizures, possible clinical-electrographic dissociation, and the real world issues of obtaining a conventional EEG on short notice in many neonatal intensive care units, especially on weekends, evenings, or holidays. Given the limited number of channels and electrodes of an aEEG, it is well recognized that seizures distant from the recording electrodes will not be detected. Time compression facilitates inspection and monitoring of background activity, but limits detection of short seizures. The identification of electrographic seizures using aEEG has improved with the inclusion of the raw EEG tracing on most current aEEG devices. Validated computerized seizure detection algorithms will further enhance the utility of aEEG. Quality assurance issues regarding the adequacy of training and expertise of providers within NICUs who interpret aEEG recordings is a difficult issue for seizure detection and characterization of background activity. Interpretation of seizures is probably more challenging, since most clinicians do not have a background in electroencephalography.

Toso et al. also describe an application of aEEG for infants with severe respiratory distress. Infants with non-neurological conditions can be challenging to assess by a conventional neurological examination. Infants with severe respiratory distress can manifest decreased activity, poor tone, and sluggish response to stimuli, all secondary to the severity of the underlying pulmonary condition. Assessment of consciousness level can be performed in very sick infants, but is often obscured by the sedative-hypnotic agents used in conjunction with respiratory support. The aEEG provides an attractive means to assess the integrity of the central nervous system of infants who are critically ill when other conventional monitoring techniques (e.g., full montage EEG) are not available. As aEEG is applied to different cohorts of infants, it will always be important to continue to critically assess the relationship between aEEG data and early childhood outcomes. Since most of these evaluations will typically be performed in the absence of a randomized trial, careful study design will be necessary in order to acquire information in a manner as unbiased as possible.

## Conflict of interest

The author declares no conflicts of interest.

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