Amplitude-Integrated EEG Is Useful in Predicting Neurodevelopmental Outcome in Full-Term Infants With Hypoxic-Ischemic Encephalopathy: A Meta-Analysis

R. Edwin Spitzmiller, DO, Tonya Phillips, MD, Jareen Meinzen-Derr, PhD, and Steven B. Hoath, MD

Hypoxic ischemic encephalopathy is a common cause of neurological complications resulting in chronic handicapping conditions, such as cerebral palsy. Amplitude-integrated electroencephalography (EEG) has been used in many European countries for more than a decade in the evaluation of infants with hypoxic ischemic encephalopathy but has not been widely used in the United States. The objective of this study was to evaluate the evidence supporting use of amplitude-integrated EEG as a quantitative predictor of neurodevelopmental outcome in full-term infants with hypoxic ischemic encephalopathy. To assess efficacy, the authors performed a meta-analysis of the literature evaluating the use of the amplitude-integrated EEG or cerebral function monitor in full-term infants with hypoxic ischemic encephalopathy and their neurodevelopmental outcome. A total of 8 studies were eligible for the primary meta-analysis. There was an overall sensitivity of 91% (95% CI 87-95) and a negative likelihood ratio of 0.09 (95% CI .06-.15) for amplitude-integrated EEG tracings to accurately predict poor outcome. Amplitude-integrated EEG is a valuable bedside tool for predicting long-term neurodevelopmental outcome in term infants with hypoxic ischemic encephalopathy. This information is useful in structuring communication and care plans for physicians and parents. Early assessment techniques such as amplitude-integrated EEG provide objective means for determining inclusion in clinical studies evaluating therapies for hypoxic ischemic encephalopathy and for predicting which patients are most likely to respond to treatment.

Keywords: amplitude-integrated EEG; full-term newborn; hypoxic ischemic encephalopathy; meta-analysis
severely asphyxiated infants, infants with intraparenchymal hemorrhages, and infants with seizures. These infants are monitored for hours to days, depending on their clinical condition. The amplitude-integrated EEG is not widely used in the United States of America at this time. To our knowledge, there is no meta-analysis of the prognostic value of the amplitude-integrated EEG in full-term infants with hypoxic ischemic encephalopathy and their neurodevelopmental outcome. In this article, we review the literature regarding the use of the amplitude-integrated EEG in full-term infants with hypoxic ischemic encephalopathy and test the hypothesis that amplitude-integrated EEG is predictive of neurodevelopmental outcome.

**Methods**

**Search Strategy**

All studies of the amplitude-integrated EEG and its use in the prediction of neurodevelopmental outcome were identified by a literature search of PubMed and Medline. The search was limited to human studies and clinical trials performed between January 1966 and February 2005. Using the search fields of the abstract, MeSH subject heading, exploded subject heading, publication type, subject heading word, text word, and title, the search strategy involved the following keywords: amplitude integrated EEG, cerebral function monitor, hypoxic-ischemic encephalopathy, neurodevelopmental follow up, clinical trial, full term infant, and electroencephalography. Articles were initially identified based on their title and references, and bibliographies from identified studies were also searched.

The outcomes of interest primarily included an abnormal neurological exam as performed by a pediatric neurologist at the time of inclusion, at discharge, and at regular intervals after discharge from the neonatal intensive care unit. At the time of inclusion, hypoxic ischemic encephalopathy was defined according to Sarnat. Cerebral palsy as defined by Hagberg, or documented developmental quotient ≤ 85 on Griffiths Developmental Scale performed at follow-up, was considered abnormal.

The primary investigator (RES) identified all published studies in peer-reviewed journals and abstracts submitted at national conferences reporting amplitude-integrated EEG and hypoxic ischemic encephalopathy and follow-up. The full text of the article was reviewed in detail, and a decision to include the study was made by the primary investigator. A second reviewer (TP) then reviewed the articles in detail. Discrepancies were discussed, and a final decision was made regarding which studies to include.

**Quality Assessment**

The quality of the trials was evaluated for blinding of the individuals interpreting the tracings to the clinical condition of the infant, the rapidity at which the amplitude-integrated EEG was applied after birth, the scales with which neurodevelopment follow-up was assessed, and the consistency of “abnormal development” definitions used by the various authors. A data collection form (Table 1) was used to aid extraction of relevant information on clinical outcomes, timing of the amplitude-integrated EEG, and the number of infants studied.

**Statistical Analysis**

The data from each of the studies were extracted as 2-by-2 tables. From these tables, we conducted our primary analysis, computing sensitivities (true positive rate), specificities (true negative rate), and likelihood ratios, which incorporate both sensitivity and specificity. The likelihood ratio for a positive result states how much the odds of the disease/outcome increase when the test is positive, whereas the likelihood ratio for a negative result states how much the odds of the disease/outcome decrease when the test is negative. All of the tests were reported with 95% confidence intervals. Confidence intervals for sensitivities and specificities were determined based on the confidence interval for proportions, and the confidence interval for the likelihood ratios used methods presented by Simel and colleagues. We used a meta-analysis to pool results for the likelihood ratios utilizing a random effects model. The random-effects model assumes that the population effect size is expected to vary from study to study, with differences caused by experimental error and differences in populations (between-study variability). Because of this additional variability, the 95% confidence interval for the pooled result is wider (less precise) than for a fixed-effect model, giving a more conservative estimate of association. The meta-analysis results include a graphic display of results to aid interpretation of the findings. The Forest plot, a widely used form of presentation that plots point estimates from different studies along with their error bars, has been created for a visual representation of individual study point estimates. Forest plots were produced for the sensitivities, specificities, and the log-likelihood ratios (positive and negative). A test for heterogeneity was performed by using the Cochran Q statistic to evaluate whether the pooled studies represent a homogeneous distribution of effect size. Missing effect sizes pose a particular problem in meta-analysis, because this jeopardizes the generalization of the results. However, all included studies had sufficient information about effect sizes to contribute to the analysis. One trial (van Rooij) used a subject inclusion criterion that differed from the other included studies. Results in this study were published in abstract form and were included after personal communication with the lead author.

The following definitions were used for each tracing: continuous normal voltage is a continuous background activity with voltage of 10 to 25 microvolts; discontinuous normal...
## Table 1. List and Description of Included Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Amplitude-Integrated EEG Timing</th>
<th>Number of Infants</th>
<th>Outcomes Studied</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eken31</td>
<td>Within 6 hours</td>
<td>31</td>
<td>3, 9, 18, 24 months Griffiths Developmental &lt;85 – abnormal</td>
<td>12 – normal voltage 10 mild encephalopathy, 2 moderate encephalopathy, 19 abnormal tracing 15 died, 4 minor handicap</td>
</tr>
<tr>
<td>Toet13</td>
<td>3 and 6 hours old</td>
<td>73</td>
<td>At 3, 9, 18, 24 months, and at 3 and 5 years. Griffith's mental developmental scale. Adverse outcome = death in neonatal period, cerebral palsy, or global delay</td>
<td>68 infants followed up to 12 mos. Predictive value of flat tracing, burst suppression, continuous low voltage, and poor outcome at 3 hours – positive predictive value 78%, negative predictive value 84%, sensitivity 85%, specificity 77%; at 6 hours positive predictive value 86%, negative predictive value 91%, sensitivity 91%, specificity 86%</td>
</tr>
<tr>
<td>ter Horst12</td>
<td>Median age 4 hours 35 minutes</td>
<td>39</td>
<td>At 24 months: 3 groups (1) normal; (2) mildly abnormal – neurologic abnormalities present other than cerebral palsy or infantile spasms; (3) severely abnormal – severe mental/motor delay, infantile spasms, or cerebral palsy</td>
<td>Burst suppression or worse if before 6 hours likelihood ratio+ 2.7 (95% CI 1.4-5.0) for adverse outcome; between 24 and 46 hours likelihood ratio + 19 (95% CI 2.8-128); after 24 hours not significant. Normal pattern likelihood ratio for severe neurodeficits at follow-up &lt; .3 through first 48 hours</td>
</tr>
<tr>
<td>Hellstrom-Westas33</td>
<td>First 6 hours</td>
<td>82</td>
<td>12-18 mos follow-up; 3 groups (1) Healthy (including minor visual and hearing deficits) (2) neurological sequelae (cerebral palsy, psychomotor retardation) (3) death</td>
<td>Normal pattern: sensitivity 89%, specificity 94.7% positive predictive value 96.2%; Abnormal pattern: sensitivity 94.7%, specificity 89.3%, positive predictive value 85.7%</td>
</tr>
<tr>
<td>al Naqeeb35</td>
<td>Median age 18 hours (range, 2 hours-21 days) 14–full term 56–encephalopathic</td>
<td>56</td>
<td>Follow-up at 18 and 24 mos. Normal = no abnormal neurological signs or developmental quotient ≥ 85, abnormal = neuromotor abnormalities and/or GQ &lt; 85</td>
<td>Positive predictive value of normal pattern with good outcome 96.2%; abnormal pattern with poor outcomes 85.7%, prognostic efficacy 91.5%</td>
</tr>
<tr>
<td>Thornberg32</td>
<td>Upon arrival to neonatal intensive care unit; 30 within first 2 hours, 8 in first 1-2 days of life</td>
<td>38</td>
<td>Denver Development at 5, 10, 18 mos. If normal at 18 months no further follow-up. 15 infants followed to 2.5 years – “severe neurological disability”</td>
<td>21- burst suppression or paroxysmal activity – 20 death or severe neurodisability; 1 severe dyskinetic syndrome but normal mental development; 17- Continuous activity; 1 died at 6 mos from SIDS but normal development at that point, the rest normal at 18 mos.</td>
</tr>
<tr>
<td>van Rooij34</td>
<td>Within 6 hours</td>
<td>160</td>
<td>Griffiths mental developmental scale and full neuro exam at postnatal age of at least 12 months</td>
<td>65 infants had initial flat tracing/continuous low-voltage pattern: 6 recovered to continuous normal voltage, and all survived neonatal period, but 1 had severe disability and 5 were normal at follow-up 25 burst suppression as initial pattern: 12 improved to normal; of those 12, 1 died, 5 moderate to severe disability, 2 mild disability, 4 were normal; if no recovery was seen in first 24 hours – death or severe disability</td>
</tr>
<tr>
<td>Shalak30</td>
<td>Within 12 hours</td>
<td>50</td>
<td>No follow-up after discharge; detailed neurological examination while in the neonatal intensive care unit and immediately prior to discharge; infants characterized into modified Sarnat stages</td>
<td>35 infants had normal tracings, and 3 of these developed persistent encephalopathy; 4 with moderately abnormal tracings, and 3 of these developed persistent encephalopathy; 11 with severely suppressed tracings, and 8 of these developed persistent encephalopathy.</td>
</tr>
</tbody>
</table>

**NOTE:** EEG = electroencephalography.
voltage is a discontinuous trace with voltage predominately >5 microvolts; burst suppression is discontinuous trace with periods of low cortical activity (<5 microvolts) with bursts of higher amplitude; continuous low voltage is continuous background pattern of very low voltage, around or less than 5 microvolts; flat tracing is a mainly isoelectric tracing of <5 microvolts; and epileptiform activity is single or repetitive events with sustained cortical activity.12,13

Results

A total of 24 studies were identified using the above search strategy. Figure 1 briefly summarizes the reasons studies were excluded. Nine studies were excluded because they used conventional EEG.14-22 One study was excluded because it utilized amplitude-integrated EEG in evaluating the outcome of infants with intraventricular hemorrhage.23 Three studies were excluded because the infants were premature24-26; one was excluded because it evaluated amplitude-integrated EEG for seizure detection,27 and in 2 studies,28-30 long-term outcome data were difficult to interpret. A total of 8 studies were used in the final meta-analysis.12,13,30-35

The pooled results of the meta-analysis, indicating the accuracy of severe amplitude-integrated EEG tracings to predict moderate/severe disability or death, are summarized in Table 2 and Figures 2-5. The sensitivities of severe amplitude-integrated EEG tracings to predict a poor outcome (as defined by this study) ranged from 73% to 100%; the specificities ranged from 73% to 100% as well. The chi-square test for negative likelihood ratios shows no significant heterogeneity among the studies (P = .19). Overall, severe amplitude-integrated EEG tracings appeared to be accurate in predicting a poor outcome, with a 91% (87-95 95% CI) pooled sensitivity and a 0.09 (.06-.15 95% CI) pooled negative likelihood ratio.

Eken et al31 enrolled 31 infants with a gestational age between 37 and 42 weeks and treated for hypoxic ischemic encephalopathy as defined by Sarnat.7 The infants were diagnosed with hypoxic ischemic encephalopathy when they met clinical criteria in the first 24 hours and met at least 3 of the following: (1) signs of intrauterine asphyxia, (2) arterial cord blood pH <7.10, (3) delayed onset of spontaneous respirations, (4) Apgar score <5 at 5 minutes, and (5) multiorgan failure. The amplitude-integrated EEG was graded as normal if background activity was continuous and of normal voltage and without seizure activity; abnormal if background activity showed burst suppression, continuous extremely low voltage defined as activity below 5 µV, flat, or when seizure patterns were present. Neurodevelopmental assessments were done at 6 to 24 months of age. Twelve of the 31 had continuous background activity, and all survived with a good outcome except 1 infant who required extra corporeal membrane oxygenation. Nineteen of the 31 had an abnormal amplitude-integrated EEG tracing. Three of the infants had continuous but extremely low voltage; all 3 died. Eleven infants had a burst suppression pattern; 7 of the 11 died. Of the surviving 4 infants, 1 had a minor handicap and 3 were normal at follow-up. Five of the 19 had an isoelectric pattern, and all died.

Toet et al13 enrolled 73 infants admitted to the neonatal intensive care unit within 3 hours after birth and treated for perinatal asphyxia if they met at least 3 of the following criteria: (1) signs of intrauterine asphyxia, (2) arterial pH<7.10, (3) Apgar score <5 at 5 minutes, or (4) multiorgan failure. Sixty-eight were followed at least to 12 months of age. The amplitude-integrated EEG was applied at 3 and 6 hours of life. At 3 hours, 36 infants had an abnormal tracing (flat tracing, continuous low voltage,
burst suppression) and 24 had abnormal outcomes including death, major handicap, or global delay. At 6 hours, 35 infants had abnormal tracings, and 31 of these had abnormal outcomes. There were 32 normal tracings at 3 hours, and 27 of these infants had normal outcome. At 6 hours, there were 33 normal tracings, and 30 of those infants had normal outcome.

Ter Horst et al\textsuperscript{12} retrospectively identified 39 full-term infants who were treated for severe perinatal asphyxia as defined by the presence of at least 2 of the following: (1) signs of fetal distress, (2) umbilical pH or first capillary pH <7.00, (3) delayed spontaneous respiration requiring artificial ventilation at 5 minutes of life, and (4) signs of multi-organ failure. Nine infants were excluded secondary to improper data collection or death. In the remaining 30 infants, amplitude-integrated EEG was recorded in the first 72 hours of life. These infants were followed until 2 years of age. Seven infants had a normal tracing throughout the 72 hours; 6 were normal, and 1 had mild deficits at follow-up. Two infants transitioned from a normal tracing to burst suppression/epileptiform activity then back to a normal tracing. These infants had mild deficits. Five infants transitioned from an abnormal tracing to normal before 12 hours of age; 4 were normal, and 1 had mild deficits. One infant transitioned before 36 hours and had mild deficits. Eight infants had a persistently abnormal tracing, and all 8 either died or had severe deficits. There was no differentiation between death and abnormal outcome in these infants.

Hellstrom-Westas et al\textsuperscript{33} enrolled 47 infants, and all amplitude-integrated EEGs were recorded in the first 6 hours of life. The infants enrolled had at least 1 sign of intrapartum distress, and they all needed resuscitation with positive pressure ventilation. Thirty-three of the infants required mechanical ventilatory support. Twenty-four of the 33 had signs of hypoxic ischemic encephalopathy. The presence of hypoxic ischemic encephalopathy was not possible to evaluate in 9 infants because of sedation. Outcome was assessed at 12 to 18 months. Twenty-six infants had continuous background activity of normal voltage, and 25 of these had normal outcome; 1 required special training for delayed psychomotor development at age 4 years. Twenty-one infants had an abnormal amplitude-integrated EEG; 9 died, 9 survived with handicap, and 3 were normal.

al Naqeeb et al\textsuperscript{35} enrolled 14 healthy full-term infants who served as controls and 56 with encephalopathy. Encephalopathy was diagnosed if there was rapid appearance of abnormal neurological signs. Neurologic assessment was performed at 18 and 24 months of age. Twenty-four infants were studied within 12 hours of birth, 9 with normal amplitude and all were normal; 4 with moderately abnormal amplitude and 1 with normal outcome; 1 abnormal outcome and 2 died. Four had suppressed amplitude; 1 with abnormal outcome, and 3 deaths. One infant had normal amplitude with seizures, and that infant had a

<table>
<thead>
<tr>
<th></th>
<th>True Positive</th>
<th>False Positive</th>
<th>False Negative</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Likelihood Ratio + (95% CI)</th>
<th>Likelihood Ratio – (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thornberg\textsuperscript{32}</td>
<td>21</td>
<td>0</td>
<td>17</td>
<td>100 (92-100)</td>
<td>100 (89-100)</td>
<td>36.2 (2.3-557)</td>
<td>.023 (.001-.35)</td>
</tr>
<tr>
<td>Hellstrom-Westas\textsuperscript{33}</td>
<td>18</td>
<td>3</td>
<td>25</td>
<td>95 (85-100)</td>
<td>89 (77-100)</td>
<td>8.8 (3.0-25.9)</td>
<td>.06 (.09-.40)</td>
</tr>
<tr>
<td>Eken\textsuperscript{31}</td>
<td>16</td>
<td>3</td>
<td>11</td>
<td>94 (83-100)</td>
<td>79 (58-100)</td>
<td>4.4 (1.6-12.1)</td>
<td>.075 (.01-.51)</td>
</tr>
<tr>
<td>Toet\textsuperscript{13}</td>
<td>28</td>
<td>8</td>
<td>22</td>
<td>88 (77-99)</td>
<td>73 (57-89)</td>
<td>3.3 (1.8-6.0)</td>
<td>.17 (.07-.44)</td>
</tr>
<tr>
<td>al Naqeeb\textsuperscript{35}</td>
<td>6</td>
<td>0</td>
<td>19</td>
<td>75 (45-100)</td>
<td>100 (92-100)</td>
<td>30.8 (1.9-489)</td>
<td>.26 (.08-85)</td>
</tr>
<tr>
<td>al Naqeeb\textsuperscript{35}</td>
<td>8</td>
<td>3</td>
<td>34</td>
<td>89 (69-100)</td>
<td>92 (83-100)</td>
<td>11 (3.6-53.2)</td>
<td>.12 (.019-.77)</td>
</tr>
<tr>
<td>Summary</td>
<td>187</td>
<td>28</td>
<td>201</td>
<td>91 (87-95)</td>
<td>88 (84-92)</td>
<td>10.1 (5.5-18)</td>
<td>.09 (.06-.15)</td>
</tr>
</tbody>
</table>
normal outcome. Eight infants had moderately abnormal amplitude with seizures; 2 had normal outcome, 3 had abnormal outcome, and 3 died; 6 infants had suppressed amplitude with seizures, 3 had abnormal outcome and 3 died.

Thornberg et al\(^3\) enrolled 38 infants with a clinical diagnosis of perinatal asphyxia. The infants included in the study were all transferred into the neonatal intensive care unit. All infants were \(> 36\) weeks gestational age and required resuscitation at delivery with a mean time to spontaneous respiration of 18 minutes. Each infant fulfilled at least 2 of the following criteria for asphyxia: (1) abnormal fetal cardiotocography, (2) meconium-stained amniotic fluid, (3) Apgar score \(\leq 6\) at 5 minutes, (4) pH 7.2 and/or bicarbonate concentration less than 15mEq/L. A follow-up neurologic exam was performed at 5, 10, and 18 months of age by a pediatric neurologist according to standardized programs including the Denver Developmental Screening Test. Children who were considered normal at 18 months of age did not usually have further follow-up. Seventeen infants had continuous activity during the first and/or second day of life, and all had a normal neurological exam at follow-up; 21 infants had burst suppression or paroxysmal activity, and all either died or developed severe disability.

van Rooij et al\(^3\) retrospectively reported 160 infants with the most severely abnormal tracings and evaluated their time course of recovery in relation to neurophysiologic and neuroimaging findings and neurodevelopmental outcome. A total of 160 infants with hypoxic ischemic encephalopathy were evaluated, 70 with continuous normal voltage/discontinuous normal voltage pattern and 90 with flat tracing/continuous low voltage/burst suppression within first 6 hours of birth. All of the survivors were seen in an outpatient clinic and were assessed using the Griffith's mental developmental scale at postnatal ages of at least 24 months. Neuromotor assessment was performed by a pediatric physiotherapist who was blinded to the amplitude-integrated EEG. Of the 70 infants with either continuous normal voltage or discontinuous normal voltage, 64 were normal at follow-up and 6 had moderate to severe handicap. Of the 90 with either a flat tracing, continuous background of very low voltage, or burst suppression pattern, 11 were normal and 79 either died or had moderate to severe handicap at follow-up.

Shalak et al\(^3\) enrolled 50 infants who met all the criteria for hypoxic ischemic encephalopathy. Specifically, delivery at \(\geq 36\) weeks gestation, admission to the neonatal intensive care unit, intrapartum distress defined as fetal heart rate abnormalities or meconium staining of the amniotic fluid, and either an Apgar score of \(\leq 5\) at 5 minutes or severe fetal acidemia defined as either an umbilical cord pH...
≤7.00 or base deficit ≥16 milliequivalents per liter. The amplitude-integrated EEG was applied within the first 12 hours of birth. A normal tracing was identified in 35 infants, and 3 of these developed persistent encephalopathy in the neonatal period. Four had a moderately abnormal amplitude-integrated EEG tracing, and 3 of these had persistent encephalopathy. Eleven infants had a severely suppressed amplitude-integrated EEG, and 8 of these developed persistent encephalopathy in the neonatal period.

Discussion

To our knowledge, this is the first meta-analysis of amplitude-integrated EEG as a predictor of neurodevelopmental outcome. This analysis clearly shows amplitude-integrated EEG to be an excellent screening tool in this population of asphyxiated full-term infants. Conventional electroencephalography has been used in the evaluation of infants with hypoxic ischemic encephalopathy for many years. Although not the primary goal of this meta-analysis, we also reviewed studies that analyzed the usefulness of conventional EEG in the outcome of infants with hypoxic ischemic encephalopathy. We found 6 studies that analyzed the predictive value of conventional EEG in regard to neurodevelopmental outcome in full-term infants with hypoxic ischemic encephalopathy.\(^\text{15,16,17,18}\)

Three studies\(^\text{15,17,18}\) analyzed either continuous or serial conventional EEG recordings. All 3 studies concluded that early conventional EEG is predictive of neurological outcome. In addition, and perhaps more important, all 3 concluded that infants who progressed to a normal tracing by 8 to 12 hours of age had better outcomes than those infants whose tracings were abnormal throughout or worsened during the monitoring period.

Three studies\(^\text{19-21}\) analyzed 1 conventional EEG either during the first 48 hours of life\(^\text{20,21}\) or during the first week of life.\(^\text{19}\) The Sinclair study was a retrospective study that analyzed infants born at ≥37 gestational weeks who had Sarnat stage I-III hypoxic ischemic encephalopathy and at least 1 conventional EEG that demonstrated burst suppression pattern or modified burst suppression. The long-term outcome was then correlated with the conventional EEG pattern, and those infants with modified burst suppression had a better outcome than those with burst suppression. These authors\(^\text{19,21}\) also concluded that conventional EEG has excellent prognostic ability in infants with hypoxic ischemic encephalopathy. As evidenced from these studies, the conventional EEG is useful in predicting the neurodevelopmental outcome in this select group of infants.

The conventional EEG, however, is cumbersome and requires expert interpretation and many years of training. Conversely, the amplitude-integrated EEG can be attached to an intravenous (IV) pole at the bedside and does not interfere with day-to-day care. Its utility and practicality have been previously described in numerous articles.\(^\text{13,27,33,35}\)

Briefly, it records a single-channel EEG from biparietal electrodes and the signal is then filtered, rectified, smoothed, and amplitude integrated. Its interpretation is based primarily on pattern recognition.

Because the amplitude-integrated EEG is less cumbersome and is easier to interpret, it is important to determine adequate correlation between amplitude-integrated EEG and conventional EEG, as the latter is considered the gold standard. Our search yielded one study\(^\text{26}\) that compared the two. The authors of this study evaluated 36 neonates with gestational age ≥ 36 weeks. The amplitude-integrated EEG and conventional EEG were recorded simultaneously and analyzed off-line and classified by 2 investigators who were blinded to the clinical condition and the neurodevelopmental outcome of each infant. They found full agreement between amplitude-integrated EEG and conventional EEG ictal activity. A normal amplitude-integrated EEG corresponded with a normal or depressed conventional EEG in 90% of cases. The positive predictive value for severely abnormal amplitude-integrated EEG to correspond with severely abnormal conventional EEG was 100%. Their conclusion was that amplitude-integrated EEG was a reliable tool for monitoring background patterns and ictal activity.

In centers using amplitude-integrated EEG regularly, it is interpreted primarily by clinicians who have no training in conventional EEG analysis and have received minimal training in amplitude-integrated EEG tracing analysis.\(^\text{27}\) Interobserver variability of the amplitude-integrated EEG was studied by al Naqeeb and colleagues. The tracings in this study were analyzed by 2 pediatric residents who had no formal training or research interests in amplitude-integrated EEG and were given brief training in its interpretation. The residents and an amplitude-integrated EEG expert evaluated the study tracings. The authors found excellent agreement between each resident and the expert with respect to background and seizure activity.\(^\text{35}\) This would indicate that a nonexpert can be taught to analyze the amplitude-integrated EEG tracing confidently, although focal low amplitude and very short periods of seizure discharges may be missed.

The results shown in Figures 2-5 and Table 2 indicate that the amplitude-integrated EEG is a useful bedside tool in predicting the neurodevelopmental outcome of full-term infants with hypoxic ischemic encephalopathy. There are novel therapies for the treatment and prevention of sequelae of hypoxic ischemic encephalopathy.\(^\text{1,5,37,38}\) Whole-body hypothermia has been used in experimental conditions to provide neuroprotection. It has recently been shown that it is safe to use whole-body hypothermia under stringent conditions in full-term infants with hypoxic ischemic encephalopathy.\(^\text{39}\)

In a recent publication, Gluckman et al\(^\text{40}\) reported that selective head cooling with mild systemic hypothermia demonstrated benefit in a population of infants with moderately abnormal amplitude-integrated EEG. Their
inclusion criteria included Apgar scores, continued need for resuscitation, severe acidosis, Sarnat staging, and the severity of amplitude-integrated EEG. Infants were randomly assigned to either cooling (n = 116) or control (n = 118). The authors performed logistic regression analysis controlling for baseline amplitude-integrated EEG amplitude (172 intermediate amplitude-integrated EEG and 46 worst amplitude-integrated EEG group), which revealed that the background amplitude-integrated EEG amplitude and the presence of seizures at the time of enrollment were independently associated with unfavorable outcome. No effect of cooling was found in the infants with the most severe baseline amplitude-integrated EEG (odds ratio 1.8, 95% CI 0.26-0.87, P = 0.021); however, a protective effect was seen in the 172 infants with intermediate amplitude-integrated EEG. The outcome was more favorable in the cooled group than in the control group (odds ratio 0.47%; 95% CI 0.26-0.87; P = 0.021).40

Infants affected by hypoxic ischemic encephalopathy can have devastating outcomes. Amplitude-integrated EEG can be used early in infants at risk for hypoxic ischemic encephalopathy based on history and physical exam. The optimal timing is unclear, although earlier and prolonged monitoring as well as repeated monitorings appear to improve determination of outcome. Five of the studies2,13,31,33,34 applied amplitude-integrated EEG within 6 hours of delivery. Normalization of the tracing earlier portends a better outcome than persistently severe tracings. Early use of the amplitude-integrated EEG will identify the infants at highest risk for poor outcomes, allowing these infants to receive prompt intervention, such as whole-body hypothermia or selective head cooling.

Shalak and her colleagues evaluated the role of coupling the amplitude-integrated EEG and early neurological examination. The neurologic exam was performed within the first 12 hours of birth, and the amplitude-integrated EEG was acquired simultaneously or within 1 hour of the exam. They report a sensitivity of 78%, specificity of 94%, positive predictive value of 85%, and negative predictive value of 92% for abnormal outcome, when there is an abnormal neurologic exam and an abnormal amplitude-integrated EEG. They conclude that the combination of the 2 had the highest predictive capacity with a specificity of 94%, a positive predictive value of 85%, and a positive likelihood ratio of 13, and a significant decrease in the number of false-positive identifications.30 There was no follow-up after discharge from the neonatal intensive care unit of these infants, but the authors state the presence of moderate or severe encephalopathy at the time of discharge is a strong predictor of poor neurodevelopmental outcome based on a number of large studies41-44 previously published. Amplitude-integrated EEG is a sensitive and specific modality for determining neurodevelopmental outcome, but the physical exam and possibly additional neurophysiological testing may assist the clinician to determine the severity of a hypoxic-ischemic cerebral insult.

The study by van Rooij et al44 analyzed neuroimaging findings and neurophysiological testing in full-term asphyxiated newborns with severely abnormal amplitude-integrated EEG tracings (flat tracing, continuous low voltage, burst suppression). The study sought to relate the imaging and the neurophysiologic testing with the neurodevelopmental outcome. Only the abstract including amplitude-integrated EEG data was available at the time of this writing, although the data regarding imaging and neurophysiological testing have been submitted for publication (personal communication with LS deVries). This large study may lend further credence to the benefit of amplitude-integrated EEG recording in asphyxiated term newborns.

Conclusion

Based on the empirical results of our meta-analyses (Figures 2-5, Table 2), we conclude that amplitude-integrated electroencephalogram should be part of the initial evaluation in full-term infants with suspected hypoxic-ischemic encephalopathy. The meta-analysis clearly shows that amplitude-integrated EEG is useful in predicting long-term neurodevelopmental outcome in the population of high-risk term infants. Amplitude-integrated EEG can be used at the bedside without interruption of daily care and can be interpreted without extensive formal training. It also is useful in determining which infants should be included in established neuroprotective protocols. These results apply, thus far, only to full-term infants. More studies are needed to determine the amplitude-integrated EEG patterns in premature infants. Although amplitude-integrated EEG technology allows us to predict which infants will have poor neurological outcomes postnatally and thus to provide early, appropriate neuroprotective measures, we are still handicapped by our limited ability to detect and prevent brain asphyxia prenatally. Further research on the prenatal continuum and prevention of hypoxic ischemic encephalopathy is desperately needed. Further research using amplitude-integrated EEG should use standard definitions of mild, moderate, or severe abnormalities when reporting to facilitate clarification in the literature.

References


