Effect of Hypothermia on Amplitude-Integrated Electroencephalogram in Infants With Asphyxia

Marianne Thoresen, Lena Hellström-Westas, Xun Liu and Linda S. de Vries

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WHAT’S KNOWN ON THIS SUBJECT: aEEG recorded within 6 hours after birth correctly predicts outcome after perinatal asphyxia in term infants. Early normalization of aEEG and early onset of SWC predicts good outcome. Corresponding information is unknown while undergoing therapeutic hypothermia.

WHAT THIS STUDY ADDS: Hypothermia changes the predictive value of early aEEG. Normalization of an infant’s aEEG while being cooled occurs later. Time to normal aEEG is a better predictor than time to SWC. Never achieving SWC always predicts poor outcome.

abstract

OBJECTIVES: Amplitude-integrated electroencephalogram (aEEG) at <6 hours is the best single outcome predictor in term infants with perinatal asphyxia at normothermia. Hypothermia has been used to treat those infants and proved to improve their outcome. The objectives of this study were to compare the predictive value of aEEG at <6 hours on outcomes in normothermia- and hypothermia-treated infants and to investigate the best outcome predictor (time to normal trace or sleep–wake cycling [SWC]) in normothermia- and hypothermia-treated infants.

METHODS: Seventy-four infants were recruited by using the CoolCap entry criteria, and their outcomes were assessed by using the Bayley Scales of Infant Development II at 18 months. The aEEG was recorded for 72 hours. Patterns and voltages of aEEG backgrounds were assessed.

RESULTS: The positive predictive value of an abnormal aEEG pattern at the age of 3 to 6 hours was 84% for normothermia and 59% for hypothermia. Moderate abnormal voltage background at 3 to 6 hours of age did not predict outcome. The recovery time to normal background pattern was the best predictor of poor outcome (96.2% in hypothermia, 90.9% in normothermia). Never developing SWC always predicted poor outcome. Time to SWC was a better outcome predictor for infants who were treated with hypothermia (88.5%) than with normothermia (63.6%).

CONCLUSIONS: Early aEEG patterns can be used to predict outcome for infants treated with normothermia but not hypothermia. Infants with good outcome had normalized background pattern by 24 hours when treated with normothermia and by 48 hours when treated with hypothermia. Pediatrics 2010;126:e131–e139
A variety of clinical, neuroimaging, physiologic, and biochemical measurements and combinations of such have been used to predict long-term outcome for infants with neonatal encephalopathy with different predictive values. The Sarnat clinical scoring system is widely used; however, it has been validated only from 24 hours onward after birth. Combination of early markers, including Apgar score, intubation in the delivery room, and umbilical cord/initial base deficit ≥20 mmol/L have been shown to correlate with adverse outcomes; however, the best single predictor of later neurologic outcome in term infants with perinatal asphyxia is amplitude-integrated electroencephalogram (aEEG) recorded before 6 hours of age. Continuous recording of aEEG has also been shown to be useful beyond the first 6 hours, especially time of normal background activity recovery and onset of sleep–wake cycling (SWC). Development of SWC before 36 hours of age in infants who were nursed at normal temperature was associated with good neurodevelopmental outcome. Al Naqeeb et al developed a scoring system that was based on assessment of the lower and upper voltage margins of aEEG background. This method was used for selecting into the CoolCap and Whole Body Hypothermia for the Treatment of Perinatal Asphyxial Encephalopathy (TOBY) trials infants with encephalopathy. In a meta-analysis, an overall specificity of 88% and a sensitivity of 91% were demonstrated for early aEEG recordings. The predictive values of the 2 methods for assessing aEEG background pattern were previously found to be comparable in a small study of infants with asphyxia; however, neither the voltage nor the pattern recognition method has been validated for prediction of outcome in a data set in which all infants were studied at <6 hours and fulfilled the same severity criteria for moderate or severe encephalopathy.

We asked whether 72 hours of hypothermia would alter the predictive value of early aEEG background patterns. Hypothermia has been shown to affect a series of physiologic processes as well as the neurologic assessment; however, the prediction of MRI performed at ~8 days is equally good in both normothermia- and hypothermia-treated infants. A recently published study of a small cohort of cooled infants indicated that delayed recovery of aEEG background is associated with normal outcome at 12 months. During hypothermia, an inactive EEG background pattern at 48 hours was shown to be related to poor outcome, whereas other patterns were associated with more variable outcomes. The aims of this study were to (1) investigate whether the predictive value of the early aEEG background activity (<6 hours) in neurodevelopmental outcome is altered by hypothermia; (2) investigate whether mild hypothermia affects the time to regain normal aEEG background and time of onset of SWC; and (3) compare the early aEEG predictability of outcome at 18 months by using pattern recognition and voltage methods.

METHODS

Since 1998, all infants who had neonatal encephalopathy and were admitted to level III NICUs in Bristol, United Kingdom, were assessed by using the entry criteria first developed for the CoolCap trial: clinical evidence of perinatal asphyxia (Apgar score <5 at 10 minutes, prolonged resuscitation, acidosis [pH <7.0], and base deficits >16) plus moderate or severe encephalopathy plus moderately or severely abnormal aEEG or seizures. Infants who met the entry criteria before 6 hours of age with parental consents were enrolled into ongoing randomized, controlled trials or approved feasibility or registry studies.

Ethical permission was granted to analyze anonymized clinical data from this cohort (REC 09/HO 106/3). From 1998 to 2008, 74 infants were eligible; 31 infants were kept at normothermia (37°C rectal temperature), and 43 infants were treated with hypothermia at either 33.5°C by using whole-body cooling (n = 23) or 34.5°C by using selective head cooling (n = 20).

Neurodevelopmental Outcome

Poor neurodevelopmental outcome at 18 months was classified as first published in the CoolCap trial (death or 1 of Mental Developmental Index <70 [Bayley Scales of Infant Development III], gross motor functional classification level 3–5, or no useful vision). Good outcome was defined as the absence of these criteria with Mental Developmental Index and Psychomotor Developmental Index scores of ≥70. The Bayley Scales of Infant Development II examination was performed by a pediatric psychologist or a trained pediatric physiotherapist, both of whom were blinded to treatment allocation.

aEEG Recording

A single-channel aEEG (electrode placement P3–P4) was recorded continuously from soon after birth until after the treatment period by using needle electrodes. For infants who received selective head cooling, the needles were secured under the CoolCap for 72 hours without complications. The median time of start cooling was 5 hours. Precooling aEEG traces (3–6 hours) were selected for early evaluation and comparison between normothermia and hypothermia groups. The aEEG background pattern was classified (in increasing severity) as described previously: continuous normal voltage (CNV), discontinuous
normal voltage (DNV), burst suppression (BS), low voltage (LV), and flat trace (FT; Fig 1). Traces with CNV or DNV backgrounds were classified as “normal.” BS, LV, and FT traces were classified as “abnormal.”

“Silent” periods of >10 seconds are seen with DNV, whereas CNV has no silent periods of low amplitude. We defined BS as virtually absent activity (<2 μV) between bursts of high voltage (>25 μV). Of note, the lower border of aEEG may be raised by continuous artifacts such as electrocardiogram. Conventional paper aEEG traces printed at 6 cm/h has limited time resolution. The aEEG recordings were also assessed according to al Naqeeb et al6 on the basis of upper and lower voltages of the background. Two voltage classifications—normal (lower margin >5 μV and upper margin >10 μV) and abnormal (moderately or severely abnormal, lower margin <5 μV and upper margin >10 μV or <10 μV; Fig 1)—were used while the predictability of outcome was estimated.8 Abnormal voltage was used as an entry criterion in the CoolCap and TOBY trials.8,10 Discontinuous periods with intermittent low amplitude on the EEG may lower the aEEG margin (<5 μV); consequently, a DNV pattern may be classified as moderately abnormal by using the voltage method.8 SWC was classified as being absent, imminent, or developed.6 Imminent SWC displayed less clear cycling changes in the lower margin between sleep stages than the fully developed mature pattern.7 Of all infants with SWC, 6 of 13 presented with an imminent SWC pattern in the normothermia group and 16 of 28 in the hypothermia group. There was no difference in outcome prediction between imminent and mature SWC. Both imminent and developed patterns were categorized as SWC in this study.

Between 1998 and 2000, 27 infants’ aEEGs were recorded on paper (6 cm/h [Lectromed, Letchworth, United Kingdom]). From 2000 to 2008, 47 infants’ aEEGs were recorded by using a combined single-channel aEEG/EEG digital device (Olympic Medical CFM 6000, Na tus Inc, Seattle, WA).

The aEEG recordings were analyzed by 2 experienced investigators who were blinded to treatment allocation and clinical information (Drs Hellström-Westas and de Vries). Four traces of aEEG pattern interpretation (3—6 hours) were not agreed on and were reassessed by all investigators for consensus. The following time epochs were chosen: every hour from start of recording until 6 hours after birth, followed by 6-hour epochs until start of rewarming (on average at 76 hours of age). All 74 infants had recordings between 3 and 6 hours, and 44 infants also had recordings during the first 3 hours of life.
hours. The median (range) recording time for infants in the normothermia and hypothermia groups was 72 hours (6–132 hours) and 92 hours (6–166 hours), respectively. Some infants had short or interrupted recordings because of death or technical problems (normothermia: 11; hypothermia: 8). We noted the age of infants whose background pattern changed from abnormal to normal and developed SWC. The predictive value by using 3- to 6-hour traces was compared between pattern recognition and voltage methods.

Statistical Analysis
Tables of $\chi^2$ were analyzed with the “$N - 1$” $\chi^2$ test. Differences in median values between groups were analyzed by using a Wilcoxon 2-sample test. Two-sided $P$ values are given. The relative importance of time to regain a normal trace and time to onset of SWC was analyzed by using logistic regression on the observed or rank-ordered data. Because the duration of recording varied between individuals, Kaplan-Meier survival plots were also used; however, this did not change the results (data not shown). The 0- to 3-hour aEEG traces were available for 44 of 74 infants, and 3- to 6-hour traces were available for all infants. The aEEG traces changed from abnormal to normal in 4 infants; in 3 infants, the aEEG trace deteriorated from normal to abnormal. Using either the 0- to 3-hour or 3- to 6-hour traces for these 7 infants did not significantly affect the results. Traces of 3 to 6 hours were used in all calculations.

Descriptive data are presented as mean ± SD or median (interquartile range, range) as appropriate. SPSS 16 (SPSS, Chicago, IL) was used.

RESULTS

Demographic and Clinical Variables
Table 1 shows similar severities of perinatal asphyxia in normothermia and hypothermia groups. Seizures and the use of anticonvulsant treatment were similar for normothermia and hypothermia groups. Mortality did not differ between normothermia (32%) and hypothermia (23%). Forty percent of cooled infants had poor outcome at 18 months as compared with 65% of infants in the normothermia group ($P = .04$). With the limitations of small numbers, the results are not affected by the mode of cooling or gender.

Predicting Outcome From Early (3–6 Hours) aEEG
Figure 2 shows positive predictive values (PPVs) of an abnormal trace (BS, LV, and FT) to predict poor outcome (death and disability) from 3 to 72 hours in normothermia and hypothermia-treated or normothermia-treated infants at age epochs as indicated on the x-axis.

| TABLE 1 | Demographic and Clinical Variables for the 2 Groups of Infants |
|-----------------|------------------|------------------|------------------|
| **Demographic and Clinical Variables** | **Normothermia** ($n = 31$) | **Hypothermia** ($n = 43$) | **$P$ ("$N − 1$" $\chi^2$ Test)** |
| Birth weight, mean ± SD, kg | $3.29 ± 0.62$ | $3.38 ± 0.80$ | NS |
| Gestational age, median (IQR), wk | 40 (2) | 40 (2) | NS |
| Female gender, % | 65 | 47 | .13 |
| Apgar score at 10 min, median (IQR) | 4 (2.75) | 5 (3.75) | NS |
| Worst pH in the first hour of life, mean ± SD | $6.90 ± 0.22$ | $6.95 ± 0.16$ | NS |
| Assisted ventilation at 10 min of age, % | 89 | 92 | NS |
| CNV or DNV pattern at 3–6 h, % ($n$) | 39 (12) | 37 (16) | NS |
| BS, LV, or FT pattern at 3–6 h, % ($n$) | 61 (19) | 63 (27) | NS |
| Normal voltage trace (>5 and >10 μV), % ($n$) | 13 (4) | 21 (9) | NS |
| Moderately abnormal voltage trace (<5 and >10 μV), % ($n$) | 64 (20) | 53 (23) | NS |
| Severely abnormal voltage trace (<5 and >10 μV), % ($n$) | 23 (7) | 26 (11) | NS |
| Seizures at any time, % ($n$) | 90 (28) | 86 (37) | NS |
| Receiving anticonvulsant drugs (up to 3 different), % ($n$) | 87 (27) | 70 (30) | NS |
| No. of different drugs, mean | 1.74 | 1.80 | NS |
| Mortality, % ($n$) | 32 (10) | 23 (10) | NS |
| Poor outcome (death or severe disability), % ($n$) | 65 (20) | 40 (17) | .04 |

NS indicates not significant; IQR, interquartile range.
At 3 to 6 hours, PPV was 84% in normothermia-treated infants and 59% in hypothermia-treated infants ($P = .05$, normothermia versus hypothermia). At 36 hours, the odd ratio (OR) for an abnormal trace to predict poor outcome was 10.70 (95% confidence interval [CI]: 1.90–59.60; $P = .007$) in normothermia-treated infants and 1.70 (95% CI: 0.56–3.78; $P = .183$) in hypothermia-treated infants. An abnormal aEEG background pattern reliably predicted poor outcome from 24 hours onward. At 3 to 6 hours, a normal trace predicted good outcome in 8 of 12 (PPV = 67%) normothermia-treated infants and in 15 of 15 (PPV = 100%) hypothermia-treated infants ($P = .014$).

**Recovery of aEEG Background Activity**

Figure 3 shows the outcome, treatment, and time to normal trace (TTNT) of the aEEG for each infant. In binary logistic regression, TTNT is the best single predictor of poor outcome in both groups. In the hypothermia group, the OR for poor outcome increased by 1.38 (95% CI: 1.12–1.68; $P = .002$) for every 1-hour delay (PPV HT-TTNT = 96.2% and negative predictive value [NPV] = 88.2%). In the normothermia group, the OR for poor outcome increased by 1.120 (95% CI: 1.016–1.234; $P = .023$) for every 1-hour delay (PPV NT-TTNT = 90.9%, NPV = 90%). All TTNT for infants with good outcomes was within 24 hours in the normothermia group and within 48 hours in the hypothermia group. All infants who never regained normal traces had poor outcomes. Among them, 72% died.

**Development of SWC**

The outcome for individual infants is shown in Fig 4. Thirteen (42%) normothermia-treated and 28 (65%) hypothermia-treated infants developed SWC. The median time of onset of SWC was 24 hours in normothermia-treated and 36 hours in hypothermia-treated infants with good outcome, respectively (no significant difference). Significantly more normothermia-treated (18 of 31) than hypothermia-
treated (15 of 43) infants never developed SWC ($P = 0.05$). Never developing SWC strongly predicted death and disability: 29 of 33 infants who did not develop SWC had a poor outcome (19 died, 10 impaired), and only 4 had a good outcome ($n = 2$ normothermia, $n = 2$ hypothermia). ORs for poor outcome increased by 1.09 (95% CI: 1.04–1.15; $P = 0.01$) for every 1-hour delay in achieving SWC in normothermia-treated infants (PPV = 63.6%, NPV = 90.0%) and by 1.05 (95% CI: 1.02–1.08; $P = 0.002$) in hypothermia-treated infants (PPV = 88.5%, NPV = 82.4%).

Figure 5 combines the TTNT and the time to onset of SWC. Infants who never achieved a normal trace or SWC are plotted in the shaded bars. The figure shows that the TTNT was a better marker to predict good outcome than the time to onset of SWC, particularly in hypothermia-treated infants. Four infants ($n = 2$ normothermia, $n = 2$ hypothermia) with good outcome despite never developing SWC all regained normal background activity early (2–18 hours). Although TTNT is a strong predictor itself, adding SWC information improves prediction value (more in the normothermia group [PPV = 90.9%, NPV = 90.1%] than in the hypothermia group [PPV = 96.2%, NPV = 94.1%]). The TTNT and time to develop SWC correlated strongly (Kendall’s $\tau = 0.57$, $P = 0.01$ for normothermia; Kendall’s $\tau = 0.53$, $P = 0.01$ for hypothermia).

**Comparison Between Pattern Recognition and Voltage Methods**

Figure 6 shows the 5 patterns plotted against the 3 voltage ranges in a 5 × 3 table. Thirteen infants had normal voltage traces at 3 to 6 hours, and 11 of 13 had good outcome. Both methods had the same good prediction (PPV = 85%). Moderately abnormal voltage characterized 58% of the patients and included mainly 2 patterns: DNV, which predicts good outcome, and BS, which predicts poor outcome. In the moderately abnormal voltage group, DNV correctly predicted good outcome in hypothermia-treated infants (PPV = 100%) and in most normothermia-treated infants (PPV = 71%). The value of PPV in the normothermia or the hypothermia group was the same for infants who were classified as having BS in the moderately abnormal voltage group. The risk for a poor outcome is considered to be low when an infant starts with a DNV pattern; however, 3 of 9 DNV infants who were treated with normothermia had poor outcomes. Conversely, all infants who started with a DNV pattern and were subsequently cooled had normal outcomes ($n = 9$, $P = 0.03$, normothermia versus hypothermia). In the severely abnormal voltage group, both methods predicted poor outcome equally well (PPV = 89%).

In Fig 7 the same data are displayed in a 2 × 2 table in which CNV and DNV are grouped as normal and BS, LV, and FT as abnormal traces. Moderately and severely abnormal voltages are grouped as abnormal voltage.

**DISCUSSION**

This study confirms previous studies that early aEEG background activity, recorded within 6 hours after birth, is a strong predictor of neurodevelopmental outcome at 18 months in infants who have asphyxia and are treated at normothermia; however, in infants who are treated with hypothermia, the predictive value of an early abnormal (BS/LV/FT) aEEG background is reduced. This suggests that hypothermia changes the early aEEG predictabilities. The delay in recovery may be attributable to hypothermia itself or potential effects of drugs during hypothermia. For cooled infants with an abnormal aEEG within 6 hours, a
good outcome is still possible, even if normalization of background patterns is delayed beyond 24 hours. Conversely, the presence of a normal aEEG pattern within 6 hours after birth is a strong predictor of a normal outcome in both normothermia-treated and hypothermia-treated infants. In our 10-year longitudinal studies that compared normothermia and hypothermia after asphyxia, poor outcome (death and disability) occurred less frequently in the hypothermia group (40%) than the normothermia group (65%). Similar data were recently reported in 24 hypothermia-treated infants with outcome at ≤12 months of age without comparable normothermia data. Ten of 15 hypothermia-treated infants with a severely abnormal BS pattern or worse at 6 hours of age did well. They suggest the cutoff value for aEEG normalizing to be 36 hours of age rather than our finding of 48 hours.

The aEEG can be classified according to pattern or voltage criteria. One previous study indicated that these 2 methods are comparable for prediction of outcome; however, these 2 aEEG scoring systems have not previously been compared in the same data set that contained comparable normothermia/hypothermia-treated infants. Our data...
show that the pattern recognition method is superior for early outcome prediction in a subgroup of patients. The appearance of the aEEG trace is influenced by several factors, including interference from the electrocardiogram, muscle activity, and inter-electrode distance. As can be expected, interobserver variability was slightly lower when voltage criteria were used as compared with pattern recognition, although both methods are equally good when compared with raw EEG.

The voltage classification is easier to use for clinicians with little experience in reading aEEG, but one should always try to assess the underlying pattern. It has been shown that a BS pattern may be read as a normal voltage pattern when a “drift of the baseline” is bringing the lower margin above 5 μV. When this artifact is not recognized, hypothermia may not be offered to eligible infants. An infant with a DNV pattern within 6 hours after birth may still develop abnormally if not treated with hypothermia. To the best of our knowledge, therapeutic hypothermia does not have any severe adverse effects. It seems reasonable to cool infants with a DNV pattern, albeit there is a lower risk (33%) for poor outcome.

Both severe hypothermia and low gestation depress aEEG voltages. Using analog equipment, Horan et al showed that mild cooling (34°C) had no effect on aEEG upper or lower margins in infants who underwent extracorporeal membrane oxygenation. Within the clinical cooling range (33.5–37.0°C), temperature did not affect aEEG in animal experiments. Anticonvulsant and sedative drugs have prolonged half-life in hypothermia-treated infants and therefore may increase plasma levels, depress aEEG, and delay the onset of normal trace or SWC. In this study, the same proportion of infants had seizures, and among them, 70% of hypothermia-treated and 87% of normothermia-treated infants received anticonvulsant drugs.

Never developing SWC within the recorded period (normally ≤96 hours) strongly predicted poor outcome in both groups. Osredkar et al examined the onset of SWC in their 10-year asphyxia cohort (n = 190). They found a strong relationship between time to onset of SWC and severity of encephalopathy. Only 8% of the infants with Sarnat grade III developed SWC with a late median onset of 62 hours, whereas the onset time was 33 hours for grade II and 7 hours for grade I. Although our cohort consisted of a more severely affected group of infants, our result was similar with a median time for SWC onset at 30 hours, and 13 of 31 normothermia-treated infants did develop SWC. A cold environment was associated with poor sleep because thermoregulation is reduced during quiet sleep. Additional hypothermia is avoided naturally by not going into quiet sleep phase. Treatment with hypothermia may consequently be associated with delayed onset of SWC.

Combined with other clinical information, aEEG background pattern has been used as a part of the evidence for justifying withdrawing intensive care. Our findings suggest that withdrawal of intensive care on the basis of a persistently abnormal background pattern at 24 hours is not feasible for hypothermia-treated infants because cooled infants with abnormal background pattern within 48 hours usually develop normally.

CONCLUSIONS

Hypothermia treatment has changed the “cutoff” values for outcome prediction by using time at onset of normal trace and SWC. Both pattern recognition and voltage methods predict outcome well, except for those classified as moderately abnormal voltage. The pattern recognition method in combination with evaluation of the raw EEG trace is superior to the voltage method. On the basis of this data set, it is unlikely that an infant who is cared for at normothermia could survive with a normal outcome if the aEEG recovered beyond 24 hours after birth; however, a hypothermia-treated infant could still develop normally as long as the aEEG recovered before 48 hours.

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