

The usefulness of early ultrasonography, electroencephalography and clinical parameters in predicting adverse outcomes in asphyxiated term infants

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ABSTRACT

Introduction: The early identification of asphyxiated infants at high risk of adverse outcomes and the early selection of those who might benefit from neuroprotective therapies are required. A prospective observational study was conducted to determine if there were any early clinical, neuroimaging or neurophysiological parameters that might predict the outcome in term newborns with asphyxia.

Methods: 44 term newborns with acute asphyxia had a cranial ultrasonography (US), electroencephalography (EEG) and clinical examination performed between three and eight hours of life to determine the parameters that might predict outcome. US findings were classified as normal or abnormal (ventricular dilatation or compression and/or focal/diffuse echogenicities). EEG background activity was classified into two categories: normal/mildly abnormal/intermediate, or severely abnormal (low voltage activity or “suppression-burst”). An intrapartum score (based on graded abnormalities of foetal heart monitoring, umbilical arterial base deficit and five-minute Apgar score) and a hypoxic ischaemic encephalopathy (HIE) score (based on graded abnormalities of the neurological and respiratory status at 3–8 hours of life) was also obtained.

Results: At one year of life, eight infants had died, six had defaulted follow-up, five had major impairment, two minor impairment and 23 were normal. On univariate analysis, poor outcome (death or major impairment) was associated with abnormal cranial US, severely abnormal EEG and a high HIE score (greater than or equal to 15). The positive predictive value was 54.5, 100 and 100 percent, respectively, while the negative predictive value was 93.8, 80.6 and 80.6 percent,

respectively. Combining these factors did not improve the predictive values.

Conclusion: There was no added advantage in combining EEG or US parameters over a clinical neurological scoring system alone in predicting the outcome of asphyxiated term newborns.

Keywords: asphyxia, cranial ultrasonography, electroencephalography, neonatal asphyxia, newborn

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INTRODUCTION

Perinatal asphyxia in term infants remains a significant cause of death and neurodevelopmental impairment. To initiate neuroprotective intervention, early and accurate identification of those at risk of developing hypoxic-ischaemic injury and subsequent poor neurodevelopmental outcome is crucial.⁽¹⁾ It is equally important to identify those who are destined to have a good outcome so as to avoid subjecting this group to therapeutic interventions that may be potentially toxic.⁽²⁾ Studies have looked at various indicators of outcome including clinical information,⁽³⁻⁶⁾ diagnostic methods based on biochemistry,^(7,8) neuroimaging^(9,10) and neurophysiology.⁽¹¹⁻¹³⁾ However, the timing of some of these indicators was often too late for neuroprotective intervention.⁽⁹⁻¹²⁾ Very early indicators (at < 8 hours of life) studied in isolation often have modest predictive values.^(3,7,8,13) In recent years, studies reported improved predictive values using various combinations of parameters.⁽¹⁴⁻¹⁶⁾ However, only in a few studies were the multimodal parameters performed early, within the therapeutic window period.^(17,18) The aim of this study was to determine if there were any obstetric, early clinical, cranial ultrasonography (US) or electroencephalography (EEG) parameters that could be easily performed at the bedside, that might predict the outcome in term newborns with asphyxia.

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METHODS

All term neonates (gestation 37–42 weeks), born between February 1, 2000 and March 31, 2001, and admitted to the neonatal intensive care unit (NICU) of Hospital Universiti Kebangsaan Malaysia with a diagnosis of acute perinatal asphyxia, were included in the study. Perinatal asphyxia was defined as the presence of two of more of the following criteria:

- (1) Signs of foetal distress as indicated by one or more of the following:
 - (a) foetal bradycardia (≤ 100 beats/minute).
 - (b) thick meconium staining of liquor.
 - (c) abnormal cardiotocography recordings.
 - (d) arterial cord blood pH < 7.2 or base deficit > 15 mmol/L.
- (2) Apgar score < 6 at five minutes of life.
- (3) Patient required > 1 minute of positive pressure ventilation before sustained respiration occurred.

The patients were managed accordingly based on their clinical condition. Standard care included appropriate blood investigations, ventilation, anticonvulsants such as phenobarbitone (Martindale Pharmaceuticals, Brentwood, UK) with or without phenytoin (Parke-Davis, Morris Plains, NJ, USA) and support for multiorgan dysfunction. Neonates with clinical evidence of the following conditions were excluded from the study: major congenital malformations, inborn errors of metabolism, intrauterine infections and those with low Apgar scores as a consequence of maternal sedation.

Two clinical scoring systems, selected for ease of scoring, were used. The first, designated as the intrapartum score,⁽³⁾ was based on graded abnormalities of the foetal heart rate, umbilical arterial base deficit and five-minute Apgar score. The score ranged from 0 (no risk factors) to 9 (high risk factors), with a score of ≥ 6 being associated with neonatal morbidity. The second, designated as the hypoxic ischaemic encephalopathy (HIE) score in this study, was based on graded abnormalities in the neurological status and respiratory pattern. This examination was performed 3–8 hours after delivery. The score ranged from 0 (normal) to 22 (maximum adverse neurological status), with a score of ≥ 15 indicating a poor outcome.⁽⁶⁾

All infants had an EEG done at 3–8 hours of life with a portable digital EEG machine (Medelac Profile, Oxford, England). Each recording lasted at least 45 minutes, utilising 16 channels (including four non-EEG polygraphic variables for electrocardiography, respiration, chin and eye movements). EEG analysis focused on the background activity and was classified into four categories: (1) normal: continuous activity with physiological EEG patterns for behavioural state; (2) mildly abnormal: isolated temporal

spikes, mild asynergy; (3) intermediate: predominant or transient discontinuous activity; (4) severely abnormal: inactive (background activity $< 5 \mu\text{V}$) or permanent discontinuous activity (“suppression-burst” or “permanent discontinuous activity plus theta activity”).⁽¹¹⁾ Paroxysmal activity and seizure patterns were assessed separately. All EEGs were read by a paediatric neurologist (OLC). Confounding factors like medication administered (muscle relaxants, sedatives and anticonvulsants) and scalp abnormalities were recorded. Repeat EEGs for the purpose of treatment (e.g. monitoring seizure control) were performed as and when clinically indicated.

Cranial US using standard coronal and sagittal views was performed and video-recorded on all infants between three and eight hours of life using a 7.5 Hz transducer (ALT-Apogee, Philips Medical Systems, Bothell, WA, USA). Two neonatologists viewed the recordings independently. If there was any disagreement about the findings, the tapes were then reviewed together for a final decision. The findings were classified as either normal or abnormal, the latter showing the presence of ventricular dilatation or compression and/or focal or diffuse echogenicities.

The maximum Sarnat grade⁽¹⁹⁾ of hypoxic ischaemic encephalopathy (categorised into Grade I: mild, Grade II: moderate, and Grade III: severe) during the patient’s stay in the NICU was documented. Survivors were followed up by one of the neonatologists at one, six and 12 months of age when new or ongoing medical problems were identified and treated accordingly. The primary outcome was the neurodevelopmental status at one year of life. A neurological examination at age one year was performed by a paediatrician, based on the method described by Amiel-Tison and Grenier.⁽²⁰⁾ A developmental assessment, using the Bayley Scales of Infant Development,⁽²¹⁾ was carried out by a child psychologist and a Mental Developmental Index (MDI) score was obtained. Both the paediatrician and psychologist had no prior knowledge of the infants’ perinatal course. The outcome at one year of life was classified either as normal (no neurological deficit and Bayley MDI score > 85); minor impairment (when only one of the following was present: minor abnormalities of posture or tone, MDI score between 70 and 85, mild to moderate hearing loss not requiring amplification, ophthalmological abnormalities like strabismus, nystagmus or visual loss correctable with spectacles); major impairment (cerebral palsy of any type, severe sensorineural hearing loss, visual loss, MDI < 69 or > 2 minor disabilities present); or death. Infants who developed postnatal brain injury as a consequence of unrelated problems (e.g. meningitis, trauma) were excluded from analysis.

Univariate analysis using the Statistical Package for

Table I. Comparison of potential risk factors associated with outcome.

Risk factors	Outcome, no. (%)		p-value
	Good (n = 25)	Poor (n = 13)	
Sarnat grade			
I	21 (84.0)	5 (38.5)	
II	4 (16.0)	1 (7.7)	< 0.001*
III	0	7 (53.8)	
Intrapartum score > 6	3 (12.0)	5 (38.5)	0.060
[mean \pm standard deviation]	[3.5 \pm 2.78]	[6.1 \pm 1.70]	0.28
HIE score \geq 15	0	7 (53.8)	< 0.001
[mean \pm standard deviation]	[3.7 \pm 2.70]	[10.2 \pm 7.03]	< 0.001
Electroencephalography			
Normal	12 (48.0)	1 (7.7)	
Mildly abnormal	11 (44.0)	3 (23.1)	< 0.001†
Intermediate	2 (8.0)	2 (15.4)	
Severely abnormal	0	7 (53.8)	
Abnormal cranial ultrasonography	10 (40.0)	12 (92.3)	0.002

Good outcome: normal or minor impairment; poor outcome: died or major impairment

* Sarnat Grade II and III vs. Grade I

† severely abnormal EEG vs. all others

Social Sciences version 11.0 for Windows (SPSS Inc, Chicago, IL, USA) was performed to determine factors associated with a poor outcome. Chi square test (Fisher exact test for cell values < 5) was used for categorical variables and Mann Whitney U test for continuous variables. A p-value of < 0.05 was considered statistically significant. The sensitivity, specificity and predictive values of the variables found to be significant on univariate analysis were then calculated.

RESULTS

There were 45 eligible newborns during the study period. One was excluded as the US and EEG were performed beyond eight hours of age. Six infants were lost to follow-up despite multiple attempts to trace them. Hence, 38 infants were studied. Most of the mothers (71.4%) were primigravidas. The mean maternal age was 28.9 (standard deviation [SD] 4.5) years. The mean birth weight was 3,029 (SD 463) g and the mean gestational age was 39.2 (SD 1.1) weeks. An Apgar score of < 6 was recorded in 30 newborns (78.9%) at one minute, 22 (57.9%) at five minutes and 14 (36.8%) at ten minutes of life, respectively. Mean cord blood pH was 6.9 (SD 0.2) and base excess was 17.2 (SD 5.6). Although all infants required resuscitation at birth, only 17 (44.7%) continued to require respiratory support (two required continuous positive airway pressure while 15 required conventional ventilation). The mean age when the infants were evaluated was 5.7 (SD 2.4) hours. The mean intrapartum score was 4.0 (SD 2.3). Eight (21.1%) infants had a score of \geq 6. The mean HIE score was 5.5 (SD 5.8) and seven (18.4%) had a score of \geq 15.

13 infants (34.2%) had a normal EEG, 14 (36.8%)

had a mildly abnormal EEG, four (10.5%) intermediate and seven (18.4%) had severely abnormal EEG (five with continuous low voltage and two with suppression-burst pattern). No infants required sedation for EEG recording. Five (13.1%) had clinical seizures. Of these, only two were on phenobarbitone at the time of the EEG recording and the drug levels were below the toxic range. 22 (57.9%) babies had an abnormal US finding. The abnormalities ranged from ventricular compression to focal or diffuse hyperechogenicity. It was not possible to group these findings as the patients had different combinations of abnormalities. 26 (68.4%) infants were categorised as Sarnat Grade I, five (13.2%) Grade II and seven (18.4%) Grade III. Eight babies died; seven within the neonatal period and one at three months of age. None of the babies died as a result of withdrawal of care. 30 survivors completed the one year follow-up; five had major impairments (four cerebral palsy, one abnormal tone with strabismus), two had minor impairments (abnormalities in tone and posture) and 23 were normal.

Table I compares the various potential risk factors associated with a poor outcome (death or major impairment). A significantly higher proportion of infants with a poor outcome had HIE scores \geq 15, abnormal US, severely abnormal EEG findings and Sarnat Grade II or III. A higher proportion of infants with a poor outcome also had high intrapartum scores \geq 6, but this did not reach statistical significance. Table II shows the predictive values, sensitivity and specificity of the various factors that were found to be significantly associated with a poor outcome. An HIE score of \geq 15 had the same predictive value as a severely abnormal EEG, and these were better

Table II. Predictive values, sensitivity and specificity of the various factors associated with poor outcome (died/major impairment) at one year of age.

Factor	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)
HIE score ≥ 15	100	80.6	53.8	100
Sarnat Grade II or III	75	80.8	61.5	84
Abnormal cranial US	54.5	93.8	92.3	60
Severely abnormal EEG	100	80.6	53.8	100
HIE score ≥ 15 & abnormal US	100	80.6	53.8	100
HIE score ≥ 15 & abnormal EEG	100	80.6	53.8	100
Abnormal US & EEG	100	80.6	53.8	100
HIE score ≥ 15 , abnormal US & EEG	100	80.6	53.8	100

US: ultrasonography; EEG: electroencephalography; PPV: positive predictive value; NPV: negative predictive value.

than a Sarnat grading of II or III. An abnormal US had a lower positive predictive value and specificity than a HIE score ≥ 15 or a severely abnormal EEG. Combining all parameters did not improve the predictive values, sensitivity or specificity. There was a high concordance between the three factors for mortality. Of the eight patients who died, seven patients had a HIE score of ≥ 15 , severely abnormal EEG and abnormal US. The association with major impairment in survivors was less strong. Of the five patients with a major impairment, four had a HIE score ≤ 15 ; two had mildly abnormal EEGs, while two had a normal EEG and one had a normal US.

DISCUSSION

The majority of babies in this study actually had a good outcome with only conservative therapy, in contrast to other studies where the incidence of disability was much higher.^(4,8,10,16,18) This could be due to the different criteria used for enrolment or the period of follow-up. Some studies included only babies with moderate to severe hypoxic ischaemic encephalopathy,^(4,6,10) while others did not follow up the babies until they were one year of age.^(3,5,7,17) As with other studies, predictive values were used to evaluate the usefulness of the various parameters. Predictive values indicate the likelihood of death or neurodevelopmental impairment, and hence are more meaningful than sensitivity or specificity, which express retrospective relationships. Specificity values are also useful to minimise the chance of subjecting babies destined for favourable outcomes to unnecessary and potentially toxic neuroprotective interventions. A limitation of our study was the small number of patients, especially survivors with impairments, and a short follow-up period of one year. This might have affected the prevalence, which in turn will affect the predictive values.

Other studies found a much stronger association between the intrapartum parameters and the adverse outcomes of babies with hypoxic ischaemic encephalopathy,^(3,4) but did not compare the parameters

against a neurological examination. Wayenberg et al reported that a single score established at 30 minutes of life based on the evaluation of consciousness, respiration and neonatal reflexes was a better predictive tool than arterial pH or base deficit.⁽⁵⁾ The HIE score in this study was also more useful than the Sarnat grading. However, the accuracy of this early examination was modest, given the low sensitivity and negative predictive values obtained. Thompson et al, using the same scoring system, found that the peak HIE score tended to occur on the third and fourth day of life, and this had better predictive value than the scores on the first day of life.⁽⁶⁾ Wayenberg et al also reported that the predictive value of their clinical score improved when the duration of persistence of abnormal signs was taken into consideration.⁽⁵⁾ Other neonatal behavioural scoring systems shown to be superior to the Sarnat grade were most accurate when the assessment was done at the time of discharge or at the end of the first week of life.^(22,23) Hence, caution is needed if prognostication is going to be based solely on a single score in the first few hours of life.

The association between the EEG background abnormalities and outcome in babies with HIE has been previously documented.^(11,14,15,24,25) In this study, an abnormal EEG pattern of suppression-burst or continuous low voltage within 3–8 hours of life was associated with a poor outcome, whereas a normal EEG almost invariably indicated a good outcome. Intermediate (mildly or moderately abnormal EEG) abnormalities posed a bigger challenge, as the outcome was less predictable. Other studies recommend repeating EEGs serially to enhance the predictive value.^(11,24) Our study did not demonstrate the superiority of a single EEG recording over a standardised clinical examination (either alone or in combination) in predicting outcome. Given that standard EEG requires considerable skill for recording and interpretation, its routine use in the selection of infants with HIE for neuroprotective interventions cannot be recommended. Improved prognostication may be achieved with

amplitude-integrated EEG (aEEG), which has been shown to have a strong association with the outcome even when used within six hours of life.^(13,18) Even then, Shalak et al recommended combining aEEG with a neurological examination to improve specificity.⁽¹⁷⁾ Other studies reported the usefulness of other neurophysiological parameters like evoked potentials,^(12,18) but this was not explored in our study.

We chose cranial US as the mode of neuroimaging as it was the only easily available neuroimaging tool that could be performed at the bedside. However, early US abnormalities had poor predictive values when used as the sole criteria for outcome and did not improve prognostication when combined with other parameters. This is in agreement with other studies.^(14,18,22) The use of Doppler cerebral blood flow abnormalities to improve prognostication has also met with limited success.⁽¹⁸⁾ Magnetic resonance (MR) imaging, MR spectroscopy and diffusion-weighted imaging have been utilised for predicting outcome.^(9,10,14-16,25) However, their usefulness in routine practice is limited by the logistics of neonatal transport and unproven prognostic utility in the first few hours of life. Moreover, studies that compared MR imaging or MR spectroscopy with other parameters found that its predictive value was either less than that of EEG,⁽¹⁵⁾ or improved when combined with other parameters.^(14,16,25) It would appear that there are currently no early neuroimaging modalities that can be utilised for neuroprotective intervention.

In conclusion, the concomitant use of a single EEG and US recording, which require mobilisation of additional manpower and technology, did not enhance the predictive value of a simple bedside neurological examination. All parameters appeared to be more useful in predicting death than the adverse neurodevelopmental outcome of survivors.

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