Research Paper

Prognostic Value of Amplitude Integrated Electroencephalography in Term Neonates With Encephalopathy

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ABSTRACT

Objective: To evaluate the prognostic value of amplitude-integrated EEG in term neonates with encephalopathy. **Methods:** In this prospective observational study we enrolled 58 term neonates with encephalopathy from March, 2019 to March, 2020. Level of alertness was ascertained as per Volpe's classification and tone as per Amiel-Tison scale of tone assessment. Abnormal aEEG was defined as background activity other than continuous normal voltage, or immature or absent sleep-wake cycle, or presence of electrical seizure. Primary outcome was abnormal neurological examination at discharge and/or death prior to discharge. **Results:** Out of 58 neonates, aEEG was abnormal for 50 (86.2%). There was a statistically significant association between abnormal aEEG findings and primary outcome (*P*=0.04). The aEEG score cut-off of >2 had satisfactory sensitivity (88.8%) and specificity (79.5%) to predict primary outcome. **Conclusion:** Abnormal aEEG had good sensitivity but low specificity to predict primary outcome in term neonates with encephalopathy.

Keywords: *Hypoxic-ischemic encephalopathy, Prognosis, Seizures***,** *Sleep-wake cycle.*

Multichannel electroencephalography (EEG) is considered as the 'gold standard' for evaluating background activity and detecting seizures, but continuous video-EEG monitoring and its interpretation is not feasible in the majority of neonatal intensive care units (NICUs), so amplitude-integrated EEG (aEEG) is used for real time monitoring of brain function and early detection of neonatal seizures [3]. In aEEG, the raw EEG signals are filtered, amplified and compressed for time to get a simplified aEEG waveform by which we can monitor long term trends in electro-cortical background activity [4].

Usefulness of aEEG in neonatal encephalopathies other than hypoxic ischemic encephalopathy has not been well studied and there is paucity of Indian data regarding the utility of aEEG monitoring in neonates. This study was planned to evaluate prognostic value of aEEG in term neonates with encephalopathy, and propose a clinically applicable aEEG scoring system to prognosticate neurological outcome.

METHODS

This prospective observational study was conducted at a tertiary care NICU in India from March 2019 to March 2020 after institutional ethics committee clearance and informed consent from parents of all participants. Term neonates between 37^{+0} to 41^{+6} weeks of gestational age with encephalopathy were included. Babies with Major lethal congenital malformations, chromosomal anomalies, neuronal migration disorders and myopathic disorders were excluded.

Encephalopathy was defined as subnormal alert state/altered neurological function which may be associated with seizures [5]. Etiology of encephalopathy was sub-grouped as hypoxic-ischemic encephalopathy (HIE), infective causes, transient metabolic causes, intracranial hemorrhage (ICH),

dyselectrolytemia, and inborn errors of metabolism (IEM). A detailed neurological examination was performed, and level of alertness was defined as per the Volpe classification, and tone was assessed as per Amiel-Tison scale of tone assessment [6,7].

The aEEG monitoring was done by CFM Olympic Brainz Monitor (Natus Medical Inc.), with 5 biparietal hydrogel electrodes. Electrode impedance was maintained below 10 ohms during monitoring. The aEEG was monitored for at least 24 hours for all enrolled neonates. A single investigator, trained for interpretation of aEEG findings in 10 aEEG recordings by pediatric neurologist, noted the aEEG findings and scored as per the scoring used by Zhang, et al. [8]**.**

Presence of any one of the following was defined as abnormal aEEG: any background activity other than continuous normal voltage, immature or absent sleep-wake cycle (SWC), and presence of any electrical seizure. Primary outcome was defined as subnormal level of alertness as per Volpe classification or any tone abnormality as per Amiel-Tison scale, at the time of discharge and/or death before discharge.

Statistical analysis: SPSS Software version 16 was used for data analysis. To determine the association between categorical variables, Chi square test was used as test of significance. $P<0.05$ was considered statistically significant. Diagnostic efficacy of aEEG background activity, aEEG sleep-wake cycle and aEEG seizures in predicting outcome at discharge was assessed by calculating specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio and negative likelihood ratio. Diagnostic efficacy of cumulative aEEG score in predicting outcome was assessed by ROC curve, suitable cut-off values were selected and AUC was calculated.

RESULTS

Of all the term neonates with encephalopathy, 58 were finally enrolled in the study and followed-up till discharge or death (**Fig. 1**). Out of these, 50 (86.2%) survived. aEEG findings were abnormal for 50 (86.2%) of enrolled neonates. Out of these 31 (62%) had normal outcome and 19 (38%) had abnormal outcome at discharge, or died prior to discharge. There was a statistically significant association between abnormal aEEG findings and primary outcome. Abnormal aEEG had 100% sensitivity, 20.5% specificity, 38% PPV, 100% NPV, positive likelihood ratio 1.26 and negative likelihood ratio 0, to predict primary outcome **(Supp. Table I).**

Out of 58 neonates, 38 (65.5%) had abnormal background activity. There was a statistically significant association between background activity and primary outcome ($P=0.001$). Out of 58 neonate, 19 (32.7%) had mature sleep-wake cycle and 39 (67.2%) neonates had immature or absent sleep-wake cycle, and there was a statistically significant association between sleep-wake cycle and primary outcome ($P=0.00$). A total of 43 (74.1%) neonates had electrical seizures, and aEEG seizures were significantly associated with primary outcome ($P=0.002$).

A cumulative aEEG score of 0-2 was seen in 32 (55%) neonates, and 26 (45%) had score >2. Out of 32 neonates with score of 0-2, 31 (97%) had normal outcome, ROC curve was plotted and cut-off value >2 was selected for high sensitivity and low false positive rate. There was a statistically significant association between cumulative aEEG score>2 and primary outcome (*P*=0.00) **(Fig. 2).**

DISCUSSION

In this prospective observational study we assessed the characteristics of aEEG in 58 term neonates with encephalopathy and we found that background activity, sleep-wake cycle and electrical seizures were significantly associated with primary outcome. In this study we also calculated cumulative aEEG scoring and we found that cumulative aEEG score of >2 was significantly associated with primary outcome. These results were largely consistent with previous studies.

In the present study we found that abnormal aEEG was significantly associated with abnormal outcome and it has high sensitivity, but low specificity to predict primary outcome. A meta-analysis by Chandrasekaran, et al. [9] showed similar results with pooled sensitivity of 87% and specificity of 36%. Similar to our findings, Van der Heide, et al. [10] noted significant association between aEEG background activity and neurologic outcome in neonates. Sewell et al [11] showed results opposite to our study with low sensitivity and high specificity. This may be due to inclusion of all grades of encephalopathy with various etiologies in our study, while they only included neonates with HIE. We found that aEEG cyclicity was significantly associated with primary outcome. Rhie, et al. [12] concluded in their study that delayed appearance of SWC was significantly associated with unfavorable neuroimaging in neonates with HIE, as was also seen in our study for all causes of encephalopathy.

Variane, et al. [13] showed that presence of recurrent aEEG seizures were associated with MRI brain abnormality and death, similar to this significant association with outcome was found in our study.

Similar to this study, Luo, et al. [14] showed that aEEG scoring system has a higher specificity but low sensitivity as compared to individual components for abnormal outcomes.

Strengths of our study include enrolment of subjects with various causes of encephalopathy, albeit majority were HIE, and detailed study of the individual components of aEEG tracing and formulation of cumulative scoring cut-offs to predict short term neurological outcome.

Limitations of our study include a relatively small sample size, and inability to study long term neurological outcomes. Neonates admitted in the late stage of encephalopathy could have had different findings in aEEG if we had had recorded aEEG at the onset of encephalopathy. Effect of ongoing drugs, and therapeutic hypothermia were not taken into account, and the effects of postnatal age on aEEG findings were not studied.

To conclude, aEEG parameters such as abnormal background activity, absent sleep-wake cycling and presence of electrical seizures, either alone or in combination are associated with primary

outcome of subnormal level of alertness or tone abnormality at discharge in term neonates with encephalopathy.

Ethical clearance: Institutional ethics committee, Kanchi Kamakoti CHILDS Trust Hospital Chennai; No. IEC-DNB/26/February2019, dated March 11, 2019.

Contributors: SGK: conceptualized the study, collected data, wrote the first draft of manuscript; NCK: study design, analysis, corrected manuscript and approved for final submission; HV: critical review of proposal, expert advice on data analysis and interpretation; SS: protocol development, supervising enrolment and outcome assessment; SSS: participated in planning of project and writing manuscript. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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WHAT THIS STUDY ADDS?

- Abnormal aEEG has high sensitivity but low specificity to predict primary outcome of subnormal level of alertness or tone abnormality at discharge, or death before discharge in term neonates with encephalopathy.

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Table I Baseline Characteristics of Study Population

Gestational age, wk[a]	38.5 (1.14)
Birthweight, g	2889 (360)
Male gender	35 (60.3)
Postnatal age	
1-3 d	36 (62)
4-7 d	8 (14)
8-14 d	5 (8.6)
15-28 d	9 (15.5)
Mode of delivery	
Vaginal delivery	24 (41)
Assisted vaginal delivery	6 (10)
Caesarean section	28 (48)
Resuscitation at birth	30 (52)
Antenatal risk factors	
Fetal distress	14 (24)
PIH	6 (10)
Oligohydramnios	7 (12)
Polyhydramnios	6 (10)
PROM	4 (7)
Etiology of encephalopathy	
HIE	36 (62)
Infective	12 (21)
Transient metabolic	4 (7)
ICH	2 (3)
Dyselectrolytemia	2 (3)
IEM	2 (3)

Variables are expressed as n (%) except [a]mean (SD)
HIE, hypoxic ischemic encephalopathy; ICH, intracranial haemorrhage; PROM, premature rupture of membranes; PIH, pregnancy induced hypertension; IEM, inborn error of metabolism

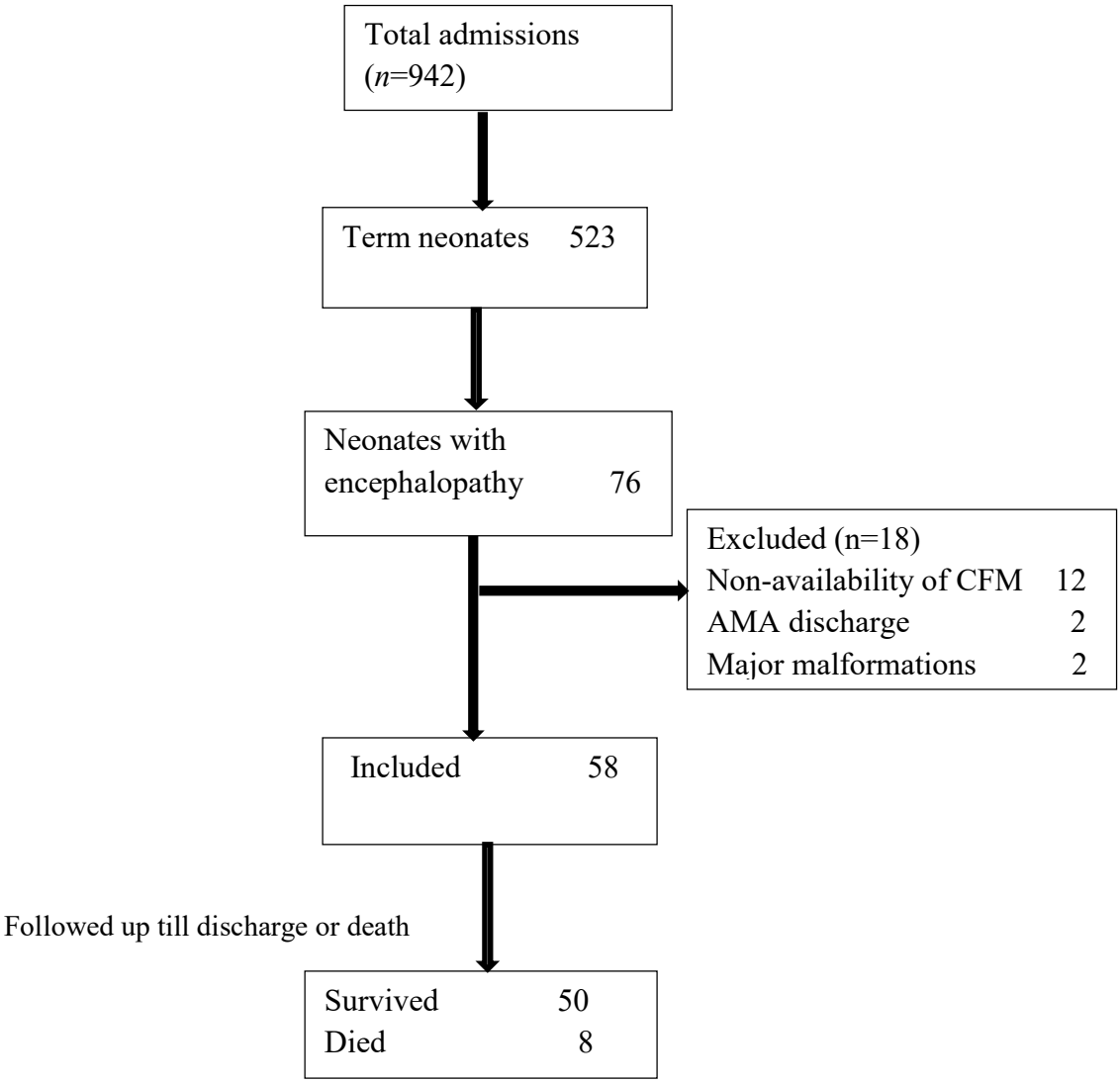

Fig. 1 Study flow diagram

CFM, cerebral function monitor; AMA, against medical advice

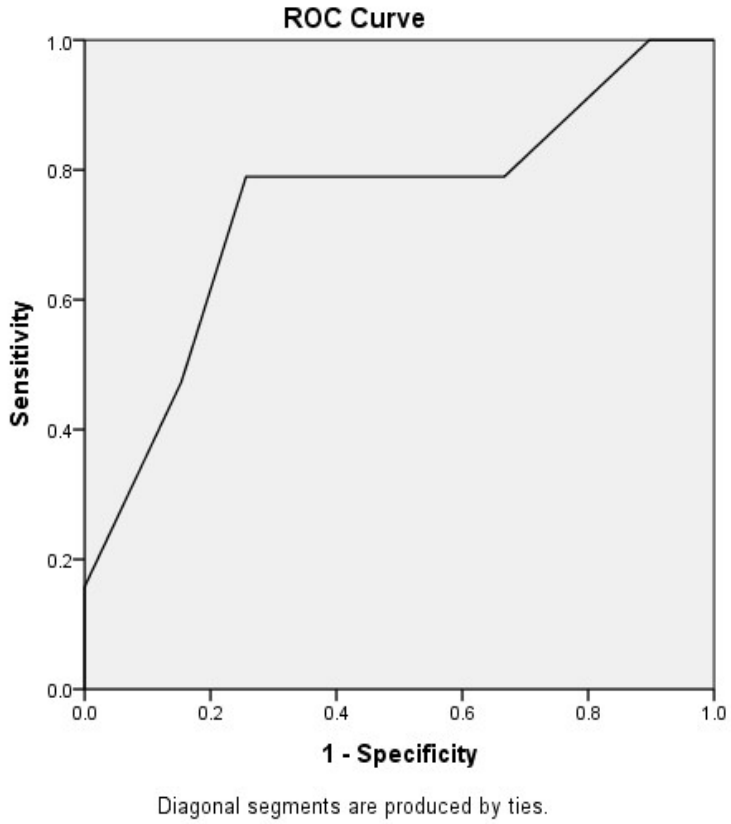

Fig. 2 *Receiver Operator Characteristic (ROC) Curve of cumulative aEEG scoring to predict abnormal neurological outcome (AUC - 0.746).*

Supplementary Table I Primary and Secondary Outcomes

Predictor	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*Positive likelihood ratio*	*Negative likelihood ratio*
Primary outcome						
Abnormal aEEG	100%	20.5%	38%	100%	1.26	0.00
Secondary outcomes						
Background activity	94.7%	48.72%	47.3%	95%	1.85	0.11
Sleep-wake cycle	100%	48.72%	48.7%	100%	1.95	0.00
aEEG seizures	100%	38.46%	44.19%	100%	1.62	0.00
Cumulative aEEG score>2	88.8%	79.49%	50%	96.8%	4.33	0.14
Cumulative aEEG score>3	47.3%	84.62%	60%	76.7%	3.08	0.62
Cumulative aEEG score>4	31.6%	92.3%	66.7%	73.4%	4.11	0.74

PPV, positive predictive value; NPV, negative predictive value