Clinical Experiences of Amplitude-integrated Electroencephalographic Monitoring in Neonatal Intensive Care Unit

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Objective: The purpose of this study was to analyze the clinical experience of amplitude-integrated electroencephalogram (aEEG) in the neonatal intensive care unit (NICU) and to evaluate the usefulness of the aEEG and to determine whether an EEG could help to identify high risk infants with later epilepsy.

Methods: Clinical data of 200 newborn infants admitted to the NICU and monitored with aEEG were reviewed retrospectively. A single- or two-channel aEEG (electrode placement P3-P4 for single, C3-C4 and P3-P4 for two) was recorded continuously by using gold cups. Background activity was assessed based on voltage and pattern recognition methods. To assess for differences in later epilepsy among infants with abnormal versus normal results, chi-square test was employed with odd ratio.

Results: Overall, 200 newborn infants were included. About half showed abnormal findings on aEEG monitoring with 34.5% abnormal background activity, 30.0% abnormal cyclicity, and 30.0% with seizures. The odd ratio for an abnormal trace on aEEG to predict later epilepsy was 7.9 (95% confidence interval; 2.8-22.0; $P < 0.001$).

Conclusion: aEEG monitoring is useful for cerebral monitoring in NICU. aEEG monitoring enabled to assess the cerebral integrity of infants by measuring background activities and detecting seizures and help to identify high-risk infant for later epilepsy.

Key Words: Brain monitoring, Electroencephalogram, Newborns

Introduction

The amplitude-integrated electroencephalogram (aEEG) has been used for monitoring cerebral integrity since it was first introduced in the late 1960s by Maynard et al.¹ at the London Hospital. aEEG began to be used in newborn infants since the 1980s.^{2,3} With the development of digital technology during the 2000s, raw EEG tracing was also displayed simultaneously with the aEEG tracing.⁴ aEEG is now a standard device for cerebral monitoring in neonatal intensive care unit (NICU) worldwide.

Of note, conventional electroencephalogram (cEEG) is the clinical standard for brain monitoring.⁴ However, cEEG may not be always available on even emergent basis. The need for a trained cEEG technologist for examination and the expertise for reading limits the use of cEEG in NICU.⁵ Newborn infants, including premature babies are vulnerable to brain damage and have a high risk of seizures; therefore cerebral function monitoring should be available in NICU.^{6,7} The emergence of aEEG has provided a complementary method that is easily accessible and applied regardless of expertise and allows long-term real-time monitoring.^{4,5} It also has been used as routine monitoring in many high level NICUs in Korea since 2008; nevertheless, there are few reports on the clinical experiences of aEEG monitoring. Therefore, the purpose of this study was to review our clinical experience, to analyze the potential of aEEG in the NICU and to determine whether aEEG could help identify infants at high risk for later epilepsy.

Methods

Total of 3,165 newborn infants were admitted to the NICU at Kyungpook National University Hospital (n=788) and Kyungpook Children's Hospital (n=2,370) between March 2014 and December 2018. Both centers are level III NICUs in Daegu, Korea. Of these, aEEG monitoring was performed in 200 newborn infants (46 and 154, respectively) for monitoring seizures or background activities. The study was approved by the authors' institutional ethical committee (approval number: KNUCH 2019-11-004, 2020-01-041-001), and the requirement for written informed consent was waived as this was a de-identified, data-only study.

By reviewing medical records, we collected clinical characteristics including gestational age, gender, birth weight, mode of delivery, 1-minute and 5-minutes Apgar scores and detailed postnatal history and clinically indicated neurologic testing results (e.g., brain ultrasonography (USG), brain magnetic resonance imaging (MRI), and cEEG retrospectively. Abnormal brain USG was defined in this study as grade III-IV intraventricular hemorrhage (IVH) or severe white matter damage.^{8,9} Brain MRI scans were considered abnormal if it showed evidence of developmental malformation, grade III or IV IVH or infarct, abnormal signal intensities within the basal ganglia, thalamus, internal capsule, subcortical white matter or cortex. The time of the events, the reason for the aEEG monitoring, and the underlying causes for events were evaluated based on the records. Cerebral causes were defined as seizure or encephalopathy while noncerebral causes were defined as nonconvulsive acute paroxysmal events (APE) or other systemic illness. APE was defined as clinically nonconvulsive and no specific findings on cerebral evaluation.¹⁰ If the infant has documented seizure, but the cause was not clear, and there were no specific findings in the evaluation, and no further seizures, the etiology was classified as unidentified, which was presumed as benign seizures. To determine whether aEEG can identify high-risk infant, we reviewed the presence of later epilepsy during follow up period, which was defined as taking antiepileptic medications for more than a year beyond neonatal period or having epilepsy diagnosis by neurologist.

The aEEG recordings were performed with the Olympic Brainz Monitor (Natus Medical Incorporated, San Carlos, CA, USA). A single- or two-channel aEEG (electrode placement parietal

[P3-P4] for single, central-parietal [C3-C4 and P3-P4] for two according to the international 10-20 system) was recorded continuously by using gold cups. aEEG monitoring had performed with single channel before but 2 channel monitoring has been performed routinely since March 2016. Most of the recordings were performed immediately after the event was recognized by the medical staff, the recording within the initial 24 hours were used for the assessment of the background activities. In the case of seizures, it was read as abnormal when confirmed through the whole aEEG monitoring. The background activities were assessed based on voltage and pattern recognition methods¹¹⁻¹³: continuous, discontinuous, burst suppression, low voltage and isoelectric trace. Cyclicity was classified as being absent, immature and mature.¹¹ Electrographic seizures in the aEEG are defined as runs of rhythmic activities that initially increases in frequency and amplitude, reaches a maximum and decrease over a time period lasting at least 10 seconds.¹⁴ The recording was interpreted as abnormal if the infants showed the abnormal background activities or inappropriate cyclicity for gestational age, or the electrical seizures during the recording. Even premature infants with discontinuous background activities were read as normal if appropriate for the gestational age. The aEEG recordings were analyzed by two experienced investigators who were blinded to clinical information (Drs. Lee and Lee). Both have experience as neurologists of over 5 years and are competent at cEEG interpretation.

Analyses were performed using IBM SPSS Statistics ver. 25.0 (IBM Co., Armonk, NY, USA). Data for normally distributed continuous variables were expressed as means and standard deviations. For non-normally distributed variables were expressed as median and interquartile ranges. To assess for differences in later epilepsy among infants with abnormal versus normal results, the chi-square test was employed with odd ratio. A *P*-value of 0.05 was taken to be statistically significant.

Results

A total of 200 infants who underwent aEEG were enrolled in the study. Table 1 shows the demographic and clinical profile of enrolled infants. Sixty-seven preterm neonates (33.5%) and 133 term infants (66.5%) were included in the study.

The purpose of cerebral monitoring is shown in Table 2, with 46.5% of recordings for monitoring seizures, 35.5% of the recording for monitoring background activities in infants who were suspected of having encephalopathy. The remainder was about 18.0% to discriminate seizures or encephalopathy for apnea. About half showed abnormal findings on aEEG monitoring, with 34.5% abnormal background activity, 30.0% abnormal cyclicality, and 30.0% seizures. In some cases, cEEG, brain USG, and brain MRI were not performed because the patient was seriously ill, died or did not need to be examined. Therefore, the number of aEEG trials was higher than that reported in other studies.

Table 3 shows the etiology of events (seizures, apnea, or encephalopathic features). About two-thirds were cerebral insults, which were manifested as seizures or encephalopathy. Among cerebral events, hypoxic-ischemic encephalopathy accounted for the largest number of infants. About one-third was considered to be other systemic illness such as sepsis and apnea of prematurity with normal aEEG tracing.

Seizures were observed in 119 of total 200 infants. Table 4 shows the phenotype of documented seizures. About a quarter did not confirm seizures. Clonic seizures were most frequently observed, and in 10.5%, only electrical seizures were observed without clinical seizure (electro-clinical dissociation).

Table 5 lists the results of brain examination and the prediction of later epilepsy/late epilepsy or death. The outcomes are available for 169 (21 died and 10 were lost to follow up). The median

Table 1. Clinical Characteristics of Newborn Infants

Variable	Value
Gestational age (weeks)	38.0 (35.3-39.7)
Birth weight (g)	2,925.0 (2,195.0-3,345.0)
Sex	
Male	112 (56.0)
Female	88 (44.0)
Delivery	
NSVD	92 (46.0)
C-sec	108 (54.0)
Inborn	84 (42.0)
1 minute Apgar score	7.0 (4.0-8.0)
5 minutes Apgar score	8.0 (7.0-9.0)
Maternal age (years)	33.0 (30.0-36.0)

Values are presented as number (%) or median (interquartile range).

Abbreviations: NSVD, normal spontaneous vaginal delivery; C-sec, cesarean section.

Table 2. Results of aEEG Monitoring and Other Modalities

Variables	Value
aEEG monitoring	
Aim of study	
Background monitoring	71 (35.5)
Seizure monitoring	93 (46.5)
Apnea monitoring	36 (18.0)
Number of channels	
1 channel	47 (23.5)
2 channels	153 (76.5)
Recording time (hours)	66.8 (18.2-134.2)
Event onset age (days)	5 (2-13)
Result of aEEG monitoring	
Normal	100 (50.0)
Abnormal	100 (50.0)
Abnormal aEEG monitoring	
Abnormal background	69 (34.5)
Abnormal cyclicality	70 (35.0)
Seizure	74 (37.0)
Background activities of aEEG monitoring	
Continuous	123 (61.5)
Discontinuous	30 (15.0)
Burst suppression	29 (14.5)
Low voltage	10 (5.0)
Isoelectric	8 (4.0)
Other modalities	
EEG	
Normal	89 (44.5)
Abnormal	40 (20.0)
Not done	71 (35.5)
Brain USG	
None or mild injury	96 (48.0)
Moderate to severe injury	55 (27.5)
Not done	49 (24.5)
Brain MRI	
Normal	52 (26.0)
Abnormal	58 (29.0)
Not done	90 (45.0)
Brain USG or Brain MRI	
Normal	93 (46.5)
Abnormal	80 (40.0)
Not done	27 (13.5)

Values are presented as number (%) or median (interquartile range).

Abbreviations: aEEG, amplitude-integrated electroencephalography; EEG, electroencephalography; brain USG, brain ultrasonography; brain MRI, brain magnetic resonance imaging.

Table 3. Underlying Etiologies of Events

Etiology	Value
With seizures or encephalopathy	124 (62.0)
HIE	45 (36.3)
Vascular	15 (12.1)
IVH/ICH	12 (9.7)
Infarction	2 (1.6)
Subgaleal hemorrhage	1 (0.8)
Metabolic problems	14 (11.3)
Hypocalcemia	11 (8.9)
Hypoglycemia	2 (1.6)
Hyponatremia	1 (0.8)
CNS infection	10 (8.1)
Rota encephalopathy	5 (4.0)
Group B streptococcus	4 (3.2)
Cytomegalovirus infection	1 (0.8)
Inborn errors of metabolism	6 (4.8)
Neonatal epileptic syndrome	6 (4.8)
Chromosome/Syndromic	5 (4.0)
Edward syndrome	3 (2.4)
Prader Willi syndrome	1 (0.8)
Spinal muscular atrophy	1 (0.8)
Structural	3 (2.4)
Neurocutaneous syndrome	2 (1.6)
Unidentified	18 (14.5)
Neither seizures nor encephalopathy	76 (38.0)
Acute paroxysmal event	11 (5.5)
Other systemic illness	47 (23.5)
Sepsis or other infection	23 (11.5)
Chromosomal/Syndromic	8 (3.5)
Apnea of prematurity	7 (4.0)
Feeding intolerance	3 (1.5)
RDS/PPHN	3 (1.5)
Heart disease (postsurgery)	3 (1.5)
Just for monitoring	15 (7.5)
Hypocalcemia	6 (3.0)
Suspected hypoxic event	4 (2.0)
Hyperbilirubinemia	4 (2.0)
Inborn errors of metabolism	1 (0.005)

Values are presented as number (%).

Abbreviations: HIE, hypoxic-ischemic-encephalopathy; IVH, intraventricular hemorrhage; ICH, intracranial hemorrhage; CNS, central nervous system; RDS, respiratory distress syndrome; PPHN, persistent pulmonary hypertension of newborn.

follow-up days (interquartile range) were 383.0 (44.5–550.5). The odd ratio (OR) for an abnormal trace on aEEG to predict later epilepsy was 7.9 (95% confidence interval [CI] 2.8–22.0, $P<0.001$). In other words, as in the case of brain USG, brain MRI and cEEG abnormalities, the risk of later epilepsy was shown to be elevated. The odd ratio for later epilepsy or death much increased with abnormal aEEG compared with normal aEEG 15.7 (95% CI 5.86–42.1, $P<0.001$).

Table 4. Phenotypes of Documented Seizures (n=119)

Seizure phenotype	Value
Documented seizure	119 (59.5)
Clonic	37 (18.5)
Subtle	23 (11.5)
Tonic	19 (9.5)
Myoclonic	6 (3.0)
Generalized tonic-clonic	5 (2.5)
Spasms	3 (1.5)
Electrical seizure only	26 (13.0)

Values are presented as number (%).

Table 5. Risk Analysis for the Later Epilepsy and Later Epilepsy or Death According to the Modalities

Modality (n)	Normal	Abnormal	Odds ratio	95% CI	P-value
Later epilepsy					
aEEG (169)	5 (5.3)	23 (30.7)	7.9	2.8–22.0	<0.001
BG	12 (9.8)	16 (34.8)	4.9	2.1–11.5	<0.001
Cyclicity	13 (10.7)	15 (31.5)	3.9	1.7–9.1	0.001
Seizures	9 (7.8)	19 (35.2)	6.4	2.7–15.4	<0.001
EEG (118)	9 (10.8)	16 (45.7)	6.9	2.7–18.1	<0.001
Brain USG (128)	6 (6.7)	12 (32.0)	6.5	2.2–18.9	<0.001
Brain MRI (104)	4 (8.3)	17 (30.4)	4.8	1.5–15.5	0.005
Later epilepsy or death					
aEEG (190)	5 (5.3)	45 (46.9)	15.7	5.86–42.1	<0.001
BG	13 (10.5)	37 (56.1)	10.9	5.1–23.1	<0.001
Cyclicity	14 (11.4)	36 (53.7)	9	4.3–18.9	0.001
Seizures	13 (10.9)	37 (52.1)	8.9	4.2–18.6	<0.001
EEG (122)	10 (11.9)	19 (50.0)	7.4	3.0–18.5	<0.001
Brain USG (144)	8 (8.7)	27 (51.9)	11.3	4.6–28.0	<0.001
Brain MRI (105)	5 (10.2)	17 (30.4)	3.8	1.2–11.4	0.011

Values are presented as number (%).

Abbreviations: CI, confidence interval; aEEG, amplitude-integrated electroencephalography; BG, background activities; EEG, electroencephalography; brain USG, brain ultrasonography; brain MRI, brain magnetic resonance imaging.

Discussion

Since aEEG has been applied to NICU since the 1980s, many advances have been made, and nowadays, early aEEG findings are helpful in identifying newborns who benefit from cooling and predicting prognosis in HIE patients,^{11,15-18} and in recent years, many studies have shown that aEEG is helpful in predicting prognosis in premature infants.¹⁹⁻²¹ Since the best advantage of aEEG is that it can be continuously monitored, it can help determine the brain condition of an infant in emergencies where conventional EEG is not available and can provide information on decision making for cooling therapy in infant with HIE.²² In cases of encephalopathy or abnormal tracing, it provides useful information for follow-up plans, evaluation of clinical improvement, the response to anticonvulsant. Actually, the number of aEEG exam is higher than the number of exams of brain USG, brain MRI, and cEEG. One cause of this observation was because in the case of immediate death in an urgent situation, further evaluation could not be performed. In other words, aEEG was useful to assess the patient even in emergency situation where other tests were not possible. In addition, initial assessment with aEEG monitoring helped to identify the patient who need to perform additional, tests that require sedation, such as brain MRI.

The enrolled patients were presented as seizures, seizure-like events, decreased activities, apnea or mental change. Some infants were taken aEEG monitoring because of increased seizure risk, such as hypocalcemia, or the need for background monitoring. More than half of them showed abnormal tracing on aEEG monitoring. Although aEEG is known to underestimate seizure than cEEG,^{3,23} in this study, there were fewer cases of seizure on cEEG because it was not immediately available and was often performed after treatment and clinical improvement. Twenty-five percent of patients suspected of seizure could not observe seizures. One possibility of these dissociation is that it was not seizure but paroxysmal event. It could be seizures, but aEEG could not detect seizures because of improvement of seizure after anticonvulsant medication. aEEG could be difficult to detect seizures at different sites besides central or parietal areas because only a small area of the brain surface is covered by limited channel electrodes. A majority of neonatal seizures are relatively brief and missed even on aEEG monitoring.¹⁵

Therefore, aEEG should be assessed comprehensively with other evaluation and the physicians should not judge solely based on aEEG.

In fact, subtle seizures have been the most frequent seizures in neonatal seizures.⁷ In this study, clonic seizures is the most frequently observed. In the case of clonic seizures, it is likely to be detected at electrodes on aEEG monitoring while involves the motor cortex. It has been shown that the majority of neonatal seizures originates in central and temporal areas.^{3,24,25} It should be noted that in some cases only electrical seizures were observed clinical seizures. Neonatal seizures may have electro-clinical dissociation, and such electrical seizures should also be considered for treatment. Only electrical seizures without clinical seizures can be detected only by EEG monitoring, so aEEG, which can be used for real-time long-term monitoring, is suitable for NICU. In practice, when monitoring seizures only visually in NICU, it underestimates actual seizures. In this study, 13.0% of seizures was only electrical seizures without no clinical seizures. Even in infants with clinical seizures, not all seizures were detected by medical staffs. Although there are still pitfalls in the interpretation of the aEEG by unskilled staff and artifacts in NICU environment,^{26,27} the aEEG monitoring could improve optimal neonatal seizure management through revealing multiple clinically silent seizures and subclinical status epilepticus in high-risk infants.²⁸

In this study, we analyzed later epilepsy in patients with aEEG monitoring and did not identify differences with respect to gender, delivery mode, or inborn/outborn status. In the context of abnormal aEEG tracing, infants had increased risk of later epilepsy. A total of 25 of 71 infants with abnormal aEEG died, and there were no deaths among newborns with normal aEEGs. In fact, the ORs for death or later epilepsy with an abnormal aEEG increased to 15.7. In other words, the higher likelihood of epilepsy in infants with abnormal aEEG tracing compared with those with normal aEEG tracing suggest that they need constant follow-up.

The limitation of this study is that it is a retrospective study based on medical records and cannot be generalized in a heterogeneous patient groups. We did not separate the premature infants and term infants in etiology analysis. Moreover, the test was not performed as a routine for premature infants who have a high risk of brain damage. The use of aEEG monitoring for

improving outcome in high-risk infants has not been directly proven. This study did not evaluate the prognostic value of aEEG monitoring for developmental outcomes other than later epilepsy. The aEEG would probably underestimate the seizure burden when compared to cEEG. Of note, interrater reliability for subjective aEEG interpretation is not perfect.²⁹ Nonetheless, it is always feasible, even if other tests are not available, and easy to run and easy to read in the NICU setting. It is also suitable for long-term surveillance of cerebral activities of newborns. If it used in conjunction with other monitoring techniques, it could obviously provide additional information about the infant's cerebral condition to aid patient management.^{3,30}

In conclusion, this study confirms observations that aEEG monitoring is useful and well-tolerated techniques for cerebral monitoring in NICU. The aEEG monitoring enable to assess the cerebral integrity of the infant through background activities, recognize seizures earlier, detect subclinical seizures, to help more precise management including anticonvulsant therapy and cooling and evaluate the clinical improvement and response to medication.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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