Amplitude-Integrated EEG for Neurological Assessment and Seizure Detection in Pediatric Intensive Care Unit

By

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Abstract

Background: Amplitude-integrated electroencephalography (aEEG) is a neurophysiology tool used at the bedside to show the trend of brain activity.

Objectives: To evaluate the diagnostic and prognostic significance of aEEG neuromonitoring in al Hussein hospital PICU. Cairo, Egypt, and its usefulness in detecting seizures to aid in improved management and identification of unnecessary indications.

Methods: This prospective observational study was carried out on 48 children aged from two months to 14 years of both sexes. The research took place from January 2022 to September 2023 .following approval from the Ethical Committee of Al Azhar University Hospitals. All patients with one or more of the following disorders,(encephalopathy. traumatic brain injury, poisoning, sepsis, post rescusitation, suffocation, post brain surgery, post ictel state and abnormal movements) were subjected to full history taking &complete clinical evaluation followed by lab..& radiological & C.T. exam. if indicated &then put into continuous aEEG monitoring. **Lastly the studied patient were classified into two sub groups ;**

A- favorable aEEG which include Continuous normal voltage (CNV), discontinuous normal voltage (DC)

B- unfavorable aEEG which include continuous low voltage (CLV), burst suppression (BS), and flat trace (FT)

Results: The mean Glasgow Coma Scale significantly improved among children with subclinical seizure after treatment (P=0.006). Children with unfavorable aEEG showed significantly higher mortality, prolonged hospital stay, and multiple anti-epileptic drugs (AED) (P<0.05) compared to favorable aEEG. There was insignificant difference between children with or without favorable aEEG regarding the causes of admission. Severe disability, death were significantly higher among children with unfavorable aEEG (P<0.05)

Conclusion: Implementing early aEEG monitoring can assist intensive care unit (ICU) providers in directing clinical care and confirmation of suspected seizure and detection of non-convulsive seizure and therapy guidance. Children with favorable aEEG associated with lower mortality rate, median days of hospital stay, less days on MV , need less anti-epileptic drug and less motor sequel on discharge compared to unfavorable aEEG.

Keywords: Amplitude-Integrated EEG; Neurological; Seizure; Pediatric Intensive Care Unit

Introduction

An issue frequently encountered in the field of pediatric intensive care is the evaluation of the neurological condition of children who exhibit changes in their mental state. Furthermore, patients frequently necessitate sedation or opiate analgesia, which further complicates the early identification of neurological complications and the need for immediate treatment. Multiple scoring systems have been developed to evaluate vigilance, pain, distress, and withdrawal. However, the assessment of vigilance still poses a difficulty **(Bruns et al., 2019)**.

Measurements of cerebral tissue oxygenation, cerebral blood flow, and metabolic state are indicative of methods used for indirect brain monitoring in the pediatric intensive care unit (PICU). Bispectral index monitoring and traditional continuous electroencephalography (cEEG) allow for the monitoring of electrical activity. An alternate tool commonly used in neonatal ICUs is an amplitude-integrated electroencephalogram (aEEG), which is a simplified and time-compressed version of the conventional EEG **(Grinspan et al., 2014 and Tschiedel et al., 2018)**.

Electrodes placed by the international 10-20 system, adjusted for newborns, constitute the gold standard for cEEG monitoring of the neonatal brain **(Shellhaas et al., 2011)**.aEEG is a tool for electroencephalography (EEG) that can be used in bedside neurophysiology. It records the raw EEG signal using a restricted number of channels, filters, rectifies, processes, and displays it on a time-compressed and semilogarithmic scale **(Borovac et al., 2024)**. For over twenty years, aEEG has been widely utilized in the ICNs of European centers because of its implementation and analysis ease and the difficulties with traditional EEG monitoring. In recent years, usage has been on the rise in North American ICNs **(De Vries et al., 2005and Boylan et al., 2010)**.

An aEEG shows trended brain activity and is an easy way to monitor brain function continuously. It uses three to five electrodes placed on the scalp to record an electroencephalogram (EEG) with one or two channels. It records the typical pattern of brain activity over a long period in real time. Depending on the situation, recordings can be kept for up to 24 hours. There is a wide variety of electrode styles available, such as hydrogel patches that self-adhesive, intradermal needles that are very thin, and the more conventional silver or gold EEG cups**(Foreman et al., 2011)**..

When it comes to monitoring the background activities of both healthy and neurologically compromised neonates, aEEG and cEEG show a strong correlation **(Klebermass et al., 2001)**.

Aim of the study

This study set out to evaluate the diagnostic and prognostic efficacy of aEEG neuromonitoring in al Hussein hospital, as well as its use in seizure detection for the purpose of improved management and the identification of unnecessary indications.

ETHICAL CONSIDERATION:

1. Approval BY the Ethical Committee of Pediatric department at the Faculty of Medicine at Al Azhar University under the registration number was obtained before the study.
2. Patients were enrolled in the study after getting informed oral and written consent from their parents.
3. Patient data confidentiality was preserved during all study procedures.
4. The patient and parents have the right to withdraw from the study at any time.
5. There was no conflict of interest regarding the study or publication.
6. There is no financial support or sponsorship

Inclusion criteria

1. Children aged from two months to 14 years old
2. both sex
3. any patient with clinical evidence or history of Encephalopathy, traumatic brain injury, poisoning, sepsis, severe infection, post resuscitation / suffocation, post brain surgery, post ictal state and abnormal movement.

Exclusion criteria:

1- children < 2 month of age or >14 years old
2- Any contraindication of aEEg as cephalohematoma

Sample size calculation ;

The sample size is calculated according to the following equation ;

Necessary sample size = $\frac{(z-score)2\ x\ stdDev\ x\ (1-StdDev)}{(margin\ of\ error)2}$

With 16% standard deviation, alpha error of 0.10 .it included 48 patient

All patient were subjected to the following:

1- History taking (from the legal guardians) with stress on:

- Demographic data.
- History of the current condition (with analysis of their onset, course, duration and precipitating factors).
- Developmental history and previous perinatal risk factors.
- Family history of similar condition.

Clinical examination:

2. Complete clinical examination including:

- Anthropometric measurements; weight, height, head circumference were measured and plotted on WHO and BMI were calculated.
- Conscious level using the Glasgow Coma Scale GCS, modified for children
- Systematic examination including (H&N – chest –heart –abd –ul- LL)
- Analysis of type of seizures (clinical, subclinical, or combined).

3 Initial laboratory investigations including: CBC, RBS, serum electrolytes.

4. Radiological imaging including :CT Brain.

5. Continuous aEEG monitoring was initiated after patient stabilization considering timing from admission to aEEG recording and duration of recording**.** aEEG readings were reported and interpreted by pediatric neurologist. aEEG tracings were assessed for background pattern and seizures. Patients were monitored for minimum 24 hours unless clinical condition necessitated shorter (as death or hospital discharge) or longer (as in ongoing seizures) period. The aEEG was recorded as a two channel EEG using gold caps electrode with BRM2 and BRM3 monitors (Neuron-spectrum-1digital neurophysiological system, Russia). Electrodes were placed on the scalp corresponding to the positions C3, P3, C4, and P4 of the international 10–20 system. A reference electrode was placed on the patients' forehead.

Background Patterns

Background patterns was distinguished into continuous normal voltage (CNV), discontinuous normal voltage (DC), continuous low voltage (CLV), burst suppression (BS), and flat trace (FT) according to the original publication. CNV was considered a normal background pattern, whereas all other background patterns were considered abnormal **(Bruns et al., 2021)**. The predominant background pattern was used for statistical analysis.

Lastly the studied patient were classified into tow sub groups ;

C- favorable aEEG which include Continuous normal voltage (CNV), discontinuous normal voltage (DC)

D- unfavorable aEEG which include continuous low voltage (CLV), burst suppression (BS), and flat trace (FT) **(Zafar et al., 2020)**

Electrographic or subclinical seizures:

Electrographic seizures were identified by an abrupt rise in the minimum amplitude (and the maximum amplitude). They were confirmed by examining the raw EEG for simultaneous seizure activity for at least 10 seconds (sharp waves, spikes, spike-slow wave).

According to their frequency of appearance we classified them as single seizure, repetitive seizures (3 or more seizures within the tracing), and electrical status (ES) (continuous seizure activity for more than 5min). According to these electrographic or subclinical seizures, patients were classified into group A (those with subclinical seizures) and group B (those without subclinical seizures) **(Bruns et al., 2019)**. Short term outcome was measured by: hospital stay, mortality, use of AED whether single, twice, or multiple, need for MV, duration on MV. Pediatric cerebral performance category (PCPC) scale was used to assess the general functional status and classify the state of disability among the studied patients **(Fiser, 1992)**

Statistical analysis

Utilizing SPSS v27 (IBM, Chicago, Illinois, United States of America), the statistical analysis was carried out. Histograms and the Shapiro-Wilks test were utilized to determine whether the data distribution in question was normal. The quantitative parametric data were expressed as the mean and standard deviation (SD), and they were analyzed using a paired T-test for comparisons between before and after, an unpaired T-test for comparisons between two groups, and an analysis of variance (ANOVA) test with a post hoc test (Tukey) for comparisons between three groups. The median and the interquartile range (IQR) were the two measures that were used to report the quantitative non-parametric data. A comparison between the two groups was made using the Mann Whitney test, and a comparison between each group was made using the Kruskal-Wallis test in conjunction with the Mann Whitney test. The Chi-square test was utilized to analyze the qualitative variables, which were presented in the form of frequency and percentage. To be considered statistically significant, a two-tailed P value that was lower than 0.05 was required.

Results:

Our results will be demonstrated in the following tables:

Table1: Patients characteristics, diagnosis and type of seizures of the studied patients

		N= 48
Age (month)		58.3 ± 33.3
Sex	**Male**	26(54.2%)
	Female	22(45.8%)
Weight (Kg)		17.2 ± 6.5
Length (cm)		102.6 ± 18.9
HC (cm)		48.2 ± 2.8
BMI (Kg/m^2)		15.8 ± 2.1
Causes of admission	**TBI**	25(52.1%)
	CNS infection	8(16.7%)
	Inborn error of metabolism	2(4.2%)
	ADEM	3(6.3%)

	Post arrest	5(10.4%)
	Post brain surgery	2(4.2%)
	Status epilepticus	3(6.3%)
Clinical characteristics	**GCS (total score 15)**	9.1 ± 2.8
	Fever	21(43.8%)
	HR (beat/min)	114.3 ± 19.9
	RR (cycle/min)	25.4 ± 9.7
	BP (SBP/DBP) (mmHg)	107.5 ± 17.6 / 64.5 ± 10.6
	Hospital stays (days)	7.0 (4.5 – 9.0)
	Need for MV	16(33.3%)
	Duration on MV (days) (n=16)	2.0 (1.0 – 8.0)
Type of seizures	**Clinical seizure**	9(18.8%)
	Subclinical seizure (based on amplitude aEEG)	10(20.8%)
	Combined	17(35.4%)
	No seizures	12(25.0%)

This table show Patients' characteristics, diagnosis and type of seizures of the studied patients

Table2: Laboratory, radiological and aEEG findings among the studied patients

		N=48
Laboratory findings	**RBG (mg/dL)**	119.8 ± 31.4
	Serum Na (mEq/L)	137.5 ± 4.9
	Serum K (mmoL/L)	4.2 ± 0.5
	Ca (mg/dL)	8.9 ± 0.5
	Mg (mg/dL)	1.8(1.7 – 2.0)
	Creatinine (mg/dL)	0.6 ± 0.1
	ALT (unit/L)	33.4 ± 10.2
	AST (unit/L)	37.0 ± 9.6
	WBC (Per µL)	11.9 ± 5.5
	Hb (gm/dL)	11.5 ± 1.5
	PLT (Per microliter)	234 (190 – 333)
Radiological findings	**Cerebral hemorrhage**	18(37.5%)
	Axonal injury	8(16.7%)

	Skull fracture	7(14.6%)
	Combined findings	7(14.6%)
	Normal	8(16.7%)
aEEG findings	**Timing from admission to aEEG recording (hour)**	9.5 ± 4.4
	Duration of recording (hour)	21.0 ± 5.4
	CNV	22(45.8%)
	DNV	16(33.3%)
	CLV	5(10.4%)
	Flat EEG	3(6.3%)
	Burst suppression	2(4.2%)

This table show Laboratory, radiological and aEEG findings in the studied patient.

Table 3: Comparison between favorable and un favorable group according to clinical course ,causes of admission, PCPC scale ,morbidity and mortality among the studied patients

		Favorable aEEG (n=37)	Unfavorable aEEG (n=11)	P
Clinical Course				
AED #	**Single**	**3(8.1%)**	0(0.0%)	**0.016***
	Twice	**3(8.1%)**	1(9.1%)	
	Multiple	6(16.2%)	7(63.6%)	
Patients need MV †		9(24.3%)	7(63.6%)	**0.027***
Duration on MV (days) (n=16) ##		2.0(1.0-4.0)	6.0(3.5-11.5)	**0.041***
Causes of admission				
TBI		20(54.1%)	5(45.5%)	0.416
CNS infection		7(18.9%)	1(9.1%)	
Inborn error of metabolism		2(5.4%)	0(0.0%)	
ADEM		2(5.4%)	1(9.1%)	
Post arrest		3(8.1%)	2(18.2%)	
Post brain surgery		2(5.4%)	0(0.0%)	
Status epilepticus		1(2.7%)	2(18.2%)	
PCPC scale				
Mild disability		20(54.1%)	2 (18.2%)	**0.001***

Moderate disability		13(35.1%)	1 (9.1%)	
Severe disability		2(5.4%)	4 (36.4%)	
Death		2(5.4%)	4 (36.4%)	
Morbidity and Mortality				
Hospital stays (days) ##		6.0(3.5 – 8.0)	9.5(7.25 – 17.0)	**0.013***
Mortality †		2(5.4%)	4(36.4%)	**0.019***
Condition on discharge	**Motor sequel**	7(18.9%)	7(63.6%)	**0.016***
	Speech	13(35.1%)	2(18.2%)	
	Cognitive function	17(45.9%)	2(18.2%)	

Children with unfavorable aEEG showed significantly higher mortality (P=0.019), significantly higher median days of hospital stay (P=0.013), and significantly higher multiple AED (P=0.016). Sixteen children (33.3%) needed MV with significantly higher need for MV (P=0.027) and significantly higher median days on MV (P=0.041) among children with unfavourable aEEG. There was insignificant difference between children with or without favourable aEEG regarding the causes of admission. Severe disability, death and motor sequel on discharge were significantly higher among children with unfavorable aEEG (P<0.05).

Table 4: Comparison for outcomes according to type of seizures among the studied patients

outcomes		**Type of seizures (n= 36)**			**P**
		Clinical (n=9)	**Subclinical (n=10)**	**Combined (n=17)**	
AED †	**Single**	1(11.1%)	1(10.0%)	1(5.9%)	0.429
	Twice	1(11.1%)	2(20.0%)	1(5.9%)	
	Multiple	1(11.1%)	5(50.0%)	7(41.2%)	
Patients need MV †		3(33.3%)	8(80.0%)	5(29.4%)	**0.028***
Duration on MV (days) # (n=16)		2.0(1.0)	5.5(4.25 – 6.75)	4.0(3.25 – 4.75)	**0.019***
Hospital stays (days) #		5.5(4.25 – 8.0)	8.5(8.0 – 9.5)	7.0(6.0 – 9.0)	**0.045***
Mortality †		0 (0.0%)	4 (40.0%)	2 (11.8%)	**0.049***

Condition on discharge	**Motor sequel**	1(11.1%)	6(60.0%)	2(11.8%)	**0.023***
	Speech	6(66.7%)	1(10.0%)	8(47.1%)	
	Cognitive function	2(22.2%)	3(30.0%)	7(41.2%)	

Children with subclinical seizures had significantly higher mortality (P=0.049), significantly higher median days of hospital stay (P=0.045), significantly higher need for MV (P=0.028), and significantly higher median days on MV (P=0.019). Children with subclinical seizures showed significantly higher motor sequel on discharge (P=0.023). **Table 4**

Discussion

The neurological assessment of pediatrics intensive care patients continues to be challenging for nurses and physicians. The aEEG monitor is easy to set up and quickly available, even out of care hours, unlike the standard EEG in many centers. This study aimed to assess the diagnostic and prognostic value of aEEG neuromonitoring, and its utility for seizure detection to help in better management and to recognize unnecessary indication.

Our study analyzed non-neonates aged from 2 month to 14 years who were admitted in PICU at Al-Hussien hospital for whom aEEG were done.

In the present study, 48 children fulfilling the inclusion criteria with mean age 58.3 ± 33.3 months ranged from 70 days to 13 years. More than half of them (54.2%) were males, the mean weight was 17.2 ± 6.5 kg ranged from 4.5 – 39 kg, the mean length was 102.6 ± 18.9 cm ranged from 54 – 135 cm, the mean HC was 48.2 ± 2.8 cm ranged from 38 – 51 cm, and the mean BMI was 15.8 ± 2.1ranged from 6.7 – 21.4 Kg/m2.

Zaitoun et al. (2022) performed a prospective cohort study on 50 children discharged from the PICU. They showed that mean age was 6.08 ± 4.05 years (range: 2–16, 54% [27/50] male) **(Zaitoun et al., 2022).**

In the current study, causes of admission among the studied patients were TBI (the most common cause, 52.1%), CNS infection (16.7%), post arrest(10.4%), ADEM (6.3%)status epilepticus(6.3%) inborn error of metabolism(4.2%)and post brain surgery(4.2%).

This was inconsistent to the study of **El-Anwar et al. (2023)** in which the most common indication for admission were pneumonia, post-operative pediatric surgery, heart failure, peritoneal dialysis and sepsis . **(El-Anwar et al., 2023).**

In our result, the mean GCS was 9.1 ± 2.8 ranged from 3 – 14, 43.8% presented with fever, the mean HR was 114.3 ± 19.9 ranged from 40 – 161 beat/minute, the mean RR was 25.4 ± 9.7 ranged from 14 – 54 cycle/minute, and the mean SBP/DBP was 107.5 ± 17.6 / 64.5 ± 10.6 ranged from 107.5 ± 17.6 / 64.5 ± 10.6 mmHg. Regarding their days of hospital stay, the median was 7 [4.5 – 9] ranged from 2 – 25 days, 16 patients representing one third of the total sample required MV with a median duration of MV of 2 [1 – 8] ranged from 3 hours to 25 days. In agreement with our results **Meligy et al. (2017)** performed a prospective observational study. They showed that 893 children were admitted and 293 were mechanically ventilated. The incidence of utilizing MV in children was 32.8%.

In the present study, seizures were recognized in 36 (75%) children while 12 (25%) children did not experience seizures. Combined seizures were the most frequent in 17 children (35.4%), followed by subclinical seizures in 10 (20.8%) children, then clinical seizures in 9 (18.8%) children. In line with our result, **MacDarby et al. (2023)** enrolled 120 patients (2 months to 16 years old) were chosen from a database of formal 10–20 system, 21-lead electroencephalography recordings (2012–2020), comprising 30 patients with seizures (25%) and 90 without (75%)

Regarding laboratory results of our patients, the mean Hb was 11.5 ± 1.5 ranged from 8–16 gm/dL, the arterial blood gas revealed an average PH of 7.36±0.10, the CRP ranged between 0.4 and 148 mg/dl, and the ESR ranged between 4 and 120. WBCs was 7.92±2.90, Platelets were 285.84±98.49, total calcium was 8.65±0.88, serum potassium was 3.62±0.88 among children with convulsive SE**.** In line with our result about seizures, **Elhady et al. (2021)** showed that the mean hemoglobin level was 10.90±1.86 mg/dl, arterial blood gas revealed average PH of 7.36±0.10, acute phase reactant was elevated in some cases: CRP ranged between 0.4-148 mg/dl and ESR ranged between 4-120. WBCs was 7.92±2.90, Platelets were 285.84±98.49, total calcium was 8.65±0.88, serum potassium was 3.62±0.88 among children with convulsive SE .

The most frequent radiological CT findings were cerebral hemorrhage in 18 patients (37.5%) including [5 intracerebral, 2 intraventricular, 4 subarachnoid, and 7 subdural] followed by axonal injury (16.7%), and skull fracture in 7 patients (14.6%) including [3 temporal, 3 frontal, and one basal] while multiple findings were detected in 7 patients (14.6%) and normal initial CT brain were found in 8 patients (16.7%). Similar result were reported by **Vaewpanich and Reuter-Ric, 2016 in which the main CT finding were**

subdural hematoma ,diffuse axonal injury and skull fracture.

In our result, the mean timing from admission to aEEG recording was 9.5 ± 4.4h ranged from 4 – 24 hours and the mean duration of recording was 21.0 ± 5.4 ranged from 6 – 24 hours.

Various studies exhibit variations in the timing and duration of aEEG. **You et al**. in their study Initiated aEEG monitoring for one week following the onset of coma, with a median time of 7.5 days (ranging from 7 to 14 days), and a duration of 8.5 hours (median of 6 to 12 hours). **(You et al., 2018)**.

In the present study, 37 (77.1%) children showed favorable aEEG, and 11 (22.9%) children showed unfavorable aEEG. Children with unfavorable aEEG showed significantly higher mortality (P=0.019), significantly higher median days of hospital stay (P=0.013), and significantly higher multiple AED (P=0.016)and good neurological outcome. Sixteen children (33.3%) needed MV with significantly higher need for MV (P=0.027) and significantly higher median days on MV (P=0.041) and poor neurological outcome among children with unfavorable aEEG.

In agreement with our results about EEG findings, **(Bruns et al., 2019)**. Among the remaining 24 children, 13 (54%) exhibited normal background patterns both at the start and end of tracing, while 2 (8%) demonstrated normalization. Out of the total number of children, 2 (8%) exhibited a consistent, but mild, abnormality, 3 (13%) experienced a worsening of their condition to a severe level, and 1 (4%) showed improvement without reaching a normal state**(Bruns et al., 2019).**

This agreed with the results of a meta-analysis by **Burns et al. (2021)** who showed that normal background patterns of aEEG and normalization are associated with better outcomes in critically ill children **(Bruns et al., 2021)**

Our findings are largely consistent with **You et al, 2018**, who evaluated the prognostic value of aEEG in patients with coma after acute brain injury. They demonstrated that a favorable aEEG pattern (CNV) was associated with a good 6-month neurological outcome with a sensitivity of 93.6% and specificity of 85.2%. An unfavorable aEEG pattern (CLV, BS, or FT) was indicative of a poor neurological outcome after 6 months with sensitivity and specificity of 76.5% and 100%. However, the intermediate pattern (DNV) showed limited predictive value for both good and poor outcomes.

In the present study, the PCPC scale where 45.8% had mild disability, 29.2% had moderate disability, and 12.5% had severe disability while death occurred in 6 children (12.5%).

Chahine et al. (2023) performed a retrospective review of neonates and children undergoing ECMO and monitored with aEEG. Amplitude-integrated EEG was summarized as an aEEG background score determined within the first 24 hours of ECMO and divided into 3-hour periods. Screening for electrical seizures was performed throughout the full ECMO duration. Neurologic outcome was defined by the pediatric cerebral performance category score at hospital discharge. They showed that Thirty-two patients had a favorable neurologic outcome and 41 had an unfavorable neurologic outcome group at hospital discharge.

Our study showed that, severe disability and death were significantly higher among children with unfavorable aEEG. This agree with **Kravljanac et al. (2011)** enrolled 302 children (age 2 months to less than 18 years; mean age ± SD 4.7 ± 4.2 years) with 489 episodes of status epilepticus (SE). They showed that neurologic sequels occurred in 12.9% of children with SE and mortality rate was 9.3% **(Kravljanac et al., 2011)**

Conclusion: Implementing early aEEG monitoring can assist intensive care unit (ICU) providers in directing clinical care and confirmation of suspected seizure and detection of non-convulsive seizure and therapy guidance. Children with favorable aEEG associated with lower mortality rate, median days of hospital stay, less days on MV , need less anti-epileptic drug and less motor sequel on discharge compared to unfavorable aEEG.

Authors' contributions:

AAE conceived and supervised the study; AMD was responsible for data collection. SMH and AYA analyzed and interpreted the data. All authors provided comments on the manuscript at various stages of development. All authors read and approved the final manuscript.

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