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Review Article

An overview of an amplitude integrated EEG

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Amplitude integrated EEG (aEEG) has been used widely in developed countries for years. It was initially developed by Maynard and Prior[1] in the early 1970s and later adapted for neonatal use by Hellstrom-Westas and Svenningsen[2]. It is especially used for monitoring term newborns after having survived from birth asphyxia.

During the last decade neonatal health care in Indonesia has developed. Monitoring of physiological parameters such as ECG, heart rate, blood pressure, oxygen saturation and temperature have been integrated in our neonatal intensive care unit but equipments like continuous EEG monitoring and aEEG to evaluate brain function have not been well-known among our neonatologists and pediatricians. The consequence is the decrease of infant mortality was not associated with the improvement of quality of life of the survivors due to neurodevelopmental problems caused by various diseases during neonatal period. In the future, it can be prevented by using brain function monitoring in high risk newborn for neurodevelopmental problem in conditions such as hypoxic-ischemic encephalopathy (HIE), prematurity, neonatal seizures, central nervous system infection, metabolic disorders, intraventricular or intracranial bleeding and brain malformation. This article gives an overview about aEEG and its role in newborn.

EEG: Definition, mechanism, and assessment

The term amplitude integrated EEG (aEEG) is currently preferred to denote a method for electrocortical whereas cerebral function monitoring (CFM) is used to refer specific equipment and it is specially designed to be operated in an intensive care unit.[3]

The EEG signal for the single channel aEEG is usually recorded from one pair of biparietally placed electrodes (corresponding to P3 and P4 according to the international EEG 10-20 classification). The use of single channel does not give information about hemispheric asymmetry while the use of two channels (bilateral frontoparietal electrodes) may be clinically significant, especially in children with a unilateral brain lesion.[3]

An aEEG uses both thin subdermal needle electrodes and disc and hydrogel electrodes. The signal from the equipment is amplified and passed through an asymmetrical band pass filter, which strongly attenuated activity below 2 Hz and above 15 Hz in order to minimize artefacts from such sources as sweating, muscle activity, ECG and other electrical interference. The signal is recorded on paper with a semilogarithmic scale at slow speed (6 cm/h) at the bed side. The band width in the output reflects variations in minimum and maximum EEG amplitude, both of

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which depend on the duration and severity of illness of the newborn infant.[3]

Assesment of the EEG recording should start with the background pattern, the presence or absence of seizure activity then sleep-wake cycle.

1. Background patterns

The classification of background patterns distinguishes five different patterns in full term infants (**Figure 1**).[4,5]

Figure 1. Different background patterns: (a) Continuous normal voltage, CNV. (b) Discontinuous normal voltage, DNV. (c) Burst suppression, BS. (d) Continuous low voltage, CLV. (e) Flat trace, FT.

(a) Continuous normal voltage pattern is a continuous trace with a voltage of 10-25 (-50) μv (figure 1A)

(b) Discontinuous normal voltage pattern is a discontinuous trace, where the low voltage is predominantly above 5 μv (no burst suppression) (figure1B)

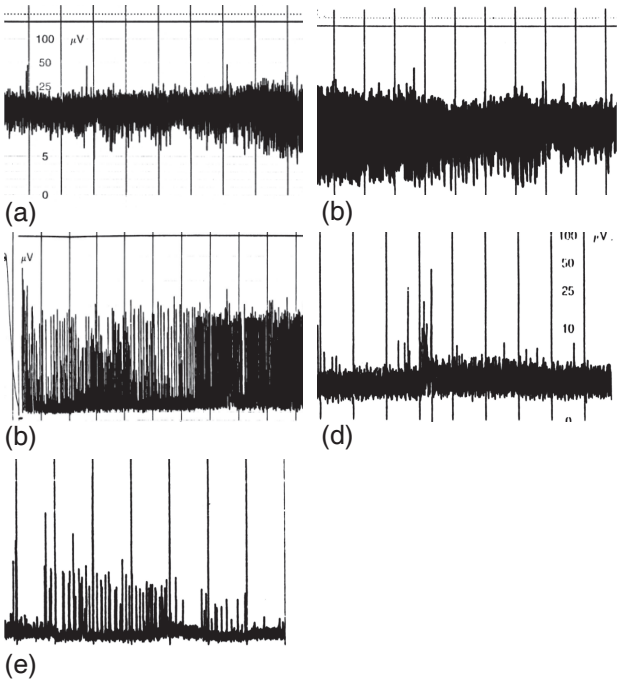

Figure 1. Different background patterns: (a) Continuous normal voltage, CNV. (b) Discontinuous normal voltage, DNV. (c) Burst suppression, BS. (d) Continuous low voltage, CLV. (e) Flat trace, FT.

(c) Discontinuous background pattern (burst suppression) : periods of low voltage (inactivity) intermixed with burst of high amplitude (figure 1C)

(d) Continuous background pattern of very low voltage (around or below 5 μv) (figure 1D)

(e) Very low voltage, mainly inactive trace with activity below 5 μv (flat trace) (figure 1E)

Both the patterns and the voltage should be considered to avoid incorrect classification of background pattern.

2. Seizure activity

Seizure are recognizable on the EEG as rapid rise of both the lower and the upper margins of tracing (reflecting

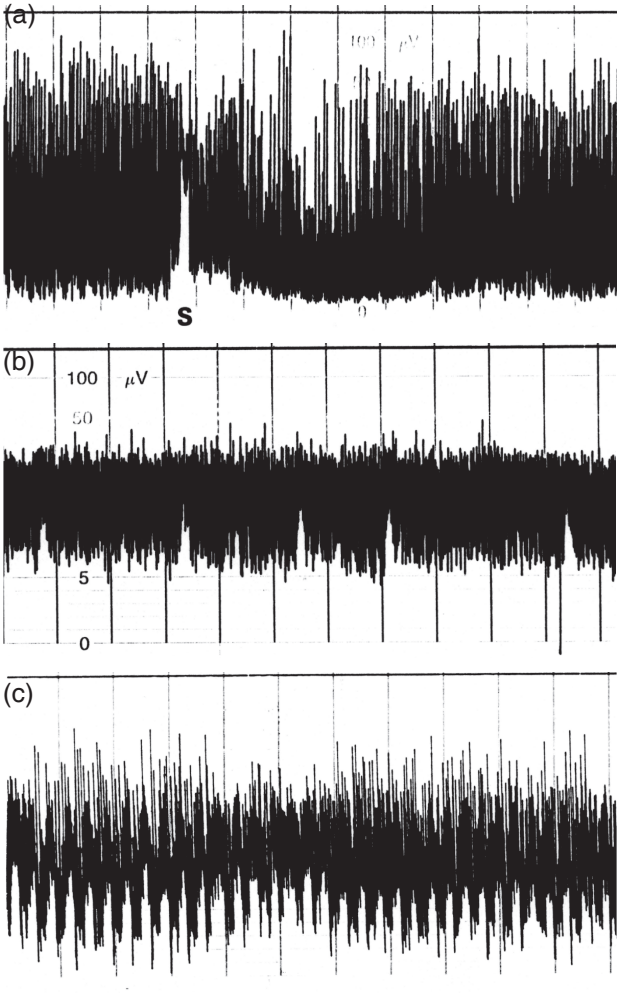

Figure 2. (a) Single seizure (SS), (b) Repetitive seizures (RS), (c) Status epilepticus (SE)

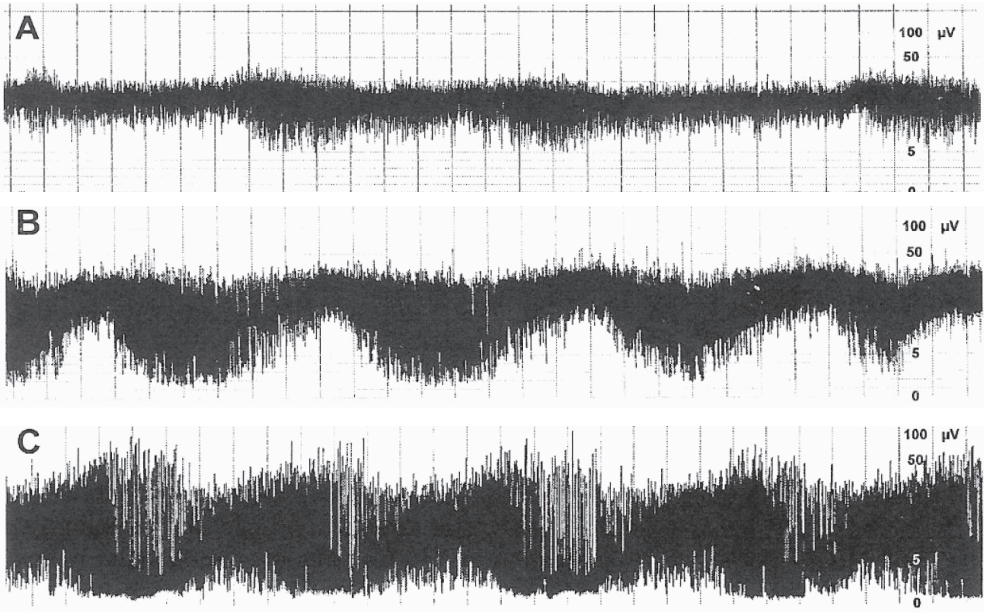

Figure 3. (a) Normal SWC (b) Abnormal SWC

the increase in EEG voltage). The trace returns to the previous appearance when the seizure activity stops. Epilepticform activity (characteristic pattern, with increased amplitude during epileptic seizure activity and lower voltage in interictal period) is classified as : [4]

Figure 2. (a) Single seizure (SS), (b) Repetitive seizures (RS), (c) Status epilepticus (SE)

(a) Single seizure (SS) (figure 2A)
(b) Repetitive seizures (RS) : $\geq$3 discharges during 30 minutes period (figure 2B)
(c) Status epilepticus (SE) : "sawtooth pattern" (figure 2C)

3. Sleep-wake cycle (SWC)

SWC is recognized as periodic changes in bandwidth of the aEEG tracing.[6] During wakefulness/active sleep the band width of the tracing is narrower, while during quiet sleep the bandwidth is broader.[7] Diagnosis of SWC was made when at least three consecutive cycles is seen on aEEG tracing of five hours period.

SWC patterns are qualitatively classified with regard to the background pattern on which they presented: [8] (**Figure 3**)

(a) Normal SWC: Presence of SWC on a CNV background pattern with the lower margin of the narrowest band width of clearly >5 μv, while the lower margin of the broadest band width is either above 5 μv (figure 3a) or below 5 μv (suboptimal variant of normal SWC, figure 3b)
(b) Abnormal SWC: Presence of SWC on a discontinuous background pattern, with the lower margin of narrowest and broadest band width is continuously below 5 μv. (figure 3c)

Indication of aEEG

Neonates, especially extremely low birth weight infants, are prone to many complications that occur during the newborn period that may result in clinically significant neurologic injury, including intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), hypoxic-ischemic encephalopathy (HIE), seizures and meningitis. Such problems may, in turn, lead to developmental delay and cerebral palsy.[9] Nowadays CFM has been used increasingly in some neonatal centers to follow hypoxic-ischemic encephalopathy brain injury, to detect seizures, to monitor the effects of different interventions and events on neonatal cerebral activity, and to predict future outcome.[3,7] Neonatal aEEG recorded by CFM has also been correlated with gestational age and maturity of preterm and term infants electrical brain activity.[7,10]

Clinical application for aEEG

1. Hypoxic ischemic encephalopathy

Hypoxic-ischemic encephalopathy (HIE) which is still experienced by three to four infants per 1000 live term births is the most common cause of seizures in the newborn period, and is associated with death or adverse neurodevelopmental outcome.[11] Most of the aEEG studies were focused on HIE. Amplitude integrated EEG monitoring of neonates with HIE has been used for assessment of aEEG background activity, early evaluation of brain function, detection of seizures, evaluation of the effect of anticonvulsive drugs, selection of patients for neuroprotective intervention and prediction of neurodevelopmental outcome as early as the first hours after birth. [5,11]

Amplitude integrated EEG can be used to assess the prognostic value at three and six hours after birth to select those infants who could benefit from post asphyxiated intervention.[5] Background pattern such as BS together with FT and CLV have been used to predict poor outcome (cerebral palsy or death) at three hours and six hours after birth.[12]

Toet *et al*[12] found that positive predictive value at six hours after birth was 86% and negative predictive value was 91%. The positive predictive value at three hours (78%) turned to be lower than the negative predictive value (84%).

CNV pattern at three hours is almost invariably a good prognostic indicator of normal outcome. DNV pattern was a good predictor of normal outcome as well, but the number of cases in this group is still limited. FT and CLV at three or six hours indicate a poor prognosis.[12]

Previous studies have already shown that aEEG can predict outcome accurately at six hours of age following perinatal asphyxia. Both studies showed a PPV of 86% and 84% respectively and a NPV of 96% and 91%, respectively.[13,14] Both positive and negative predictive values were slightly lower when aEEG assessed at three rather than at six hours after birth, but they were still considered sufficiently high to use this technique for early selection to hypothermia intervention studies.[5]

Sleep characteristics have been used for prediction of neurodevelopmental outcome. Sleep wake cycling is present in healthy term newborns and is sign of brain integrity. In newborn with HIE sleep organization can be altered.

Ter Horst's study[15] of 30 full term newborns with HIE found normal outcome of sleep-wake cycling in 10/13 newborns, mild abnormal outcome in 3/6 newborns, and none of 11 had an abnormal outcome or died.

The present aEEG study confirmed that the presence of normal SWC early after birth in a valuable predictor for good neurodevelopmental outcome in fullterm infants with HIE. Cohort study of newborns showed that SWC was significantly more often present in surviving infants than in those who died in the neonatal period.[8]

The presence of normal SWC pattern early after birth noted on aEEG is considered a good prognostic sign in full-term infants with HIE. An earlier onset of SWC was related to better outcome. Every one hour increase of time interval between birth and onset of SWC was associated with a 0.96-fold decrease in the odds of good outcome (95% CI:0.938-0.981;P<0.001, logistic regression).[8]

The data clearly demonstrated, that an earlier onset of SWC was related to a better neurodevelopmental outcome. Time of onset of 36 hours after birth was found to be the most valuable cutt-off point for predicting neurodevelopmental outcome.[8]

2. Neonatal seizures

The incidence of neonatal seizures is 3.5/1000 live birth.[11] Clinical manifestations of neonatal convulsions are very diverse and not always easy to recognize, especially when they are subtle. Without the use of continuous monitoring, subclinical seizure discharges will not be detected. Continuous EEG monitoring often reveals electroclinical (seizure discharges without clinical manifestations), especially following initiation of therapy for clinical seizure.[16-19]

Epileptic seizures are common in full-term infants admitted with HIE. Several studies have shown that, although the initial seizures are often clinical, subsequent seizures after administration of the first anti-epileptic drug are often subclinical. This refers to as electroclinical dissociation or "uncoupling". Sher *et al*[17] found that 58% of the infants with seizures persisting after treatment with phenobarbitone or phenytoin showed uncoupling of electrical and clinical seizures.

Amplitude integrated electroencephalography is used for monitoring seizure activity and response to treatment. The clinical diagnosis of seizures during the recording had a good correlation with amplitude-integrated electroencephalographic seizures. During the recordings, no infant with overt clinical seizures had normal aEEG, 97% had clear electrical seizures. Fifty-nine percent of infants with subtle clinical seizures had clear aEEG seizures. Fifteen percent of these high risk infants with no abnormal clinical signs had clear amplitude-integrated electroencephalographic seizures. Moreover, considering that aEEG detects more reliably generalized seizures than short, focal and low amplitude seizures, the percentage of silent seizures in high risk neonates might even be higher.[20]

According to Shany *et al*[20] the single channel CFM is not a suitable tool for the diagnosis of seizure in babies, particularly when used by non-expert. Their evaluation shows that it is not sensitive enough for clinical use. If seizures are suspected, a full EEG should be obtained and interpreted by trained neonatal EEG experts. In a unit with a CFM, a simultaneous EEG tracing may show that, in an individual baby, seizures can be detected. When this is known to be the case, the CFM is useful tool for monitoring the response to treatment. The newer CFMs offer the capability to study up to four channels and to review the raw EEG signal at the bed side. These monitors may perform better in asimilarly rigorous analysis in which the original CFM failed.

Comparison between EEG and aEEG

It has been claimed that aEEG , based on one channel EEG, has a very high concordance with multichannel standard EEG.[3,15] For a standard neonatal EEG, 9 electrodes are used to produce 14 bipolar derivations (channel) of EEG together with channels for eye movement, muscle activity and RCG. The standard duration of recording is about 30 minutes.[21]

In the study by Toet *et al*[22], interobservers agreement for both aEEG and standard EEG was obtained in the majority of traces. They found that PPV of severely abnormal aEEG background pattern (FT<CLV<BS) was 100% for severely abnormal EEG (excessive discontinuity, burst suppression, low voltage undifferentiated, no activity). A CNV pattern on aEEG corresponded well with normal or depressed background pattern on standard EEG. Correlation of ictal activity on standard EEG and ictal activity (SS,RS,SE) on aEEG was 80%. In two traces the ictal activity was missed, and both patients already received anti-epileptic drugs for ictal activity, seen on the aEEG, before the EEG was recorded. One would expect that very short, low voltage and certain focal ictal activity would be missed on aEEG. And if ictal activity was missed on aEEG during the period of simultaneous recording, it was picked up somewhere on the aEEG trace before or after the standard EEG was done in all patients. Thus monitoring for long period of time with aEEG, in contrast with usually short (30 minutes) period of standard EEG recording, compensates for not detecting all ictal discharges.[22]

Amplitude integrated EEG appeared to be a reliable tool for monitoring both background pattern (especially normal and extremely abnormal) and ictal activity. Due to long period of registration, aEEG is especially useful to evaluate changes in background pattern overtime and detect the occurrence of seizures.[22]

Prognostic factors for postnatal epilepsy

The incidence of postnatal epilepsy (PNE) following neonatal seizures reported in the literature is about 20-50%.[23] These data are based on overt clinical seizures subsequently confirmed by EEG. Most studies are based on clinical diagnosis of seizures. Brunquell *et al*[24] reported 21% PNE among 77 survivors with a significantly higher prevalence of PNE in those with subtle and generalized tonic seizures. In another study using continuous aEEG monitoring, both clinical and subclinical neonatal seizure discharged were treated. In this study subsequent PNE was found in only 8.3% of the children.[14] This cohort consisted of both preterm and full-term infants. The incidence of PNE will depend on both the maturity of the infant and the underlying etiology.[14] This results is almost the same as those studied by Toet *et al*[25] which showed low incidence of PNE (9.4%) in their population of full-term infants, who received treatment for both clinical and subclinical seizures.

Clancy *et al*[23] found that PNE was significantly related to CP, mental retardation and more than 10 electrographic seizures per hour detected in the neonatal EEG recorded at random. Apart from the multifactorial etiology of neonatal seizures the number of AEDs needed to control the neonatal seizures was associated with the risk of developing PNE. Duration of seizure activity also appeared to be of importance as only two of our infants developed PNE following seizure control within 48 hours after birth.[26]

Advantage

One of the great advantages of CFM is its simplicity and the possibility of quick on-line interpretation and analysis of overall brain function.[12] The system of aEEG also has been shown to be a user friendly technique in high risk newborn infants, based on pattern recognition and aEEG has a very high concordance with standard EEG.[3]

The aEEG gives a long-term, bedside, on-line, trend recording of cerebral electric activity, readily available at any time of the day. Although it does not give information about localization, changes in background activity and seizure activity are easy to identify.[12] Although standard EEG is widely applied, aEEG is more easily to apply and available especially during night time, and especially suitable for continuous monitoring.[2] Due to long period of registration, aEEG is especially useful to evaluate changes in backgrounds pattern over time and detect the occurrence of seizures.[22]

The method of an aEEG is easy to apply and to interpret and the attending neonatal intensive care unit (NICU) staff can continuously follow changes in the electrocortical background and responses to medical interventions.[26]

CFM is a bedside, readily available, user-friendly device for continuous recording of aEEG data. The compressed form of this recording allows evaluation of baseline brain wave activity in the underlying brain regions that receive the bulk of cerebral blood flow. CFM has been used increasingly in some neonatal centers to follow hypoxic ischemic brain injury, detect seizures, monitor the effects of different interventions and events on neonatal cerebral activity and predict future outcome.[27] Some investigators recommend to use aEEG as a monitoring device, and to perform intermittent standard EEG, whenever there is any doubt about the classification of the aEEG.[22]

Disadvantage

Seizure may only be identified if they are sufficiently prolonged, more than 2-3 minutes, shorter lasting discharge may be missed since the CFM records at a very low speed. CFM was also not reliable for the diagnosis of seizure in neonates when interpreted by the non-expert user.[20]

Owing to the nature of the single channel recording, it is not surprising that very brief seizure activity, as well as focal seizure activity, may be missed. aEEG cannot provide information on cerebral activity outside the pick-up area, background activity and generalized seizure activity can be easily identified.[22] It should be remembered that some manipulations by the nurse may change the aEEG which could be mistaken for an electrical discharge.[22]

Rennie *et al*[28] stated that the single channel CFM is not a suitable tool for the diagnosis of seizures in babies, particularly when used by non-expert. Their evaluation showed that it is not sensitive enough for clinical use. If seizures are suspected, a full EEG should be obtained and interpreted by trained neonatal experts. In a unit with a CFM, a simultaneous EEG tracing may show that, in an individual baby, seizures can be detected.

In cases of focal seizures, aEEG detected only 70% of electroencephalography confirmed seizures.[20] Moreover, considering that aEEG detects more reliably generalized seizures then short, focal, and low amplitude ones, the percentage of silent seizures in high risk neonates might even be higher.[20]

Conclusion

EEG or amplitude integrated EEG (aEEG) provides informations about brain function. Since continuous EEG are expensive, need more skills to do and it is also difficult to interpret in neonatal intensive care setting, an aEEG could be an alternative to evaluate brain function in neonates, provides informations

about functional integrity of the brain and can be used immediately after admission or even in the referring hospital.

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