Sevilay Topcuoglu*, Leyla Daban Kolsuz, Tugba Gursoy, Fahri Ovali and Guner Karatekin

Effects of preeclampsia on the amplitude integrated electroencephalography activity in preterm infants

DOI 10.1515/jpm-2015-0096

Received March 17, 2015. Accepted June 17, 2015. Previously published online July 15, 2015.

Abstract

Objective: Preeclampsia leads to chronic intrauterine hypoxia by interfering with placental blood supply. The aim of this study was to investigate whether preeclampsia exposure has an influence on the central nervous system of infants, as monitored by amplitude integrated electroencephalography (aEEG).

Methods: We recruited 52 infants with gestational age between 30 and 34 weeks. Twenty-seven infants were born to preeclamptic mothers, and 25 gestational age-matched infants whose mothers were healthy were enrolled as a control group. aEEG recordings were performed between 24 and 48 h of life using a cerebral function monitor (CFM) (Olympic Brainz monitor). Along with aEEG, middle cerebral artery (MCA) blood flow velocities (BFV) were measured using Doppler ultrasound.

Results: The duration of quiet sleep was significantly shorter ($P=0.001$), and Burdjalov score was lower ($P=0.04$) in the preeclampsia group. However, there was no change in MCA BFV in this group.

Conclusions: Preeclampsia altered cerebral electrical activity of premature infants born to preeclamptic mothers.

Keywords: aEEG; cerebral blood flow; preeclampsia; preterm.

Introduction

Preeclampsia is a common gestational pathology that often leads to premature birth and intrauterine growth retardation. By interfering with placental blood supply, it leads to chronic intrauterine hypoxia that may decelerate fetal brain growth and can cause ischemic brain damage [1]. According to Cheng et al. [2], preeclampsia is a risk factor for delayed mental developmental index scores at 24 months of age, independent from complications of prematurity.

The amplitude-integrated electroencephalogram (aEEG) is a simple bedside tool that assesses and monitors the neurological condition of the infant. In recent years, aEEG monitoring has been increasingly used in neonatology units. There are several studies pertaining to normative aEEG findings of premature babies according to gestational and postmenstrual age [3–5]. It has been widely used to select infants for early intervention following perinatal asphyxia [6, 7]. Besides early identification of acute brain injury, aEEG was shown to be helpful in predicting the neurological outcome of preterms with intraventricular hemorrhage [8, 9]. In a recent study, Wikström et al. [10] indicated that in very preterm infants, early aEEG monitoring at 24–48 postnatal hours is predictive of long-term outcome with 80% accuracy.

There is no study that assesses the effects of preeclampsia on brain development in the first days of life. Thus, the aim of this study was to investigate whether aEEG tracings of preterm babies exposed to preeclampsia differ from unexposed premature infants.

Patients and methods

Patients

This study was conducted at the Neonatology Unit of Zeynep Kamil Maternity and Children's Training and Research Hospital, Istanbul, Turkey. Twenty-seven infants born to preeclamptic mothers with gestational ages ranging between 30 and 34 weeks were prospectively enrolled in the study and constituted the study group. The

*Corresponding author: Sevilay Topcuoglu, Neonatal Intensive Care Unit, Zeynep Kamil Maternity and Children's Training and Research Hospital, Opr. Dr. Burhaneddin Ustunel Cad. No: 10, Uskudar, Istanbul, Turkey, Phone: +90-216-391-0680 ext. 1105, Fax: +90-216-391-0690, E-mail: sevilaymd@yahoo.com

Leyla Daban Kolsuz, Fahri Ovali and Guner Karatekin: Neonatal Intensive Care Unit, Zeynep Kamil Maternity and Children's Training and Research Hospital, Istanbul, Turkey

Tugba Gursoy: Koc University, School of Medicine, Istanbul, Turkey

control group consisted of 25 gestational age-matched infants whose mothers did not have any sign of preeclampsia and were not treated with MgSO₄. Gestational age was determined by the first day of the last menstrual period or prenatal ultrasound performed at 17–18 weeks. Preeclampsia was diagnosed using the National Institutes of Health's clinical criteria (proteinuria >300 mg/day and diastolic blood pressure >90 mm Hg in two measurements 4 h apart, occurring after the 20th week of pregnancy and regressing after delivery) [1].

Patients with the following conditions were excluded: presence of chromosomal or congenital malformation, perinatal asphyxia, intra-ventricular hemorrhage, presence of any cerebral anomaly detected in cranial ultrasound, chorioamnionitis, hemodynamically significant patent ductus arteriosus, hypotension, and seizures. Patients treated with sedative or analgesic medications were also excluded. Cranial ultrasonography was performed on all infants before aEEG evaluation.

Gestational age, birth weight, route of delivery, gender, cranial ultrasound findings, medications, clinical condition, magnesium level at the 24th hour of life, Doppler ultrasound measurements of middle cerebral artery (MCA) blood flows, and aEEG findings were recorded for all patients. The study was approved by the Zeynep Kamil Maternity and Children's Training and Research Hospital Ethics Committee, and written informed consent was obtained from the parents of each patient before recruitment.

aEEG recordings

aEEG recordings were performed within 24–48 h of life using the cerebral function monitor (CFM) (Olympic Brainz monitor; Natus Medical Incorporated, San Carlos, CA, USA), a two-channel bedside monitor that uses five electrodes to monitor electrical brain activity. Ag/AgCl-coated electrodes (disc electrode, Nihon Kohden Corp, Tokyo, Japan) filled with transmitter paste (Konix, EEG paste, Istanbul, Turkey) were used. A reference electrode was placed over the frontal midline region of the scalp, and an aEEG was used to record the two parietal and two frontal electrodes. Transparent film (Tegaderm Film, 3 M Health Care, Neuss, Germany) and head caps were used to stabilize the electrodes. The sweep speed of the aEEG was 6 cm/h. The quality of the recordings was monitored by continuous impedance tracing, and aEEG tracings with an impedance of ≥ 15 k Ω were not assessed. Continuous CFM recording was performed on each patient for at least 6 h without any artefacts or interruption. All aEEG records were performed by the same attending neonatologist (ST).

Interpretation of aEEG tracings

The aEEG tracings were assessed by a clinician blinded to the clinical data of the patients (LDK). Analysis of the aEEG recordings was carried out quantitatively by the method described by Burdjalov et al. [3]. Continuity, cycling, lower border amplitude, and bandwidth span of the aEEG tracings were determined to compute the Burdjalov scores of each patient. With this score, low span (<15 μ V), moderate span (15–20 μ V), and high span (>20 μ V) bandwidth can be distinguished.

In addition to Burdjalov scores, quiet sleep lower border (the minimum cerebral activity during quiet sleep), active sleep lower border (the amplitude of lower margin during active sleep or wakefulness), bandwidth spans of quiet and active sleep, and duration of quiet sleep variables were evaluated in terms of their relationships to preeclampsia exposure.

Doppler ultrasound

Middle cerebral artery blood flow velocities (BFV) were measured with Doppler ultrasound scanning (Philips EnVisor C HD, Royal Philips Electronics, Amsterdam, The Netherlands) just before the aEEG recordings started. After an initial 2-dimensional vessel visualization, BFV were measured by Doppler ultrasound scanning as the infants lay quietly in the supine position.

The right MCA was visualized in the axial plane through the right temporal window. Velocities were measured from the proximal portion of the vessel three times during a minimum of five cardiac cycles with an isonation angle of <10°. The highest value in each set of measurements was taken for the study. Doppler ultrasound scanning measurements of each patient were performed by a single operator (ST).

Data analysis

We used the SPSS software for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA) for statistical analyses. The variables were investigated using visual (histograms, probability plots) and analytical methods (Shapiro-Wilk test) to determine if they are normally distributed. Parametric results were expressed as means $\pm$ SD. Median values of nonparametric tests were reported with interquartile range. Non-normally distributed numerical and ordinal variables were compared with the Mann-Whitney *U*-test. The Student's *t*-test was performed for comparison of parametric variables. The χ^2 -test was used to compare the categorical variables, and $P < 0.05$ was considered to indicate a significant difference.

Results

Clinical characteristics

The demographic and clinical characteristics of the infants are given in Table 1. Birth weights of the infants in the study group were significantly lower than the control group ($P = 0.001$). Five (20%) patients in each group received surfactant therapy for respiratory distress syndrome. All of the patients had been extubated before aEEG recordings and Doppler ultrasound measurements. Five patients from the preeclampsia group and nine patients from the control group were on continuous positive airway pressure during measurements.

aEEG analysis and MCA BFV

The aEEG analysis and MCA BFV measurements of infants are shown in Table 2. Analysis of covariance with birth weight as covariate revealed that preeclampsia group had a significantly lower Burdjalov score ($P = 0.04$) and shorter duration of quiet sleep ($P = 0.001$) compared

Table 1: Demographic and clinical characteristics of infants.

	Preeclampsia (n=27)	Control (n=25)	P-value
Gestational age, weeks (IQR)	33 (31–34)	33 (30–34)	0.5
Birth weight, g	1582±390	1977±330	0.001
Casearen section, n (%)	24 (88.8)	18 (72)	0.15
Male, n (%)	12 (44)	18 (72)	0.08
Cord blood pH (IQR)	7.34 (7.31–7.38)	7.33 (7.29–7.36)	0.32
Surfactant, n (%)	5 (18.5)	5 (20)	0.62
CPAP, n (%)	7 (26)	9 (36)	0.27

CPAP=continuous positive airway pressure, IQR=interquartile range. Statistically significant P values are given in bold.

Table 2: aEEG analysis and MCA BFV measurements of infants adjusted for birth weight.

	Preeclampsia (n=27)	Control (n=25)	P-value
Quiet sleep lower border, μ V (IQR)	3 (2.5–3.5)	3 (2–4)	0.79
Bandwidth of quiet sleep, μ V	34.8±9.8	35.8±8.8	0.768
Active sleep lower border, μ V (IQR)	7 (7–8)	7 (6–8)	0.979
Bandwidth of active sleep, μ V (IQR)	18 (16–25.5)	18 (14–23)	0.428
Duration of quiet sleep, min	23.5±5	29.8±7.6	0.001
Burdjalov score (IQR)	8 (6–10)	10 (8–11)	0.04
Mean MCA BFV, cm/s (IQR)	19 (15.5–16.8)	18 (14–19)	0.26

Data are shown as mean±SD or median (IQR).aEEG=amplitude-integrated electroencephalogram, MCA BFV=middle cerebral artery blood flow velocity, IQR=interquartile range. Statistically significant P values are given in bold.

to controls. There was no other significant difference between the two groups in terms of aEEG analysis and MCA blood flow.

Discussion

The results of the present study suggest that there were differences in aEEG recordings of infants of preeclamptic mothers when compared with their gestational age-matched controls. The major significant differences were shortened duration of quiet sleep and lower Burdjalov scores in the preeclampsia group. Preeclampsia did not affect the neonatal MCA BFV.

There are few studies about the impact of maternal preeclampsia on the neurodevelopmental outcome of preterm babies, with conflicting results [11, 12]. According to Schlappbach et al. [11], preeclampsia has a relatively minor impact on long-term neurodevelopmental outcome in very preterm infants. They emphasized that postnatal risk factors such as mechanical ventilation, bronchopulmonary dysplasia, postnatal growth failure, and sepsis have a much stronger effect on long-term neurodevelopmental outcome. However, some authors reported that the risks of poor outcome appear to be greater than those in infants born at the same gestational age but without

preeclampsia [2, 12, 13]. In the report of Cheng et al. [2], preeclampsia itself is accused of causing neurodevelopmental delay in infants rather than the complications of prematurity. A scientific, evidence-based explanation for this association is lacking.

Evidence from studies on infants with hypoxic ischemic encephalopathy and premature infants has shown that the aEEG can be used for early prediction of neurodevelopmental outcome [10, 14–16]. Absence of cyclicity, depressed aEEG voltage, and seizures are important predictors of poor neurological outcome in preterm infants. The rise in amplitude of the lower border of the quiet sleep period is an important indicator of brain maturation [17, 18]. In this study, there was no significant difference in amplitude of the lower border and the bandwidth span between the two groups. However, the Burdjalov score of the infants of preeclamptic mothers was lower than the control group. The Burdjalov scoring system evaluates the continuity and cycling in addition to lower border amplitude and bandwidth span [3]. Continuity is one of the indicators of maturation in preterm infants with brain damage but also has been shown to be abnormal in preterm infants with brain injury [19]. The lower Burdjalov score in the preeclampsia group may be indicative of *in utero* brain damage as a result of several factors detected in preeclamptic mothers such as increased oxidative

stress, reduced levels of angiogenic factors, and lower levels of nerve growth factor in plasma [20].

Sleep wake cycling (SWC) patterns in aEEG can be observed at 25–26 weeks of premature infants without intraventricular hemorrhage. Emergence and establishment of SWC are determined by the level of integration of higher central nervous system functions [3]. Since distinct sleep patterns of active and quiet sleep begin at 30 weeks of postmenstrual age, premature newborns born between 30 and 34 weeks of gestation were involved in this study. Burdjalov et al. [3] suggest that an earlier onset of SWC could be considered the best predictor of brain integrity among all the factors in aEEG. Kidokoro et al. stated that SWC is a technical term referring to biological pattern of alternating sleeping and waking states which is difficult to define with only aEEG without physical parameters [21]. We did not use any other methods to ascertain the SWC recorded on aEEG in this study. However, there are recent neurophysiological studies demonstrating that aEEG has a consistency with long-term polysomnographic recordings in detection of SWC in preterm infants [22, 23]. In this study, shortened duration of quiet sleep in the preeclampsia group was remarkable. Although there is no information on premature infants, it is known that term infants with asphyxia have decreased quiet sleep periods [21]. It is well known that impaired fetal circulation secondary to disrupted placental perfusion and consecutive hypoxia may develop in fetuses exposed to preeclampsia [1]. Shortened duration of quiet sleep in the preeclampsia group might be a result of the intrauterine adverse effect of preeclampsia on the cerebral blood flow within the developing fetal brain.

The hemodynamic effects of antenatal MgSO₄ on preterm infants' immature cerebral circulatory control are still poorly understood. According to research by Shokry et al. [24], antenatal MgSO₄ promotes decreased neonatal cerebral perfusion during the critical first few days of life. Rantonen et al. [25] also showed that maternal MgSO₄ treatment is associated with lowered cerebral perfusion in preterm infants. Because of poorly developed autoregulatory control mechanisms in premature babies, loss of autoregulation of cerebral blood flow may result in decreased cerebral perfusion. Impaired cerebral blood flow has been associated with discontinuous EEG activity that in turn has been associated with poor long-term prognosis in preterm infants [26, 27]. To rule out the depressive effect of low cerebral blood flow on electrocerebral activity, MCA BFV was measured with Doppler ultrasonography in this study. Normative Doppler indices of MCA in premature infants during the first month after birth were detected by Romagnoli et al. [28]. In the present study, none of the

patients had MCA BFV below the 10th percentile according to gestational and postnatal age described. Hence, preeclampsia itself was thought to be responsible for abnormal aEEG findings in the study group.

The main limitation of this study might be that birth weight of infants of preeclamptic mother was lower than birth weight of control group. It is well known that preeclampsia is associated with intrauterine growth restriction (IUGR) [1]. IUGR in premature infants has been shown to be a risk factor for adverse cognitive outcome [29]. Since aEEG is a highly predictive tool for long-term neurological outcome, it may be speculated that IUGR may have an influence on aEEG activity in neonatal period. Hence, comparison of aEEG findings and MCA blood flow velocity between two groups was made adjusted with birth weight to eliminate unfavorable effects. The significant difference persisted after the correction for birthweight. This result indicates that preeclampsia might be an additional factor contributing to the adverse fetal environment in case of IUGR.

In conclusion, the results of this small, observational, and controlled study indicate that preeclampsia exposure is associated with delayed brain maturation and decreased duration of quiet sleep. However, since this study does not address the long-term neurological outcome, the impact of this relevance is not clear. A prospective study conducted with a larger sample size with longer aEEG recordings and long-term neurological follow up will help to explain these results.

References

- [1] Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet*. 2005;365:785–99.
- [2] Cheng SW, Chou HC, Tsou KI, Fang LJ, Tsao PN. Delivery before 32 weeks of gestation for maternal pre-eclampsia: neonatal outcome and 2-year developmental outcome. *Early Hum Dev*. 2004;76:39–46.
- [3] Burdjalov VF, Baumgart S, Spitzer AR. Cerebral function monitoring: a new scoring system for the evaluation of brain maturation in neonates. *Pediatrics*. 2003;112:855–61.
- [4] Sisman J, Campbell DE, Brion LP. Amplitude-integrated EEG in preterm infants: maturation of background pattern and amplitude voltage with postmenstrual age and gestational age. *J Perinatol*. 2005;25:391–6.
- [5] Olischar M, Klebermass K, Kuhle S, Hulek M, Kohlhauser C, Rücklinger E, et al. Reference values for amplitude-integrated electroencephalographic activity in preterm infants younger than 30 weeks' gestational age. *Pediatrics*. 2004;113:61–6.
- [6] Hellström-Westas L, Rosén I, Svenningsen NW. Predictive value of early continuous amplitude integrated EEG recordings on outcome after severe birth asphyxia in full term infants. *Arch Dis Child Fetal Neonatal Ed*. 1995;72:34–8.

- [7] al Naqeeb N, Edwards AD, Cowan FM, Azzopardi D. Assessment of neonatal encephalopathy by amplitude-integrated electroencephalography. *Pediatrics*. 1999;103:1263–71.
- [8] Hellström-Westas L, Klette H, Thorngren-Jerneck K, Rosén I. Early prediction of outcome with aEEG in preterm infants with large intraventricular hemorrhages. *Neuropediatrics*. 2001;32:319–24.
- [9] Olischar M, Klebermass K, Kuhle S, Hulek M, Messerschmidt A, Weninger M. Progressive posthemorrhagic hydrocephalus leads to changes of amplitude-integrated EEG activity in preterm infants. *Childs Nerv Syst*. 2004;20:41–45.
- [10] Wikström S, Pupp IH, Rosén I, Norman E, Fellman V, Ley D, et al. Early single-channel aEEG/EEG predicts outcome in very preterm infants. *Acta Paediatr*. 2012;10:719–26.
- [11] Schlappbach LJ, Ersch J, Adams M, Bernet V, Bucher HU, Latal B. Impact of chorioamnionitis and preeclampsia on neurodevelopmental outcome in preterm infants below 32 weeks gestational age. *Acta Paediatr*. 2010;99:1504–9.
- [12] Silveira RC, Procianny RS, Koch MS, Benjamin AC, Schlindwein CF. Growth and neurodevelopment outcome of very low birth weight infants delivered by preeclamptic mothers. *Acta Paediatr*. 2007;96:1738–42.
- [13] Gray PH, O'Callaghan MJ, Mohay HA, Burns YR, King JF. Maternal hypertension and neurodevelopmental outcome in very preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 1998;79:88–93.
- [14] Toet MC, Hellström-Westas L, Groenendaal F, Eken P, de Vries LS. Amplitude integrated EEG 3 and 6 hours after birth in full term neonates with hypoxic-ischaemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed*. 1999;81:19–23.
- [15] Thornberg E, Ekström-Jodal B. Cerebral function monitoring: a method of predicting outcome in term neonates after severe perinatal asphyxia. *Acta Paediatr*. 1994;83:596–601.
- [16] Soubasi V, Mitsakis K, Sarafidis K, Griva M, Nakas CT, Drossou V. Early abnormal amplitude-integrated electroencephalography (aEEG) is associated with adverse short-term outcome in premature infants. *Eur J Paediatr Neurol*. 2012;16:625–30.
- [17] Verma UL, Archibald F, Tejam NA, Handwerker SM. Cerebral function monitor in the neonate. I: normal patterns. *Dev Med Child Neurol*. 1984;26:154–61.
- [18] Viniker DA, Maynard DE, Scott DF. Cerebral function monitor studies in neonates. *Clin Electroencephalogr*. 1984;14:185–92.
- [19] Greisen G, Hellstrom-Westas L, Lou H, Rosen I, Svenningsen NW. EEG depression and germinal layer haemorrhage in the newborn. *Acta Paediatr Scand*. 1987;76:519–25.
- [20] Morsing E, Maršál K. Pre-eclampsia- an additional risk factor for cognitive impairment at school age after intrauterine growth restriction and very preterm birth. *Early Hum Dev*. 2014;90:99–101.
- [21] Kidokoro H, Inder T, Okumura A, Watanabe K. What does cyclicity on amplitude-integrated EEG mean? *J Perinatol*. 2012;32:565–9.
- [22] Stevenson NJ, Palmu K, Wikström S, Hellström-Westas L, Vanhatalo S. Measuring brain activity cycling (BAC) in long term EEG monitoring of preterm babies. *Physiol Meas*. 2014;35:1493–508.
- [23] Palmu K, Kirjavainen T, Stjerna S, Salokivi T, Vanhatalo S. Sleep wake cycling in early preterm infants: comparison of polysomnographic recordings with a novel EEG-based index. *Clin Neurophysiol*. 2013;124:1807–14.
- [24] Shokry M, Elsedefy GO, Bassiouny MM, Anmin M, Abozid H. Effects of antenatal magnesium sulfate on cerebral and systemic hemodynamics in preterm newborns. *Acta Obstet Gynecol Scand*. 2010;89:801–6.
- [25] Rantonen T, Kääpä P, Grönlund J, Ekblad U, Helenius H, Kero P, et al. Maternal magnesium sulfate treatment is associated with reduced brain-blood flow perfusion in preterm infants. *Crit Care Med*. 2001;29:1460–5.
- [26] West CR, Groves AM, Williams CE, Harding JE, Skinner JR, Kusche CA, et al. Early low cardiac output is associated with compromised electroencephalographic activity in very preterm infants. *Pediatr Res*. 2006;59:610–5.
- [27] Victor S, Marson AG, Appleton RE, Beirne M, Weindling AM. Relationship between blood pressure, cerebral electrical activity, cerebral fractional oxygen extraction, and peripheral blood flow in very low birth weight newborn infants. *Pediatr Res*. 2006;59:314–9.
- [28] Romagnoli C, Giannantonio C, De Carolis MP, Gallini F, Zecca E, Papacci P. Neonatal color Doppler US study: normal values of cerebral blood flow velocities in preterm infants in the first month of life. *Ultrasound Med Biol*. 2006;32:321–31.
- [29] Vossbeck S, de Camargo OK, Grab D, Bode H, Pohlandt F. Neonatal and neurodevelopmental outcome in infants born before 30 weeks of gestation with absent or reversed end-diastolic flow velocities in the umbilical artery. *Eur J Pediatr*. 2001;160:128–34.

The authors stated that there are no conflicts of interest regarding the publication of this article.