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Original Research

aEEG Assessment for Short-Term Outcome Prognosis Prediction in Hypoxic-Ischemic Encephalopathy: An 11-Year Experience

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Abstract

Objectives: Hypoxic-ischemic encephalopathy (HIE) continues to be a predominant cause of morbidity and mortality in neonates. Therapeutic hypothermia (TH) is the only method with proven neuroprotective effects, and the aim of this study was to evaluate the short-term results of patients treated with TH.

Methods: Demographic, clinical characteristics, laboratory and aEEG results of patients who received TH treatment with a diagnosis of Stage II or Stage III HIE according to modified Sarnat staging in the Neonatal Intensive Care Unit were analyzed retrospectively.

Results: A total of 101 patients were included in the study. The mean gestational age of the patients was 38.8±1.5 weeks, the mean birth weight was 3215±499.5 g, and 40.6% were female. According to the modified Sarnat staging, 50.5% of the patients were evaluated as Stage II, and the others as Stage III HIE. The most common peripartum risk factors were meconium delivery (25.7%) and prolonged or difficult labor (20.7%). Mortality rates in patients with Stage II and Stage III HIE were 5.9% and 26%, respectively. In one of the patients who died, the 6th-hour aEEG background activity was moderately abnormal, and in 15 patients there was a severely abnormal voltage pattern. Acute kidney injury was found to be the most effective factor in mortality.

Conclusion: In our study, it was concluded that the mortality rate of newborns diagnosed with Stage III HIE was higher, the biggest impact factor on mortality was acute kidney injury, and 6th-hour voltage activity in aEEG monitoring was useful in predicting prognosis.

Keywords: Electroencephalography, hypoxic-ischemic encephalopathy, neonate, therapeutic hypothermia

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Hypoxic-ischemic encephalopathy (HIE) is a condition of brain damage, characterized by reduced blood (ischemia) and oxygen (hypoxia) flow in the fetus or infant during or after birth.[1] Both preterm and term newborns are affected, and it is seen at the rate of 1-4/1000 live births in developed countries and 26/1000 in developing countries. HIE continues to be one of the most common causes of neurological disability and death in newborn infants (>1 million neonatal deaths per year worldwide).[1,2] According to the 2008 and 2023 data of the Turkish Neonatology Society Hypoxic-Ischemic Encephalopathy Working Group, HIE was determined in 2.6/1000, 2.13/1000 live births and in 1.2%, 1.55% of patient in Neonatal Intensive Care Units in Türkiye, respectively.[3,4]

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Currently, the only treatment method proven to be neuroprotective in HIE is therapeutic hypothermia (TH). It has been shown in many studies and meta-analyses that TH leads to a decrease in the rates of neurological sequelae and mortality in newborns with moderate (Stage II) and severe (Stage III) HIE, and it has thus become the standard treatment.[5,6] In 2014, criteria for patients to undergo TH were defined by the American Pediatrics Academy. In addition, when the defined criteria are not met, TH treatment can be applied according to the clinical status of the newborn infant and the decision of the clinician. The therapeutic window required for the initiation of TH is accepted as the 1-6 hour latent phase in which the cerebral oxidative mechanisms can be reversed in HIE.[7]

The cardiovascular system, respiratory system, and primarily the central nervous system are usually affected in HIE. In addition, acute kidney injury (AKI), coagulopathy, liver damage, and blood glucose and electrolyte disorders are commonly seen.[8] Supportive treatments should also be planned in the treatment process. The application of amplitude-integrated electroencephalography (aEEG) can provide support in the detection of subclinical seizures in patients, determination of the severity of encephalopathy, and estimation of prognosis.[8]

The aim of this study was to analyze the factors affecting mortality in newborns applied with TH because of a diagnosis of Stage II and Stage III HIE, through evaluation of laboratory and aEEG findings together with demographic, etiological, and clinical characteristics. Furthermore, the relationship between aEEG background pattern and mortality was evaluated.

Methods

The study included patients monitored in the Neonatal Intensive Care Unit (NICU) with a diagnosis of Stage II or Stage III HIE, who underwent TH treatment between August 2013 and August 2024. The study was designed retrospectively.

Study Inclusion Criteria

Patients who underwent TH for a diagnosis of Stage II or Stage III HIE were included in the study. The decision to start TH was made according to the following criteria.[5]

a. Gestational age ≥36 weeks,
b. Birth weight ≥2000 g
c. The neonates who are in the first postnatal 6 hours,
d. Values of pH≤7.00 or BE ≤-16 mmol/l in umbilical cord or 1st-hour of life,
e. 10th minute APGAR score <5 or a continuing need for resuscitation,
f. Findings of Stage II or III encephalopathy in the clinical evaluation,
g. In infants with inappropriate laboratory values determined in the "d" option, a low APGAR score and findings of encephalopathy or a moderate-severe effect on aEEG.

Study Exclusion Criteria

a. Unavailable records data,
b. The presence of congenital heart disease,
c. Findings of Stage I encephalopathy in the clinical evaluation,
d. The presence of congenital malformation, genetic disease, or congenital metabolic disease,
e. Patients who developed bradycardia and hypotension during TH and patients who did not respond to medical treatment and treatment were terminated early.

A record was made for each case of gestational age, birthweight, gender, mode of birth, maternal age, number of pregnancies, APGAR scores, need for postnatal resuscitation, prenatal/natal conditions in respect of etiology, cord blood gas or blood gas values obtained in the first postnatal hour, full blood count, infection markers with liver and kidney function tests, and thyroid hormone results. AKI was accepted as a 1.5-fold increase in the creatinine value together with oliguria (≤0.5ml/kg/hour) throughout at least 6 hours.[9]

The need for resuscitation in the delivery room was evaluated as positive pressure ventilation and cardiac compression. The values of pH, pCO_2, HCO_3, and base deficit were examined from the parameters of cord blood gas or 1-hour blood gas.

The modified Sarnat staging system was used for the clinical evaluation and the cases were classified as Stage I, Stage II, or Stage III HIE. TH was applied to the patients classified as Stage II and Stage III HIE. A servo-controlled full-body cooling system was used for TH (Comen P3/P6, Shenzhen Comen Medical, China or Tecotherm Neo, Tec Com GmbH, Germany). The targeted rectal temperature was 34°±0.5°C, and the treatment time was planned as 72 hours with a rewarming time of at least 6 hours. For patients who experienced a seizure during the rewarming period, the treatment was extended to 96 hours.

Patients who received postnatal respiratory support were examined in respect of non-invasive and invasive respiratory support. Invasive respiratory support was classified as conventional (MV) and high-frequency oscillation ventilation.

Seizure activity and the severity of encephalopathy of the cases were evaluated with aEEG monitorization (Olympic CFM 6000, Natus Medica, USA, which has three channels aEEG). Observation was continued throughout the TH treatment and results were recorded. The first evaluation was conducted at 30-60 minutes. The aEEG evaluation parameters were non-continuous normal voltage: non-continuous base activity at lower amplitude always <5μV and upper amplitude >10μV; Burst suppression: non-continuous base when non-variable lower amplitude is 0-1 μV and bursts are >25μV amplitude. Continuous very low voltage: base pattern when there is continuous very low voltage (approximately ≤5μV). Straight line pattern: classified as inactive base (isoelectric line) when there is no activity below 5μV. Clinical interpretations were defined as normal trace: lower line >5μV, upper line >10μV, moderately abnormal: lower line ≤5μV, upper line >10μV, severely abnormal: lower limit <5μV, upper limit <10μV (burst suppression, continuous very low voltage, and straight line pattern were classified in this group). The evaluation of aEEG was carried out by one physician who specializes in child neurology.

Echocardiography was conducted on all the patients. The oxygenation index values, calculated as OI = (average airway pressure x FiO_2 ÷ PaO_2) x 100, were assessed in patients diagnosed with persistent pulmonary hypertension (PPHT). Patients with OI index ≥25 were given inhaled nitric oxide (iNO), with the initial dose targeted to be 20 parts per million (ppm). Dose adjustment was made automatically with a servo-controlled device (NOXtec 2000, Spain). The dose was gradually reduced according to the clinical evaluations. Methemoglobinemia in the blood gas was monitored. For patients with a methemoglobin level ≥5%, the iNO dose was reduced or the treatment was ceased.

Phenobarbital (loading dose 20 mg/kg-max 40 mg/kg, maintenance dose 5 mg/kg/day) was started as the first choice for patients with clinical or subclinical seizures on aEEG. When seizures could not remain under control phenytoin was added (loading dose 20-30 mg/kg, 5mg/kg maintenance). For unresponsive or resistant cases, midazolam and levatiracetam treatments were added.

This study was conducted by the ethical principles stated in the Declaration of Helsinki. Ethics Committee approval was received from the Gazi Yasargil Training and Research Hospital on 30/7/2015 with number 6. No artificial intelligence was used to generate content in this document.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS software version 24 (IBM Corp., Armonk, NY, USA). Conformity of the data to normal distribution was examined with histograms and skewness and kurtosis values between -1.5 and +1.5. Descriptive statistics of continuous variables were stated as mean±standard deviation (SD) values for parametric data and as median (minimum-maximum) values for non-parametric data. In paired groups, the chi-square test was applied in the evaluation of categorical variables, and for measurements showing normal distribution, the independent samples t-test was used. The Mann-Whitney U-test was applied to continuous variables not showing normal distribution. To determine the factors affecting mortality, binary logistic regression analysis was performed. A value of $p<0.05$ was accepted as the level of statistical significance.

Results

The study initially included 114 patients diagnosed with HIE. After excluding eight patients with incomplete prenatal data, four patients with congenital malformations or heart disease, and one patient whose treatment was ceased earlier than planned, the study was completed with 101 patients.

The demographic characteristics of the patients are presented in Table 1. Of the total 101 patients, 98 (97%) were transferred to our hospital from other centers and 3 were born in our center. The time to starting TH was postnatal 3.2±1.7 hours. Chest compression together with positive pressure ventilation was performed postnatally on half of the cases.

According to the modified Sarnat staging, 51 cases were classified as Stage II, and 50 cases were Stage III. Clinical convulsions were observed in 48 patients within the first 24 hours and in 3 patients on the 2nd day. In 4 patients, although there were no clinical convulsions, as they were determined on aEEG and anticonvulsion treatment was started. A single anticonvulsant was administered to 41 patients, whereas multiple agents were used for 14 patients. aEEG was performed on 94 patients for follow-up. According to the aEEG classifications in the first 30-60 minutes and 6th-hour were presented in Table 1 and 2. AKI developed in 15 patients and peritoneal dialysis was applied to 6 patients who did not respond to medical treatment. Complications of TH are shown in Table 2.

Mortality developed in a total of 16 (15.8%) patients; 13 (26%) were Stage III and 3 (5.9%) were Stage II according to the modified Sarnat staging. In 15 of the exitus patients, there was severely abnormal voltage on the 6th-hour aEEG and there was seen to be no improvement in the aEEG findings throughout the follow-up period. Of the patients determined with normal or moderately abnormal aEEG findings, only 1 patient was exitus. The factors affecting

Table 1. Demographic characteristics and clinical follow-up information of patients

	n 101
Gender, n (%)	
Male	60 (59.4)
Female	41 (40.6)
Gestational age, weeks	38.8±1.5
Birth weight, grams*	3215±499.5
Mode of delivery, n (%)	
Vaginal	63 (62.4)
Cesarean section	36 (35.6)
Vaginal Vacuum	2 (1.9)
Maternal age, year**	28 (16-45)
Peripartum risks, n (%)	
Meconium-stained amniotic fluid	26 (25.7)
Prolonged or difficult labour	21 (20.7)
Umbilical cord prolapse - entanglement	9 (25.7)
Placental abruption	8 (8.9)
Shoulder dystocia	3 (2.9)
Uterine rupture	2 (1.9)
APGAR scores*	
1st minute	1.5±1.3
5 st minute	3.7±1.2
10 st minute	4.7±1.4
Resuscitation at delivery room, n (%)	
PPV	47 (46.6)
PPV+ Cardiac compression	54 (53.4)
HIE stage, n (%)	
Stage II	51(50.5)
Stage III	50 (49.5)
Blood gas, (umbilical cord or 1 st hour of life) *	
pH	6.89±0.12
Bicarbonate, mmol/l	51.3±12.6
Base excess, mmol/l	-20.9±4.6
Seizure during admission, n (%)	
Clinical seizures	51 (50.4)
Only aEEG seizures	4 (4)
Respiratory support, n (%)	
Invasive	71 (70.3)
Non-invasive	16 (15.8)
aEEG classification in the first 30-60 minutes after starting TH, n (%)	
Normal voltage	11 (11.7)
Moderately abnormal voltage	51 (54.2)
Severely abnormal voltage (Burst suppression-continuous very low voltage- straight line)	32 (31.6)
Duration of hospital stay (day), median (min-max)	14 (1-115)
Death, n (%)	16 (15.8)
Stage II	3 (5.9)
Stage III	13 (26)

* mean±SD; ** median (min-max); aEEG: Amplitude integrated electroencephalography; HIE: Hypoxic ischemic encephalopathy; PPV: Positive pressure ventilation.

mortality are shown in Table 3. AKI was determined to be the most significant factor affecting mortality.

Discussion

This study presents the 11-year results of HIE patients in NICU, most of whom were transferred from other centers, who were treated and followed up with continuous aEEG monitorization and whole-body hypothermia.

Although the effect mechanism of TH remains incompletely understood, energy consumption is reduced together with a decrease in cerebral metabolism. Neurotoxicity is prevented with a delay in cell depolarization together with a decrease in intracellular Ca^{+2} flow and extracellular excitatory amino acids such as aspartate and glutamate. A decrease in neuronal damage is achieved with inhibition of inflammatory mechanisms and the cascades causing neuronal apoptosis.[10] Following resuscitation and reperfusion, there is a latent period of 1 to 6 hours where the impairment of cerebral oxidative metabolism can at least partially recover, before irreversible failure of mitochondrial function. This latent phase is the therapeutic window for neuroprotective interventions.[11] In a study by Shankaran et al.[12], controlled TH started within the first 6 hours of life and continued for 72 hours was seen to reduce morbidity and mortality in patients with moderate-severe HIE. TH is currently accepted as standard treatment for HIE.[13]

Many preclinical studies support the early initiation of TH. It has been shown that when started within postnatal 90 minutes the neuroprotective effect is high, after 5.5 hours it is partially effective, and there is no effect after 8.5 hours.[14,15] However, clinical studies have reported no neurodevelopmental difference at 18 months of TH started early (median 1.4 hours) or late (median 4.4 hours).[16] In a recent study in which almost all the patients were admitted from other centers, the time to starting TH was determined to be mean postnatal 5 hours, and the analyses determined no effect of this on early mortality.[17] In another multicenter study, the initiation time of TH (<3 hours, 3-6 hours, and >6 hours) showed no effect on reducing mortality.[4] In the current study, 97% of the patients had been transferred from other centers and the mean time to starting TH was 3.2 hours. There was no statistically significant difference in mortality rates between the group receiving TH within 0-2 hours and 5-6 hours. Compared with other studies with a high rate of patients transferred from other centers, this shorter time can be attributed to increased awareness of HIE in Türkiye and the development of facilities for transfer to higher-level centers.

Many antenatal and intrapartum factors may contribute to the development of HIE. Antenatal risk factors have been found to

Table 2. The factors affecting mortality

	Discharged groups (n=85)	Exitus groups (n=16)	p
Gender, n			
Male	49	11	0.43
Female	36	5	
Gestational age, weeks*	39.03±1.2	38.25±1.5	0.07
Birth weight, grams*	3235±473.3	3109±567.2	0.17
Mode of delivery (Cesarean section), n	30	6	0.83
APGAR scores			
1st minute**	3 (0-5)	0 (1-3)	0.02
5st minute*	3.9±1.09	2.8±1.4	0.012
10st minute*	4.9±1.3	3.8±1.4	0.007
Resuscitation at delivery room, n			
PPV+ Cardiac compression	40	14	0.04
HIE stage, n			
Stage II	48	3	0.005
Stage III	37	13	
Blood gas, (umbilical cord or st hour of life) *			
pH	6.90±0.12	6.82±0.11	0.003
Bicarbonate, mmol/l	10.9±2.8	8.5±2.4	0.001
Base excess, mmol/l	20.5±4.2	23.6±3.9	0.004
Seizure, n	38	13	0.01
Respiratory support, n			
Invasive	55	16	0.001
Non-invasive	16	0	
aEEG classification at the 6th hour after starting TH, n			
Normal voltage	44	0	0.000
Moderately abnormal voltage	26	1	
Severely abnormal voltage (Burst suppression- continuous very low voltage- straight line)	8	15	
TH starting time, hours			
0-2 , n	30	6	0.74
2-5 , n	34	5	
5-6 , n	21	5	
1st day laboratory values			
White blood cell 10^3/ul*	20767±8815		
26105±12307			
0.16			
Hemoglobin, g/dl*	17.1±2.4	16.7±1.9	0.29
Platelet, 10^3/ul*	167988±58509	170563±56115	0.97
Urea, mg/dl*	26±10.8	28.1±15.6	0.89
Creatinine, mg/dl*	0.8±0.2	0.9±0.3	0.37
Aspartate aminotransferase, U/l**	160 (37-2851)	191 (53-1491)	0.18
Alanine aminotransferase, U/l**	53.5 (9-1250)	49.5 (7-306)	0.84
INR*	1.7±0.8	2±0.5	0.03
AKI	6	9	0.000
Peritoneal dialysis, n	0	6	0.000
Pulmoner hemorrhage, n	0	1	
Pneumothorax, n	0	2	
Hypothyroidism, n	2	2	
iNO, n	4	3	
Proven bacterial sepsis	2	0	

* mean±SD, ** median (min-max), aEEG: Amplitude integrated electroencephalography; AKI: Acute kidney injury; HIE: Hypoxic ischemic encephalopathy; INR: International normalized ratio; iNO: Inhaler nitric oxide; TH: Therapeutic hypothermia.

Table 3. Logistic regression analysis of factors affecting mortality

				%95 C.I.	
	B	S.E.	Sig.	Lower	Upper
AKI	2.890	0.844	0.001	30443	93.990
pH	-5.138	4.220	0.223	0.000	22.970
Base excess, mmol/l	0.242	0.118	0.040	1.011	1.606
PPV+Cardiac compression	1.466	0.851	0.085	0.817	22.986
The time to starting TH	0.152	0.204	0.454	0.781	1.736

AKI: Acute kidney injury; PPV: Positive pressure ventilation; TH: Therapeutic hypothermia.

be related to primigravida, thyroid diseases, pre-eclampsia, infertility treatment, and intrauterine growth restriction.[18] Intrapartum factors, which are frequently observed and typically associated with fetal distress, include delivery by cesarean-section, as well as less common occurrences such as moderate to intense meconium staining of the amniotic fluid, placental abruption, and uterine rupture. Cesarean-section delivery is likely a consequence, not a cause, of HIE since identified fetal distress typically leads to an emergent cesarean-section delivery.[18,19] The rate of cesarean-section in HIE patients was reported as 56.8% by Peebles et al.[19] and 50.6% by Nieves et al.[17] In the current study, this rate was 35.6%. The risk factors of amniotic fluid with meconium and prolonged-difficult labor were determined to be the most common causes, and these findings were evaluated as consistent with previous studies that have shown an increased risk of HIE together with perinatal events.

An interesting observation in our study was that 60 (59.4%) cases were male. In a study published in 2017 by Odd et al.[20] 69% of 130 HIE patients were observed to be male. A previous study in Türkiye showed that 61.7% of the cases were male.[21] Yadav et al.[22] reported that 90% of cases were transferred and 70% were male. Nearly all of the cases in the current study had been transferred from other centers. This could indicate a gender bias in favor of males because of the geographic region. However, there is a need for further studies to be able to reach the evidence of whether there is sensitivity to gender-related HIE or social behavior orientation.

In a multicenter cohort study by Massaro et al.[23] 945 newborns with HIE were evaluated as 16.9% Stage I, 52.1% Stage II, and 31% Stage III. Nieves et al.[17] reported that 71.3% of cases were Stage II and 28.7% were Stage III, and Yadav et al.[22] reported the classifications as 53.3% Stage II, 39.2% Stage I, and 7.5% Stage III. When compared with these studies, in which most of the patients were similarly transferred from other centers, the rate of Stage III patients in the current study was seen to be high. This difference may be due to transfer bias, and that some cases born in other centers were observed and referred, resulting in a concentration of transfer of mostly Stage III patients.

It has been reported that aEEG monitorization of patients treated with TH is useful in predicting prognosis and neurodevelopmental.[24] Hellstrom-Westas et al.[25] evaluated the background pattern on aEEG in the first 6 hours and reported 100% survival rate of infants evaluated as continuous and normal voltage, and 9 of the 21 patients with abnormal aEEG findings were exitus. In a study of 160 cases by van Rooij et al.[26] the survival rate was 100% in cases with normal or slightly abnormal findings according to the 6-hour aEEG background pattern, whereas mortality developed in 66.6% of the 90 patients with burst suppression, continuous very low voltage and straight line patterns. Nearly all of the exitus patients in that group showed no improvement in the aEEG findings at 24 hours. According to the Sarnat classification in a meta-analysis of 30 studies, the cases were evaluated as 150 mild, 1182 moderate, and 386 severe. The findings obtained showed that the prognostic value of aEEG was similar at 24 and 72 hours and the best results were evaluated to be at 36 hours. As high sensitivity and low specificity were determined for aEEG at 6 hours, it was concluded that this could be more important than high specificity in the early period to determine infants that are potentially at risk.[24] In another meta-analysis, 520 patients were evaluated and abnormal aEEG background activity was reported to have 0.95, 0.85, and 0.67 sensitivity at 24, 48, and 72 hours, respectively, and 0.75, 0.93, and 0.97 specificity.[27] In the current study, 1 (1/62) patient with moderately abnormal 6th-hour aEEG background activity, and 15 (15/32) patients with a severely abnormal voltage were exitus. In light of all these studies, it was concluded that 6th-hour aEEG background activity is important data for the prediction of short-term outcomes.

In previous studies in Türkiye, Satar et al.[28] reported mortality rates of 15% for Stage II and 78.6% for Stage III HIE, and in a 2008 multicenter study by the Turkish Neonatology Society, these rates were 16.7% and 51.7%, respectively.[3] In a more recent study in 2021 by Deveci et al.[29] the mortality rates of Stage II and Stage III HIE were 9% and 86.1%, respectively. In a 2023 study by the Turkish Neonatology Society, in which the participating centers were almost the same as in the previous study, mortality rates were reported of 2.3% Stage II cases and 29.8% Stage III HIE.[4] The mortality rates of the current study of 5.9% Stage II and 26% Stage III were seen to be consistent with the recent literature. The decrease in the mortality rates compared to previous years can probably be attributed to the availability of TH in recent years, the accumulated treatment experience, and an increase in overall awareness in Türkiye.

When there is exposure to asphyxia, blood flow is reorganized and while trying to protect organs such as the heart and brain, the rate of damage is increased in organs such as the liver, kidneys, and intestines, which are directly affected by hypoxia. AKI is one of the complications associated with mortality and is seen most often in newborns experiencing asphyxia.[29] Grossman et al.[30] reported the frequency of AKI to be 45% and found that it was related to the newborn mortality rate. In an 8-year retrospective study by Michniewicz et al.[31] the liver function and creatinine levels were reported to be significantly higher in the severe HIE group. When the factors affecting mortality were examined in this study, AKI was determined to be the most significant factor.

To our knowledge, our study was one of the first to include continuous aEEG monitoring in investigating neurological outcomes in HIE patients in our regions. The study was conducted at the neonatal center with many years of experience in implementing hypothermia therapy for HIE cases. Our study had limitations due to the single center, relatively small sample size, retrospective design, and short-term outcome assessment. Therefore, further long-term follow-up studies are needed to validate reliable aEEG interpretation factors for the HIE population.

Conclusion

In this study, the data were analyzed of patients with Stage II and Stage III HIE who underwent TH treatment. Compared to previous studies in Türkiye, there was a decrease in the mortality rate. The predominant intrapartum risk factors identified were meconium-stained amniotic fluid and prolonged or difficult labor. The biggest impact factor on mortality was AKI. However, no association was detected between the time of initiation of TH and mortality. In nearly all patients who died, the 6th-hour findings of aEEG were severely abnormal. In contrast, among patients with normal or moderately abnormal aEEG findings, only one patient was observed to have died. It was concluded that the background activity of aEEG) at the 6th hour was useful in predicting short-term prognosis.

Disclosures

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