Neurophysiologie Clinique/Clinical Neurophysiology (2019) 49, 41—47

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

ORIGINAL ARTICLE

Prognostic value of continuous electroencephalography in children undergoing therapeutic hypothermia after cardiac arrest: A pilot study

Tharapong Prajongkit[a,b], **Montida Veeravigrom**[a,b,*], **Rujipat Samransamruajkit**[c]

[a] *Division of neurology, department of pediatrics, faculty of medicine, Chulalongkorn University, Thailand*
[b] *Division of neurology, department of pediatrics, King Chulalongkorn Memorial Hospital/The Thai Red Cross Society*
[c] *Division of pulmonary and critical care, department of pediatrics, faculty of medicine, Chulalongkorn University, Thailand*

Received 13 April 2018; accepted 27 September 2018
Available online 12 October 2018

KEYWORDS
Cardiac arrest;
Electroencephalography;
Outcome;
Prognosis;
Therapeutic hypothermia

Summary
Objective. — To determine the prognostic value of continuous electroencephalography (EEG) in children undergoing therapeutic hypothermia after cardiac arrest.
Method. — We retrospectively reviewed medical records and continuous EEG of all patients undergoing therapeutic hypothermia after cardiac arrest from November 2013 to September 2016. Demographic, clinical data and immediate complications were collected. Characteristics of continuous EEG including EEG background, time to normal trace (TTNT) and electrographic seizures were reviewed by investigators. Cerebral performance category scales at 6 months' follow up were evaluated and divided into good (grade 1—2) and poor (grade 3—5) outcome groups.
Result. — Six patients were included (two boys and four girls) with median age of 19.5 months (range13—128 months). Five patients (83.3%) presented with cardiac arrest from near-drowning and one patient with underlying acute lymphocytic leukemia presented an in-hospital cardiac arrest. Initial EKG rhythm was asystole in 3 patients (50%), pulseless activity in 1 patient (16.7%) and initially unknown in 2 patients (33.3%). Two patients (33.3%) who had EEG reactivity and TTNT within 5 minutes and 2.5 hours had good neurological outcome (CPC1). Four patients

* Corresponding author. Division of neurology, department of pediatrics, Queen Sirikit Building (floor11), faculty of medicine. Chulalongkorn University, 1873 Rama IV Road, Pratumwan, 10330 Bangkok, Thailand.
E-mail addresses: vmontida@hotmail.com, Montida.V@chula.ac.th (M. Veeravigrom).

https://doi.org/10.1016/j.neucli.2018.09.002

(66.7%) with absent EEG reactivity had poor neurological outcome (CPC4, 5 in 3 and 1 children respectively). Three patients from the poor outcome group had electrographic seizures, of whom 2/3 progressed to status epilepticus. Three out of four patients in the poor outcome group had the following complications: pneumonia, bleeding and pancreatitis.
Conclusion. — Early TTNT and EEG reactivity help to predict good neurological outcome in children undergoing therapeutic hypothermia after cardiac arrest. Seizures and status epilepticus may predict poor neurological outcome.

Introduction

Therapeutic hypothermia (TH) has shown to effectively improve neurological outcomes and has become the standard of care in post cardiac arrest (CA) adult patients [3,4]. Temperature management post CA in children also has demonstrated improvement in neurological outcome. However, normothermia and hypothermia did not demonstrate different outcomes in children [12]. Continuous electroencephalography (CEEG) has been recommended for assessment of cerebral function during targeted temperature management by the International Liaison Committee on Resuscitation for post CA children [2,9]. Early EEG monitoring of children with cardiac arrest undergoing TH enables early prediction of neurological outcome [15]. Moreover, EEG is important to detect subclinical seizure activity in post CA patients. Limited study data has demonstrated that electrographic seizures and post anoxic status epilepticus were associated with morbidity and mortality [1,5,8,17]. On the other hand, higher initial Glasgow coma score and preserved sleep architecture were associated with better clinical outcome [7]. The goal of our study is to determine whether there is a relationship between CEEG monitoring pattern and prognosis of post CA children undergoing TH.

Methods

This observational study was approved by local Institutional Review Board at Faculty of Medicine, Chulalongkorn University and performed at Department of Pediatrics, King Chulalongkorn Memorial Hospital.

Six children underwent TH after cardiac arrest during November 2013 to September 2016. All patients who had successful resuscitation were considered for therapeutic hypothermia and CEEG monitoring with amplitude-integrated electroencephalography (aEEG) in the pediatric intensive care unit (PICU). TH was started as soon as possible in PICU. The patients were cooled to $33 \pm 0.5\,^{\circ}C$ using an automated surface-cooling device (Artic-Sun) and given sedating medication and analgesia. A neuromuscular blocking agent such as vecuronium was used to prevent shivering in selected cases. Sedation was weaned after rewarming. Antiepileptic drugs were only given in patients with electrographic seizures detected on CEEG monitoring. Exclusion criteria were: successful resuscitation and spontaneous regaining of consciousness without TH, or unavailable EEG trace. Four post CA patients were excluded from the study due to successful resuscitation and returned to their baseline without TH.

Therapeutic hypothermia protocol

All pediatric patients who had successful resuscitation were considered for TH as soon as possible after patients were admitted to PICU. Before the induction of TH, sedating medication and analgesia (midazolam 0.1 mg/kg/hour, fentanyl 1 μg/kg/hour intravenously) were given. The target temperature of $33 \pm 0.5\,^{\circ}C$ was maintained for 48—72 hours. After maintenance temperature, we started rewarming at rate of $0.25\,^{\circ}C$/hour until patient's temperature achieved $36.5\,^{\circ}C$.

EEG and clinical assessment

We monitored CEEG as soon as possible after patients were admitted to PICU. EEG was recorded using 9 to 16 electrodes arranged according to the international 10—20 system and maintained for at least 6 hours after rewarming. Amplitude integrated EEG was performed using F3—C3 and F4—C4 derivatives with low frequency filter at 1 Hz, high frequency filter at 70 Hz without notch filter. EEGs were reviewed and interpreted by a single investigator blinded to clinical history. All patients were routinely examined for Glasgow coma score (GCS), pupillary response and motor reactivity to painful stimulation.

Data collection

Demographic data were collected, including: medical history/pre-existing medical conditions, characteristics of cardiac arrest, characteristics of initial rhythm, CPR information, TH data, EEG data, complication and outcome of treatment. EEG findings (reviewed at 10 seconds/page in repeated 8-hour blocks for a total of 120 hours) were categorized as: focal slowing, generalized slowing, background pattern, electrocerebral inactivity, burst suppression, seizure and status epilepticus.

Outcome was assessed by using the Glasgow-Pittsburgh Cerebral Performance Categories (CPC) scale at six months after completed TH protocol. A good outcome is defined by CPC1 (Good cerebral performance: conscious, alert, able

Table 1 Demographic data, etiology, clinical characteristics and outcome in patients with therapeutic hypothermia post cardiac arrest.

Patient characteristics	*n* = 6
Age, month (median, min—max)	19.5 (13—128)
Male, *n* (%)	2 (33.3)
Pre-existing medical condition	
Lung or airway disease, *n* (%)	0
Neurological condition, *n* (%)	0
GI condition, *n* (%)	0
Congenital heart disease, *n* (%)	0
Hematologic condition, *n* (%)	1 (16.7)
Characteristic of cardiac arrest	
Respiratory event, *n* (%)	(0)
Cardiac event, *n* (%)	4 (66.7)
Unknown, *n* (%)	2 (33.3)
Performed CPR by medical person, *n* (%)	4 (66.7)
Characteristic of initial rhythm	
Asystole	3 (50)
Bradycardia	0
Pulseless activity	1 (16.7)
VF/VT	0
Unknown	2 (33.3)
Time from CA to CPR (minutes) (median, min—max)	17 (3—30)
Time from CA to induction of hypothermia (hours) (median, min—max)	12.5 (2—29)
Time from CA to EEG monitoring (hours) (median, min—max)	6.8 (3.5—19)
Duration of CPR (minutes) (median, min—max)	15 (4—20)
CPC at 6 month	
CPC1, *n* (%)	2 (33.3)
CPC2, *n* (%)	0
CPC3, *n* (%)	0
CPC4, *n* (%)	3 (50)
CPC5, *n* (%)	1 (16.7)

GI: Gastrointestinal tract; CPR: Cardiopulmonary resuscitation; VF/VT: Ventricular Fibrillation/Ventricular Tachycardia; CA: Cardiac arrest; CPC: Cerebral Performance Categories

to work, might have mild neurologic or psychologic deficit) and CPC2 (Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life). A poor neurological outcome is defined by CPC3 (Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis), CPC4 (Coma or vegetative state: any degree of coma without the presence of all brain death criteria), and CPC5 (Brain death: apnea, areflexia, EEG silence).

Statistical analysis

Data were analyzed using SPSS 17.0 for windows (SPSS, Inc., Chicago, IL, USA) Baseline characteristics and categorical variables were summarized using descriptive statistics and shown in percentage, median and range.

Results

In our study CEEG with aEEG were performed in 6 patients surviving from cardiac arrest undergoing TH. Two (33.3%) patients were male and 4 (66.7%) patients were female with median age on admission of 19.5 months (range 13—128 months). All children were previously healthy except one (16.7%) patient with underlying acute lymphocytic leukemia (ALL).

Five patients (83.3%) presented with cardiac arrest from near-drowning. The patient with underlying ALL developed cardiac arrest in hospital. Initial EKG rhythms were: asystole in 3 patients (50%), pulseless activity in 1 patient (16.7%) and unknown initial rhythm in 2 patients (33.3%). Median time from CA to start of cardiopulmonary resuscitation (CPR) was 17 minutes (range 3—30 minutes), and median duration for CPR time was 15 minutes (range 4—20 minutes). Median time from CA to induction of TH was 12.5 hours (range 2—29 hours). Median time from CA to CEEG monitoring was 6.8 hours (range 3.5—19 hours).

Based on CPC score, 2 patients with CPC score of 1—2 had good neurological outcome and 4 patients with CPC score 3—6 had poor neurological outcome. Baseline characteristics of patients and neurological outcome are presented in Tables 1 and 2. Target temperature of hypothermia was at $33 \pm 0.5\,^{\circ}C$ in all patients. Median duration of hypothermia was 72 hours (range 48—72 hours) and median time to reach target temperature was 4.5 hours (range 2.5—8 hours) (Table 3).

Table 2 Summary of demographic data, complication and outcome by cases.

	Sex, age, underlying disease (UD)	Time from CA to CPR (minute)	Initial BT (°C)	CPR duration (minute)	Event	GCS before TH, pupil size and RTL (both eyes)	Initial rhythm	Complication	Outcome at 6 months
Case I	Female 1yr 8mo, ALL	3	36	15	CA during medical procedure	E1VTM1, 2 mm, slight RTL	Sinus rhythm after CPR for 3 minutes	Status epilepticus	CPC4
Case II	Male 1yr 7mo, no UD	30	36.5	15	Near-drowning	E1VTM1, 2 mm, no RTL	Asystole	Pneumonia, status epilepticus	CPC5
Case III	Female 7yr 3mo, no UD	20	37.2	4	Near-drowning	E1VTM1, 2 mm, slight RTL	Asystole	None	CPC1
Case IV	Female 1yr 3mo, no UD	15	38.5	10	Near-drowning	E1VTM1, 2 mm, no RTL	Asystole	Bleeding, seizure, pneumonia, pancreatitis	CPC4
Case V	Male1yr 1mo, no UD	19	39.5	20	Near-drowning	E1VTM1, 1 mm, no RTL	Pulseless activity	Seizure	CPC4
Case VI	Female 10yr 8mo, no UD	5	38.3	15[a]	Near-drowning	E1VTM1, 2.5 mm, RTL	Sinus rhythm after CPR for 15 minutes	Pneumonia	CPC1

ALL: acute lymphocytic leukemia; UD: Underlying disease; CA: Cardiac arrest; CPR: Cardiopulmonary resuscitation; BT: Body Temperature; GCS: Glasgow coma scale; TH: Therapeutic Hypothermia; E1VTM1: Eye(1)-Verbal(Tube)-Motor(1); RTL: Reaction to light; CPC: Cerebral Performance Categories.

[a] By non-medical person.

Table 3 Therapeutic hypothermia data.

	Median (min—max), $n = 6$
Target temperature of hypothermia (°C)	33 (32.5—33.5)
Maintenance time (hour)	72 (48—72)
Time to get target temperature (hour)	4.5 (2.5—8)

In the poor neurological outcome group, CEEG showed intermittent focal slowing in 1 patient and continuous generalized slowing in 3 patients. In the good neurological outcome group, CEEG demonstrated intermittent generalized slowing in one patient. EEG reactivity is defined as the presence of change in amplitude or frequency following external stimulus (as in Fig. 1); in our study, EEG reactivity was assessed when external stimulation was performed, including calling the patient's name, sensory stimulation by physical examination and routine nursing care. EEG reactivity was detected in all cases in the good outcome group and was absent in the poor outcome group (Table 4). One patient in the good neurological outcome group showed EEG reactivity to stimuli during hypothermia within 1 hour, and the other showed reactivity from 8 hours after EEG monitoring onwards. Time to normal trace (TTNT) was 0.08 and 2.5 hours after onset of EEG recordings in the good neurological outcome group ($n = 2$). Absence of normal trace throughout the 120 hours of monitoring was observed in the second, poor outcome group (Fig. 2).

Three patients initially developed subclinical seizures. Two patients progressed to non-convulsive status epilepticus (SE). The patient who had prolonged SE for 56 hours deceased and the other patient had SE controlled within 15 hours after administration of antiepileptic drugs (Fig. 3). The onset of all cases of SE was before the rewarming period.

Table 4 Electroencephalography (EEG) characteristics in good outcome and poor outcome group.

EEG characteristic ($n = 6$)	Good outcome ($n = 2$)	Poor outcome ($n = 4$)
Focal slowing		
Intermittent	0	1
Continuous	0	0
Generalized slowing		
Intermittent	1	1
Continuous	0	3
Alpha coma	0	0
Beta coma	0	0
Triphasic wave	0	0
PLED	0	0
Time to normal trace (minutes) (Min, Max)	5,150	Not seen TTNT during monitoring
Reactivity	2	0
Burst suppression	0	0
Seizure	0	3
Status epilepticus	0	2

PLED: periodic lateralized epileptiform discharges; TTNT: time to normal trace.

Four out of five patients in the poor neurological outcome group had the following complications: pneumonia, pancreatitis, and bleeding. The patient with ALL did not have bleeding complications. Bleeding complications occurred in patients who had pneumonia and developed coagulopathy. Only 1 patient in the good neurological group had pneumonia (Table 5).

Cases 1, 3 and 4 have had long-term follow-up for at least 2 years. Case 3 (good outcome group) was able to return to school with good functional level. Antiepileptic drugs (AED) were weaned after 3 months. Cases 1

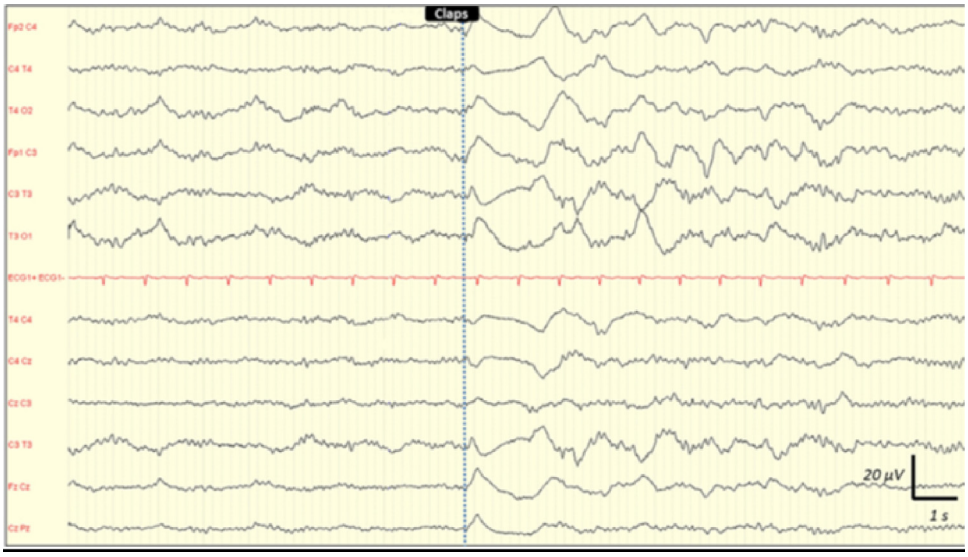

Figure 1 EEG reactivity demonstrating increase in amplitude and frequency of EEG waves after tactile stimuli at blue line.

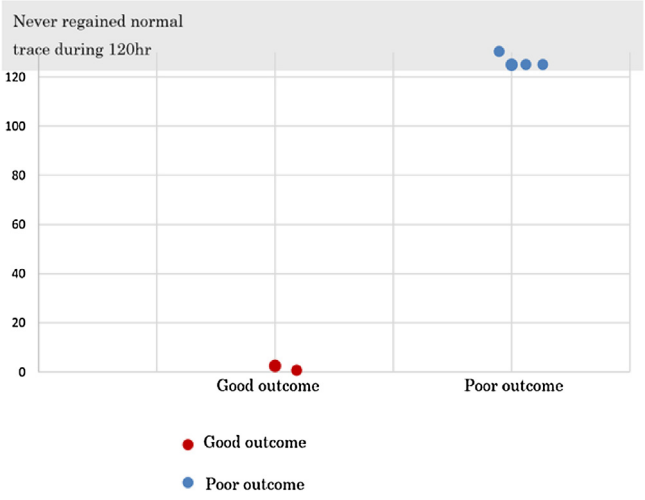

Figure 2 Time to normal trace for the patients in both groups.

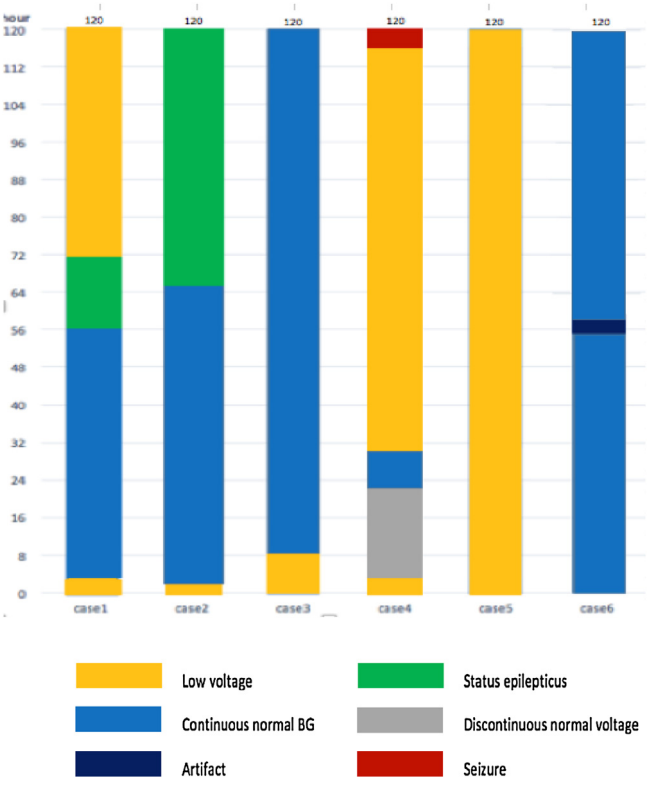

Figure 3 Background EEG evolution during 120 hours of continuous EEG monitoring. Patients in the good outcome group (cases 3, 6) showed continuous EEG background from the early hours of monitoring onwards. Patients in the poor outcome group showed prolonged status epilepticus for 16 hours and 56 hours (cases 1 and 2, respectively). Case 4 also had seizures during last 3 hours of EEG monitoring. The Y-axis indicates the time point after EEG monitoring (hours).

and 4 (poor outcome group) had CPC scores of 4 at two-year follow up and remain on antiepileptic medication. Case 4 has intractable epilepsy despite multiple AEDs.

Table 5 Therapeutic hypothermia complications in good outcome and poor outcome group.

Complication	Good outcome ($n=2$)	Poor outcome ($n=4$)
Bleeding	0	1
Pneumonia	1	2
Renal failure	0	0
Cardiac arrest	0	0
Pancreatitis	0	1
Pulmonary edema	0	0
Lethal/lasting arrhythmia	0	0

Discussion

In our study, we evaluated the prognostic value of CEEG in pediatric hypothermia patients after cardiac arrest, during 120 hours following PICU admission. Our study found that when reactivity of EEG was present, and early normal continuous normal voltage (CNV) trace was detected, good neurological outcome might be predicted. Secondly, SE at any time and lack of CNV trace were associated with poor neurological outcome.

These findings are consistent with those previously published by Oh SH et al. [14], who reported that TTNT less than 24 hours and presence of normal trace within 36 hours were associated with good neurological outcome in adult patients. Tjepkema-Cloostermans MC et al. [21] reported that an EEG with continuous background observed within 12 hours after arrest could be used to predict a good neurological outcome with a positive predictive value of 100 [95% CI 69—100].

Our findings showed that presence of EEG reactivity is a good predictor for neurological outcome. EEG reactivity is considered to be a marker of thalamocortical networks underlying vigilance; therefore unreactive background rhythms may indicate impaired connections that make substantial neurological recovery impossible [10,13,16]. Our findings were consistent with a previous study by Rossetti AO et al. [18], showing that EEG reactivity to painful stimuli in post cardiac arrest patients during the hypothermia period had predictive value of good neurological outcome, which was greater than that of somatosensory evoked potentials (SSEPs), whereas absent EEG reactivity during the maintenance phase of TH was associated with poor neurological outcome.

Electrographic seizures and epileptiform activity were common findings in comatose patients undergoing TH [18—20]. Some studies reported that the majority of seizures usually occurred before rewarming, could evolve to status epilepticus (SE) and were associated with poor neurological outcome despite multiple antiepileptic drugs being given [6,11,13]. Three patients initially developed subclinical seizures. Two patients progressed to non-convulsive SE. The patient who had prolonged SE for 56 hours deceased and the other patient had SE controlled within 15 hours after administration of antiepileptic drugs (Fig. 3) The onset of all cases of SE was before rewarming period. Our findings are consistent with previous recent studies indicating that seizures may occur during the maintenance phase of TH

[11,18,20]. Seizures and status epilepticus were predictors of poor neurological outcome [11].

Our study has some limitations, notably the small number of subjects. Thus, our result is to be considered as preliminary and larger study groups are needed to confirm our conclusion. In addition, our study was performed at single medical center; a multicenter study may be the next step for further research.

Conclusion

We studied the prognosis of post cardiac arrest pediatric patients undergoing therapeutic hypothermia. EEG characteristics related to good neurological outcomes were reactivity during external stimulation and early time to normal trace, whereas EEG characteristics related to poor neurological outcome were seizures and status epilepticus.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgment

The authors would like to thank Tayard Desudchit, MD, Krisnachai Chomtho, MD, Khemmachart Pongsanon, MD, Lalida Kongkiattikul, MD for excellent patient care.

References

[1] Abend NS, Topjian A, Ichord R, Herman ST, Helfaer M, Donnelly M, et al. Electroencephalographic monitoring during hypothermia after pediatric cardiac arrest. Neurology 2009;72:1931—40.
[2] Abend NS, Mani R, Tschuda TN, Chang T, Topjian AA, Donnelly M, et al. EEG monitoring during therapeutic hypothermia in neonates, children, and adults. Am J Electroneurodiagnostic Technol 2011;51:141—64.
[3] Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557—63.
[4] Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;46:549—56.
[5] Kessler SK, Topjian AA, Gutierrez-Colina AM, Ichord RN, Donnelly M, Nadkarni VM, et al. Short-term outcome prediction by electroencephalographic features in children treated with therapeutic hypothermia after cardiac arrest. Neurocrit Care 2011;14:37—43.
[6] Krumholz A, Stern BJ, Weiss HD. Outcome from coma after cardiopulmonary resuscitation: relation to seizures and myoclonus. Neurology 1988;38:401—5.
[7] Lan YH, Zhu XM, Zhou YF, Qiu PL, Lu GP, Sun DK, et al. Prognostic value of continuous electroencephalography monitoring in children with severe brain damage. Neuropediatrics 2015;46:211—20.
[8] Legriel S, Bruneel F, Sediri H, Hilly J, Abbosh N, Lagarrigue MH, et al. Early EEG monitoring for detecting post anoxic status epilepticus during therapeutic hypothermia: a pilot study. Neurocrit Care 2009;11:338—44.
[9] Maconochie IK, de Caen AR, Aickin R, Atkins DL, Biarent D, Guerguerian AM, et al. Part 6: Pediatric basic life support and pediatric advanced life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation 2015;95:e147—68.
[10] Madhok J, Maybhate A, Xiong W, Koenig MA, Geocadin RG, Jia X, et al. Quantitative assessment of somatosensory-evoked potentials after cardiac arrest in rats: prognostication of functional outcomes. Crit Care Med 2010;38:1709—17.
[11] Mani R, Schmitt SE, Mazer M, Putt ME, Gaieski DF. The frequency and timing of epileptiform activity on continuous electroencephalogram in comatose post-cardiac arrest syndrome patients treated with therapeutic hypothermia. Resuscitation 2012;83:840—7.
[12] Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. N Engl J Med 2015;372:1898—908.
[13] Muhlhofer W1, Szaflarski JP. Prognostic Value of EEG in Patients after Cardiac Arrest-An Updated Review. Curr Neurol Neurosci Rep 2018;18:16.
[14] Oh SH, Park KN, Shon YM, Kim YM, Kim HJ, Youn CS, et al. Continuous Amplitude-Integrated Electroencephalographic Monitoring Is a Useful Prognostic Tool for Hypothermia-Treated Cardiac Arrest Patients. Circulation 2015;132:1094—103.
[15] Topjian AA, Sánchez SM, Shults J, Berg RA, Dlugos DJ, Abend NS. Early Electroencephalographic Background Features Predict Outcomes in Children Resuscitated from Cardiac Arrest. Pediatr Crit Care Med 2016;17:547—57.
[16] Rosanova M, Gosseries O, Casarotto S, Boly M, Casali AG, Bruno MA, et al. Recovery of cortical effective connectivity and recovery of consciousness in vegetative patients. Brain 2012;135:1308—20.
[17] Rossetti AO, Logroscino G, Liaudet L, Ruffieux C, Ribordy V, Schaller MD, et al. Status epilepticus: an independent outcome predictor after cerebral anoxia. Neurology 2007;69:255—60.
[18] Rossetti AO, Urbano LA, Delodder F, Kaplan PW, Oddo M. Prognostic value of continuous EEG monitoring during therapeutic hypothermia after cardiac arrest. Crit Care 2010;14:R173.
[19] Rundgren M, Rosen I, Friberg H. Amplitude-integrated EEG (aEEG) predicts outcome after cardiac arrest and induced hypothermia. Intensive Care Med 2006;32:836—42.
[20] Rundgren M, Westhall E, Cronberg T, Rosen I, Friberg H. Continuous amplitude- integrated electroencephalogram predicts outcome in hypothermia-treated cardiac arrest patients. Crit Care Med 2010;38:1838—44.
[21] Tjepkema-Cloostermans MC, Hofmeijer J, Trof RJ, Blans MJ, Beishuizen A, van Putten MJ. Electroencephalogram predicts outcome in patients with postanoxic coma during mild therapeutic hypothermia. Crit Care Med 2015;43:159—67.