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COMPARISON BETWEEN OUTCOME PREDICTORS OF HYPOXIC ENCEPHALOPATHY

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ABSTRACT

Hypoxic encephalopathy after cardiac arrest is a common cause of coma requiring intensive care of survivors. Certain malignant electroencephalographic (EEG) patterns have been shown to correlate with poor prognosis. Neuron specific enolase (NSE) released after cardiac arrest is regarded as a severity indicator of postanoxic neuronal injury. We investigated the EEG findings in post-cardiac arrest patients and compared these findings with clinical parameters and NSE levels and outcome scales.

Material and methods: 40 Egyptian patients after resuscitation from cardiac arrest were subjected to Glascow coma scale (GCS), corneal reflex, pupillary reflex, EEG, NSE measurement, and Glasgow outcome scale (GOS).

Results: There was high statstically significant difference between good and bad outcome groups as regards corneal and pupillary reflexes on first day, GCS on first and third days, EEG patterns on first and seventh days and NSE levels on first and third days.

Conclusion: In post cardiopulmonary arrest patients, certain clinical parameters like corneal and pupillary reflexes in first day and GCS on first and third days post arrest are good predictors of outcome. Also malignant EEG patterns (burst suppression, unreactive background and low voltage background) and NSE levels post arrest are good predictors of bad outcome of post arrest with higher sensitivity and specificity of NSE levels than malignant EEG patterns to predict bad outcome.

INTRODUCTION

Despite advances in the treatment of heart disease, the outcome of patients experiencing SCA remains poor (Rea TD *et al*).

The need for protracted high-intensity care of neurologically devastated survivors presents an immense burden to healthcare systems, patients' families, and society in general (Hamel MB *et al*).

To limit this burden, clinical factors and diagnostic tests are used to prognosticate functional outcome. With the limitation of care or withdrawal of life-sustaining therapies as a likely outcome of prognostication, studies have focused on poor long-term prognosis (vegetative state or death) based on clinical or test findings that indicate irreversible brain injury (Geocadin RG *et al*).

Recently, several systematic reviews evaluated predictors of poor outcome, including clinical circumstances of cardiac arrest and resuscitation, patient characteristics, neurological examination, electrophysiological studies, biochemical markers, and neuroimaging (Wijdicks EF *et al*).

EEG has been used to assist in determining the prognosis following cardiac arrest since the 1960s, when Hockaday *et al.* advised an EEG rating scale to predict neurologic outcome in this setting. This scale was found to have an accuracy of 80% (Hockaday JM *et al*).Certain malignant EEG patterns including a nonreactive background (Rossetti AO *et al*), burst suppression and low voltage 20 <μV (Fugate JE *et al*).

Neuron-specific enolase (NSE) is an intracellular enzyme found in neurons and other cells of neurodermal origin (Schmechel D *et al*). Elevation of serum NSE 1-3 days after cardiac arrest is regarded as a severity of postanoxic neuronal injury; it has been shown to be released in the serum of patients after CA, with a half-life of about 24 hours (Oksanen T *et al*).

The current study aimed to investigate the EEG findings in post-cardiac arrest patients and to compare its predictive value with that of serum neuron-specific enolase levels.

MATERIAL AND METHODS

The study was approved by the ethical committee of the Alexandria faculty of medicine and an informed consent signed by patients relatives.

Patients we prospectively studied a cohort of 40 normothermic consecutive comatose adults admitted between January 2014

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and january 2015 to the Department of Intensive Care Medicine of Alexandria main university hospital, after successful resuscitation from CA. we excluded patients who were less than 16 years old, or with recent intake of sedatives, head trauma, metabolic derangments, or diagnosed as brain death.

Outcome assessment Functional neurologic outcome was assessed at 3 months through a phone interview by trained personnel of the EEG unit who had no access to study data, and categorized according to the Glasgow outcome scale Categories (GOS) (B. Jennett *et al*). In line with the vast majority of studies on this topic, outcome was dichotomized as good (GOS 3 – 4 - 5) vs poor (GOS 1 - 2).

EEG data EEG monitoring was done within the first day of admission for about 30 minutes and repeated on the seventh days after cardiac arrest. Stimulation (nail bed pressure, passive eye opening, and shouting in the ear) was routinely performed to show the reactivity of background. recording was done using Nicolet (21 channels) machine, using both bipolar and referential montages with the electrodes (21 electrodes) placed according to the international 10-20 system using EEG free electrodes with filter setting low cut filter of 1.6Hz and high cut filter 35 Hz.

EEG classification on days 1and 7 post-arrest according to Young *et al* (Young GB *et al*).

1. Delta/theta > 50% of recording
2. Triphasic waves
3. Burst-suppression pattern: with or without epileptiform activity
4. Alpha/theta/spindle pattern coma (no reactivity).
5. Suppression (generalized) : <20 microvolts

EEG patterns will be divided into benign and malignant according to Synek *et al*. benign consisted of patterns I&II, while malignant consisted of III, IV & V (Synek VM *et al*).

NSE will be sampled at both day 1 and 3 after cardiac arrest. Serum concentrations of NSE will be measured using ELISA technique.

Statistical Analysis

Qualitative data were described using number and percent. Quantitative data were described using mean and standard deviation, median, minimum and maximum. Agreement of the different predictives with the outcome was used and was expressed in sensitivity, specificity, positive predictive value, negative predictive value and accuracy. Receiver operating characteristic curve (ROC) was plotted to analyze a recommended cut off, the area under the ROC curve denotes the diagnostic performance of the test. Area more than 50% gives acceptable performance and area about 100% is the best performance for the test.

RESULTS

This study included 40 post cardiopulmonary arrest patients, 11 with good outcome and 29 with bad outcome.

Comparison of baseline characteristics (table 1)

Table 1 Baseline characteristic (n=40)

	Good (I) (n = 11)	Bad (II) (n = 29)	P value
Sex n (%)			
Male	7(63.6)	18(62.1)	1.000
Female	4(36.4)	11(37.9)	
Age years(**Mean ± SD)**	55.4 ± 11.43	47.7 ± 15.1	0.137
Place of arrest n (%)			
Inside icu	10(90.9)	16(55.2)	.061
Outside icu	1(9.1)	13(44.8)	
Resuscitation time minutes (Median)	10	12	0.035

25 male patients (62.5%) and 15 female patients (37.5%). Their ages ranged from 19 to 72 years (mean 50.88 ± 14.99); none of our patients was treated with hypothermia protocol. This shows no significance difference between the two groups as regards age and sex.

26 patients (65%) arrested in the ICU while 14 (35.0%) arrested outside the ICU inside the hospital. Resuscitation time had median of 10 minutes in good outcome group while had median of 12 minutes in bad group. This shows that there was no significant difference between the two groups as regards place of arrest but there was significant difference as regards resuscitation time.

Comparison of Clinical Parameters (Table 2)

Table 2 comparison of clinical parameters (n=40)

	Good (I) (n = 11)	Bad (II) (n = 29)	P value
Corneal reflex 1st day			
Preserved	11(100)	15(51.7)	0.004*
Lost	0(0.0)	14 (48.3)	
Corneal reflex 3rd day			
Preserved	11(100)	17(58.6)	0.017
Lost	0(0.0)	12 (41.4)	
Pupillary reflex 1st day			
Preserved	11(100)	5(17.2)	<0.001*
Lost	0(0.0)	24(82.8)	
Pupillary reflex 3rd day			
Preserved	11(100)	17(58.6)	0.017
Lost	0(0.0)	12(41.4)	
GCS on day 1 (Median)	8.0	5.0	<0.001*
GCS on day 3 (Median)	14.0	4.0	<0.001*
Myoclonus n (%)			
Present	0(0.0)	6(20.7)	0.162
Absent	11(100.0)	23(79.3)	

This shows Corneal and pupillary reflexes were lost only in bad outcome group on day 1 and 3. Corneal reflex was lost in 14 patients on day 1 and in 12 on day 3.Pupillary reflex was lost in 24 patients on day 1 and in 12 patients on day 3. There was statistically significant difference between the two groups as regards corneal and pupillary reflexes in first and third days after arrest.

Clinical observation revealed 6 (20.7%) patients with myoclonus with no significant difference between the two groups.

GCS scores in good group had median of 8 and 14 on day 1 and 3 respectively, while in bad group had median of 5 and 4 on day 1 and 3 respectively. There was statistically significant difference between the two groups as regards GCS in first and third day after arrest.

Comparison of EEG patterns (Table 3 - 4)

Table 3 Comparison between two groups regarding nonconvulsive seizures and status

	Good (n = 11)	Bad (n = 29)	P
Nonconvulsive seizures n (%)	0 (0%)	5 (17.2%)	0.297
Nonconvulsive status n **(%)**	0 (0%)	8 (27.5%)	0.803

Table 4 Impact of EEG patterns on outcome (n=40)

EEG	**GOS**			
	Good (n = 11)		**Bad (vegetative or dead) (n = 29)**	
	No.	**%**	**No.**	**%**
1st day				
I. (delta/theta > 50%)	6	54.5	2	6.89
II. (triphasic waves)	3	27.2	1	3.44
III. (burst suppression)	1	9.09	9	31.0
IV. (unreactive background)	1	9.09	4	13.7
V. (low voltage < 20 µV)	0	0.0	13	44.8
(p)			(<0.001*)	
7th day				
I. (delta/theta > 50%)	7	63.6	0	0.0
II. (triphasic waves)	2	18.1	2	6.89
III. (burst suppression)	1	9.09	4	13.7
IV. (unreactive background)	1	9.09	7	24.1
V. (low voltage < 20 µV)	0	0.0	16	55.1
(p)			(<0.001*)	

29 patients had bad outcome (vegetative or dead). Malignant patterns were found in 26 of them. Burst suppression was found in 9 patients on first day and 4 patients on seventh day (Figure1). Unreactive background was found in 4 patients on first day and in 7 patients on seventh day. Low voltage background < 20 microvolts was found in 13 patients on first and 16 patients on seventh day. There was statistically significant difference between the two groups as regards incidence of malignant EEG patterns.

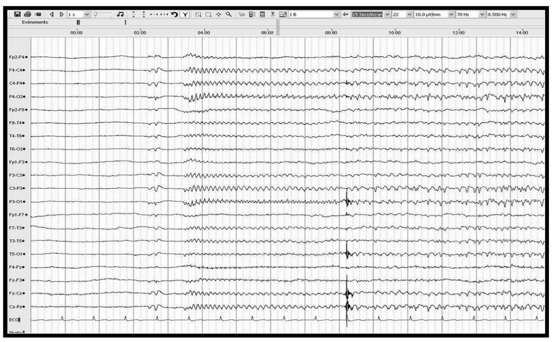

Figure 1 EEG shows discontinuous EEG background activity ("burst-suppression pattern").

Nonconvulsive seizures were found only in 5 Patients (17. 2 %) in bad group, while nonconvulsive status epilepticus was found in 8 patients (27.5 %). There was no stastically significant difference between the two groups as regards incidence of nonconvulsive seizures and status.

Prognostic predictive value of malignant EEG patterns on bad outcome (Table 5)

Table 5 Prognostic predictive value of malignant EEG patterns for bad outcome.

	Sensitivity	Specificity	PPV	NPV
Mailgnant EEG day1	89.6	81.8	74	75
Malignant EEG day3	93.1	81.1	75	81.1

EEG on first day, malignant patterns had sensitivity of 89.6 %, specificity of 81.8 %, PPV of 74 % and NPV of 75 % to predict bad outcome. While malignant patterns on seventh day had sensitivity of 93.1 %, specificity of 81.1 %, PPV of 75 % and NPV of 81.1 to predict bad outcome.

Comparison of NSE Levels (Table 6)

Table 6 comparison of NSE levels in both groups

	Good (n = 11)	Bad (n = 29)	P
NSE 1st day Median.	6	43	0.001*
NSE 3rd day Median	5	24	<0.001*

NSE on first day had median of 6 in good outcome while had median of 43 in bad outcome group with statistically significant difference between two groups (p = 0.001).

While on seventh day had median of 5 in good outcome while had median of in bad outcome group with statistically significant difference between two groups (p < 0.001).

Prognostic predictive value of neuron specific enolase on bad outcome (Table 7)

Table 7 Agreement (sensitivity, specificity and accuracy) for N SE in 1st and 3rd days with bad GOS.

	Sensitivity	Specificity	PPV	NPV
NSE day1 cut-off value ≥ 10	96.6	100	71.8	91.7
NSE day3 cut-off value ≥ 8.5	96.6	100	71.8	91.7

Table (7) showed the agreement (sensitivity and specificity) for neuron specific enolase (NSE) in predicting bad outcome with cut-off point ≥ 10 on first day and ≥ 8.5 on third day it came clear that NSE level had sensitivity of 96.6 %, specificity of 100 %, PPV of 71.8 % and NPV of 91.7 % to predict bad outcome.

DISCUSSION

In the last few decades, several clinical and electrophysiological variables have been reported to be strongly associated with a poor outcome in comatose survivors of cardiac arrest, these include absence of pupillary and corneal reflexes, absent motor response to pain (Chen R *et al*), myoclonus or epilepticus status (Thomke F *et al*), an increase of neuron specific enolase (NSE) in serum and a burst-suppression or isoelectric electroencephalography (EEG) pattern (Zandbergen EG *et al*).

Our results regarding EEG findings revealed that 29 patients had bad outcome (vegetative or dead). EEG on first day, malignant patterns had sensitivity of 89.6 %, specificity of 81.8 %, PPV of 74 % and NPV of 75 % to predict bad outcome. While malignant patterns on seventh day had sensitivity of 93.1 %, specificity of 81.1 %, PPV of 75 % and NPV of 81.1 to predict bad outcome.

In a study by Young *et al*., patients with burst suppression or who had low voltage less than 20 µV did not survive (Neurocrit. Care 2005). While in a study by Rossetti *et al*., patients with burst suppression, unreactive background or low voltage < 20µv had PPV OF 100% to predict bad outcome (Neurology 2012).

In the American Academy of Neurology (AAN) recommendations, so-called “malignant” EEG patterns (such as generalized background suppression< 20µv; burst-suppression with generalized epileptiform activity, or unreactive background) during the three first days after cardiac arrest were associated with poor outcome with a FPR of 3% (95% CI: 0.9-11%) (Bonifacio SL *et al*).

Regarding nonconvulsive seizures (NCSz) and status (NCSE) our study showed that nonconvulsive seizures were found only in 5 Patients (17. 2 %) in bad group, while nonconvulsive status epilepticus was found in 8 patients (27.5 %). There was no stastically significant difference between the two groups as regards incidence of nonconvulsive seizures and status.

Seizure activity especially nonconvulsive seizures (NCSz) or nonconvulsive status epilepticus) is common in patients with anoxic–ischemic encephalopathy and may contribute to brain damage and prolonged coma (Neurology.2006). In a series of comatose patients with NCSE, 42% of the patients had hypoxic-anoxic injury after cardiac arrest (Neurology 2012).

Clinical observation revealed 6 (20.7%) patients of bad outcome group with myoclonus with no significant difference between the two groups. Compared to our results, in a group of 67 patients with epileptic myoclonus 22% had a good outcome, myoclonic phenomena in the 1st 3 days were predictors of poor outcome (Neurocrit. Care 2005).

Regarding neuron specific enolase (NSE) sampling, there was highly statistically significant difference between two groups as regards NSE levels on first and third days. NSE level had cut-off point ≥ 10 µg/l on first day and ≥ 8.5 µg/l on third day it came clear that NSE level had sensitivity of 96.6 %, specificity of 100 %, PPV of 71.8 % and NPV of 91.7 % to predict bad outcome.

In one prospective, multicenter study involving 231 patients, NSE level of more than 33 µg per liter, sampled between 1 and 3 days after cardiac arrest, was strongly predictive of a poor outcome (Thomke F *et al*).

Other study showed that an NSE cutoff of 71.0 g/L drawn between 24 and 48 hours after ROSC was required to achieve an FPR of 0% (95% CI (0% to 43%) for predicting poor outcome with a sensitivity of 14% (Grubb NR *et al*). Numerous other studies show various thresholds from 30 to 65 g/L for poor outcome and mortality (Tiainen M *et al*).

CONCLUSION

In post cardiopulmonary arrest patients, certain clinical parameters like corneal and pupillary reflexes in first day and GCS on first and third days post arrest are good predictors of outcome. Also malignant EEG patterns (burst suppression, unreactive background and low voltage background) and NSE levels post arrest are good predictors of bad outcome of post arrest with higher sensitivity and specificity of NSE levels than malignant EEG patterns to predict bad outcome.

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