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Clinical paper

Continuous versus routine EEG in patients after cardiac arrest

Analysis of a randomized controlled trial (CERTA)

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Abstract

Background: Electroencephalography (EEG) is essential to assess prognosis in patients after cardiac arrest (CA). Use of continuous EEG (cEEG) is increasing in critically-ill patients, but it is more resource-consuming than routine EEG (rEEG). Observational studies did not show a major impact of cEEG versus rEEG on outcome, but randomized studies are lacking.

Methods: We analyzed data of the CERTA trial (NCT03129438), including comatose adults after CA undergoing cEEG (30–48 hours) or two rEEG (20–30 minutes each). We explored correlations between recording EEG type and mortality (primary outcome), or Cerebral Performance Categories (CPC, secondary outcome), assessed blindly at 6 months, using uni- and multivariable analyses (adjusting for other prognostic variables showing some imbalance across groups).

Results: We analyzed 112 adults (52 underwent rEEG, 60 cEEG,); 31 (27.7%) were women; 68 (60.7%) patients died. In univariate analysis, mortality (rEEG 59%, cEEG 65%, p = 0.318) and good outcome (CPC 1–2; rEEG 33%, cEEG 27%, p = 0.247) were comparable across EEG groups. This did not change after multiple logistic regressions, adjusting for shockable rhythm, time to return of spontaneous circulation, serum neuron-specific enolase, EEG background reactivity, regarding mortality (cEEG vs rEEG: OR 1.60, 95% CI 0.43–5.83, p = 0.477), and good outcome (OR 0.51, 95% CI 0.14–1.90, p = 0.318).

Conclusion: This analysis suggests that cEEG or repeated rEEG are related to comparable outcomes of comatose patients after CA. Pending a prospective, large randomized trial, this finding does not support the routine use of cEEG for prognostication in this setting.

Trial registration: Continuous EEG Randomized Trial in Adults (CERTA); NCT03129438; July 25, 2019.

Keywords: EEG monitoring, Prognosis, Outcome, Anoxic-ischemic encephalopathy

Introduction

Out-of-hospital cardiac arrest (CA) represents the third cause of death in Europe.[1] Half of these patients receive cardio-pulmonary resuscitation and 10% of them survive at 30 days.[1] The vast majority of resuscitated patients are comatose when arriving at hospital following post-cardiac arrest brain injury.[2] These patients' outcome depends on many factors, such as underlying CA cause, age, initial cardiac rhythm, time of no-flow and return of spontaneous circulation (ROSC), if CA is witnessed,[3] and seizures.[4] In order to assess early prognosis of comatose patients after CA, several tools have been

Abbreviations: CA, cardiac arrest, ROSC, return of spontaneous circulation, EEG, electroencephalography, SSEP, somatosensory evoked potentials, NSE, neuronal-specific enolase, SE, status epilepticus, cEEG, continuous electroencephalogram, rEEG, routine electroencephalogram, CERTA, Continuous EEG Randomized Trial in Adults, ACNS, American Clinical Neurophysiology Society, CPC, Cerebral Performance Categories, TTM, targeted temperature management, WLST, withdrawal of life-sustaining treatment, MRI, magnetic resonance imaging, GCS, Glasgow Coma Scale, mRS, modified Rankin Scale, GPDs, generalized periodic discharges, LPDs, lateralized periodic discharges, LRDA, lateralized rhythmic delta activity, IQR, interquartile range.

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studied and are now routinely used, such as clinical findings (brainstem reflexes and motor reactions), electroencephalography (EEG), somatosensory evoked potentials (SSEP) and biological markers, particularly neuronal-specific enolase (NSE).[5]

To assess prognostication, early EEG has an essential role in these patients' setting to evaluate brain function and to determine the magnitude of brain injury post-CA[6–8]; it also allows identification of repetitive epileptiform activity, translating into seizures or status epilepticus (SE).[9,10] In general, the use of continuous EEG (cEEG) is steadily increasing in intensive care units patients,[11,12] and international guidelines recommend this approach.[13, 14] Indeed, it has been demonstrated that cEEG proves more sensitive for seizure or SE detection than routine EEG (rEEG, typically lasting 20–30 minutes).[15,16] On the other hand, it is more time-, resource- and person-consuming,[11,15–17] which may lead to questioning the cost-effectiveness in some settings.[18] Therefore, large-scale cEEG implementation in many centers outside North America is still somewhat limited.[19]

Furthermore, the optimal duration of EEG recordings in post CA setting still appears unclear. Several experts recommend cEEG to optimally follow the evolution of background activity in the first few days after CA,[8,10,20–23] while others point out that cEEG may not be related to improved outcome[24,25] nor more informative about prognosis.[26]

The impact of cEEG versus repeated rEEG on clinical outcome has been assessed in a recent multicenter randomized controlled trial (Continuous EEG Randomized Trial in Adults (CERTA); NCT03129438) in adults with acute consciousness impairment of different etiologies [16]: it showed no difference between groups regarding mortality and functional outcomes at 6 months. The aim of the present study is to analyze the subgroup of patients who had a CA and assess the relationship of these two EEG procedures with outcome.

Methods

Study population, clinical variables and outcomes

This is a post-hoc analysis of prospectively acquired data from the CERTA study, conducted in four Swiss hospitals (Centre Hospitalier Universitaire Vaudois in Lausanne, Inselspital Bern, Universitätsspital Basel, and Hôpital du Valais Sion) between April 2018 and September 2019. In this trial, 364 adults were randomized 1:1 to cEEG (lasting 30–48 hours) or two rEEG (20–30 minutes each, repeated within the same timeframe), with interpretations performed according to the American Clinical Neurophysiology Society (ACNS) recommendations at that time.[27] Demographic and clinical variables were recorded prospectively. Outcome at six months, assessed blindly, included mortality and Cerebral Performance Categories (CPC; good outcome defined by a CPC 1 (no impairment) and CPC 2 (moderate impairment)[28]). Patients in palliative care, with recent seizures (within 36 hours) or SE (within 96 hours before randomization) were not enrolled. Methods[29] and the study protocol[16] have been published previously. This study was approved by the ethics committee of each participating center (leader: Commission cantonale d'éthique de la recherche sur l'être humain, protocol 2017–00268).

Of the 364 enrolled patients, 112 (representing 30.8% of the trial cohort) had a hypoxic-ischemic encephalopathy following CA. They were kept at a targeted temperature management (TTM) of 36 °C for 24 hours; they were sedated with propofol (2–3 mg/kg/h) or midazolam (0.1 mg/kg/h), and fentanyl (1.5 μg/kg/h) during TTM.[30] Withdrawal of life-sustaining treatment (WLST) was decided multidisciplinary at each site, on similar criteria across the participating hospitals, including at least two items with low false-positive rate assessed at $\geq$ 72 hours, off sedation: lack of pupillary reflexes, lack of bilateral SSEP responses, lack of EEG background reactivity after rewarming, treatment resistant SE; high serum NSE (>75 μg/l) and extensive anoxic magnetic resonance imaging (MRI) alterations represented additional criteria.[30,31]

For the present study, we retrieved information about the two randomization EEG arms and assessed several demographical and clinical variables relevant for post-CA prognosis: demographics, Glasgow Coma Scale (GCS), modified Rankin Scale (mRS) before admission, CA etiology (cardiac versus other), initial rhythm (shockable versus non-shockable) and time to ROSC. We also retrieved specific EEG items related to prognosis after CA from the recorded data[9], such as best background continuity, reactivity,[32] any occurrence of sporadic epileptiform discharges, any occurrence of items of the ictal-interictal continuum (generalized periodic discharges (GPDs), lateralized periodic discharges (LPDs) and lateralized rhythmic delta activity (LRDA)), any seizures or SE detection, and any occurrence of "highly malignant" EEG patterns (i.e., suppressed or burst-suppressed background, with or without repetitive epileptiform discharges).[33] Other prognostic variables were bilateral absence of pupillary reflex, bilateral absence of median nerve cortical somatosensory evoked potentials (SSEP, typically performed at 36–48 hours post-CA), and highest serum NSE (typically measured at 24 and 48 hours). We also considered the duration of hospitalization until discharge or death. Mortality was the primary outcome, and CPC 1–2 the secondary outcome. The design and methodology of the study are reported according to STARD guidelines concerning the diagnostic accuracy of the data[34] and Standards for Studies of Neurological Prognostication in Comatose Survivors of Cardiac Arrest edited by American Heart Association.[35] Data are presented according to CONSORT reporting guidelines.

Statistical analysis

Patients were stratified based on EEG type (cEEG versus rEEG) to explore variables distribution. Comparisons were assessed using Mann-Whitney U, 2-sided Fisher, Student t, or chi-square tests, as appropriate. Multivariable logistic regressions were applied to identify independent variables related to mortality and good outcome, adjusting for variables showing some imbalance across EEG groups ($p \leq 0.15$ in univariate analyses); goodness of fit was assessed through Hosmer-Lemeshow tests. Calculations with p-value ≤ 0.05 were considered statistically significant. We used Stata, version 17 (College Station, TX).

Results

A total of 112 patients with consciousness impairment (Glasgow Coma Scale = 3) post-CA were analyzed: 60 underwent cEEG and 52 rEEG.[16] There were 31 women (27.7%) with a mean age of 64.3 years (standard deviation [SD] ± 13.4); 68 patients died (60.7%). Table 1 illustrates the distribution of demographical, clinical and electroencephalographic variables, and outcome stratified by EEG type.

The EEG groups were comparable for most assessed variables, including demographics, CA etiology, initial rhythm, time to EEG, sporadic epileptiform discharges, patterns of the ictal-interictal continuum (GPDs, LPDs and LRDA), and the proportion of highly malignant EEG. Some items showed some asymmetry, albeit non-significant (see below), and time to ROSC, EEG background reactivity, as well as serum NSE were asymmetrically distributed across the groups.

In order to assess the relationship of the EEG recording types with clinical outcome, we conducted multivariable logistic regressions, adjusting for potentially prognostic variables having a p-value $\leq$ 0.15 in univariable analyses (i.e.: time to ROSC, initial CA rhythm, EEG detection of seizure or SE, EEG background reactivity, SSEP, serum NSE peak). After adjustment, EEG type was not correlated to mortality (Table 2), or good outcome (CPC 1 or 2, Table 3) at 6 months, while first cardiac rhythm and serum NSE peak were independently correlated to them (the models had excellent goodness of fit: p = 0.952, respectively p = 0.961, Hosmer-Lemeshow). Of note, SSEP, seizure/SE detection and background reactivity were omitted from the models as they completely explained the outcomes.

Discussion

This analysis suggests that the use of cEEG or repeated rEEG in comatose adults post-CA is not correlated to mortality or functional clinical outcome. To our knowledge, this relies for the first time on data from a randomized clinical trial, and complements the original publication [16] by adding several details regarding the CA etiologic group, and adjusting for possible confounders in the outcomes' analyses.

Variables related to unfavorable and, more recently, favorable outcomes after CA, have been extensively reported, such as type of arrest, time to ROSC, clinical examination, EEG background continuity and reactivity, occurrence of repetitive epileptiform discharges, SSEP cortical responses, and serum NSE peak.[5,7,9,31,36–38] In our patients, time to ROSC and serum NSE peak were higher in the cEEG group, this constellation likely reflected a higher extent of brain injury severity and explains a higher proportion of nonreactive or discontinuous EEG background in this arm. Nevertheless, adjustment for these and other variables having some asymmetrical distribution across the EEG intervention groups did not modify the final results. Of note, EEG latency since admission was comparable across groups, replicating the recent data grouping all etiologies.[39]

A recent study on CA patients estimated that cEEG may prove superior to rEEG (artificially clipped from cEEG) in detecting some potentially prognostic variables, especially if limited to one short clip within 24 hours of CA, but not in detecting potentially treatable seizures.[40] In our analysis, while rEEG was not-significantly less sensitive than cEEG to detect seizures or SE, sporadic epileptiform discharges, patterns of the ictal-interictal continuum and of highly malignant EEG were highly comparable between the two EEG arms; of note, our study relied on repeated rEEG, which may offer a reasonable follow up of the electrical brain activity. Thus, cEEG does not seem to provide significant additional information regarding prognostication after CA. In fact, seizures and SE, which are related to

Table 1 – Exploratory analysis of type of EEG recording, demographic, and clinical characteristics of post cardiac arrest patients. Values represent numbers (and percentages), or medians (and interquartile ranges). Bold values are significant.

	cEEG (60; 53.6%)	**rEEG** (52; 46.4%)	p-value	test
Age (yrs ± SD)	64.3 (±12.1)	64.2 (±14.8)	0.949	t
Female gender	14 (23.3%)	17 (32.7%)	0.270	Chi2
GCS on admission	3 (IQR: 3–3)	3 (IQR: 3–3)	0.184	U-test
mRS before admission	0 (IQR: 0–2)	0.5 (IQR: 0–2)	0.392	U-test
Time to ROSC [min]	27.0 (IQR: 13.0–45.0)	18.0 (IQR: 10.0–26.0)	**0.011**	U-test
Cardiac etiology of CA	40 (66.7%)	33 (63.5%)	0.723	Chi2
Non-shockable initial rhythm (pulseless electrical activity, asystole)	29 (48.3%)	33 (63.5%)	0.108	Chi2
Time to EEG after admission [hrs]	22.0 (IQR: 15.8–43.8)	24.6 (IQR: 17.9–64.6)	0.179	U-test
Detection of seizure or SE	12 (20%)	5 (9.6%)	0.127	Chi2
Sporadic epileptiform discharges	21 (35%)	19 (36.5%)	0.865	Chi2
Ictal-interictal continuum (GPD, LPD, LRDA)	11 (18.3%)	7 (13.5%)	0.484	Chi2
Best background continuity (continuous or discontinuous)	40 (66.7%)	39 (75.0%)	0.335	Chi2
Background reactivity	34 (56.7%)	41 (78.9%)	**0.013**	Chi2
Highly malignant EEG [33] at any time	26 (43.3%)	18 (34.6%)	0.346	Chi2
Pupillary reflex bilaterally absent at 72hrs	13 (21.7%)	10 (19.2%)	0.750	Chi2
Cortical SSEP bilaterally absent	18 (36.7%)	10 (22.2%)	0.124	Chi2
Peak NSE [ug/L] within 48 h	46 (IQR: 29.6–83.2)*	27.4 (IQR: 19.7–51)**	**0.008**	U-test
Duration of admission until discharge or death [days]	7.9 (IQR: 3–19.4)	8.8 (IQR: 4.3–27.6)	0.320	U-test
Mortality at 6 months	39 (65%)	29 (55.8%)	0.318	Chi2
CPC at 6 months	5 (IQR: 2–5)	5 (IQR: 1–5)	0.247	U-test
CPC 1–2 at 6 months	16 (26.7%)	17 (32.7%)	0.485	Chi2

CA = cardiac arrest, cEEG = continuous electroencephalography, CHUV = Centre Hospitalier Universitaire Vaudois, CPC = Cerebral Performance Category scale, EEG = electroencephalography, GCS = Glasgow Coma Scale, GPD = generalized periodic discharges, LPD = lateralized periodic discharges, LRDA = lateralized rhythmic delta activity, mRS = modified Rankin Score, NSE = neuron-specific enolase, rEEG = routine electroencephalography, ROSC = Return Of Spontaneous Circulation, [min] = minutes, SE = status epilepticus, SSEP = somatosensory evoked potentials.

* Assessed in 47 patients in the cEEG arm.

** 37 patients in the rEEG arm.

Table 2 – Result of the multivariable logistic regression for mortality at 6 months.

	OR	p-value	95% CI
Continuous EEG	1.6	0.48	0.44–5.83
Time to ROSC	1.03	0.24	0.98–1.07
Non-shockable initial rhythm (pulseless electrical activity, asystole)	6.01	**0.01**	1.61–22.48
Peak NSE [ug/L] within 48 h	1.07	**0.01**	1.02–1.12

EEG = electroencephalography, NSE = neuron-specific enolase, ROSC = return of spontaneous circulation.

Table 3 – Result of the multivariable logistic regression for CPC 1 and 2 at 6 months.

	OR	p-value	95% CI
Continuous EEG	0.51	0.32	0.14–1.9
Time to ROSC	0.98	0.46	0.94–1.03
Non-shockable initial rhythm (pulseless electrical activity, asystole)	0.19	**0.01**	0.05–0.71
Peak NSE [ug/L] within 48 h	0.93	**0.01**	0.88–0.99

EEG = electroencephalography, NSE = neuron-specific enolase, ROSC = return of spontaneous circulation.

poor outcome, usually occur early after CA.[22] Moreover, despite seizure treatment, the outcome often does not improve,[41,42] apart from relatively few selected patients.[43–45] This global lack of improvement can be explained, at least in part, by the extent of the underlying brain injury rather than seizures themselves.[46] The present findings support previous retrospective observational assessments suggesting that the quality of prognostic information is comparable across different EEG recording lengths.[24–26] A previous analysis on whole CERTA cohort pointed out that several EEG patterns used for post-CA prognostication are actually readily available in repeated rEEG, such as background continuity, frequency and reactivity,[47] even if a granular follow-up is not allowed. On the other side, several aspects of EEG prognostication were not evaluated in the present study, such as identical bursts, time to a continuous background or to ictal-interictal continuum patterns, seizure burden, or sleep elements; these features may provide additional prognostic information and be more easily available from cEEG.[48]

One of the study strengths is the randomized allocation to the EEG recording length; also, the multicenter design supports generalizability to other clinical cohorts. All data were prospectively acquired using standardized and pre-defined measures, which underscores its internal validity. Furthermore, functional outcome and mortality were assessed blindly at 6 months, representing a robust outcome. Nevertheless, these results should be interpreted in light of limitations. This analysis explores a diagnostic tool (EEG) with an outcome (mortality) that may not be affected by the tool; choosing WLST as an outcome would have been more precise, but, unfortunately, we lack this information in the CERTA data. Nevertheless, the comparable admission duration across EEG groups seems to argue against a major difference of WLST timing, and the present results inform on a relevant practical question (i.e., is EEG duration related to outcome?) in this diagnostic group. Evaluation of the prognostication process is anyway complex, due to the multiple prognostic tools that are used. The relatively limited number of patients in each CA group reduces statistical power: CERTA was designed to assess a survival difference between EEG intervention groups taking into account all causes of consciousness impairment, while this is a post-hoc analysis, focusing only on one etiology. However, it seems unlikely that the small, non-significant trend of the point estimate towards worse outcome in the cEEG group may be reversed increasing the sample size. This raises the question whether the cEEG group had greater disease severity; we adjusted for potential confounders but some unmeasured factors may have been missed. The treatment teams knew the EEG arms allocation. In theory, it is possible that a systematic differential approach in terms of treatment strategy and prognostication (both were not specifically protocolled in CERTA, which was intended as a pragmatic study, and in this patient group relied on WLST guidelines at each center) was used according to the EEG intervention types. This, however, seems unlikely, as all involved caregivers used similar WLST criteria; again, duration of hospital stay was comparable across groups. Finally, unfortunately the dataset does not have detailed information on MRI.

Conclusion

This analysis of data from a randomized trial suggests that cEEG or repeated rEEG are related to comparable outcomes of comatose patients surviving a CA. Pending a larger, prospective trial, ideally with EEG results provided blindly to caregivers (regarding the EEG intervention), the present findings do not appear to support the routine use of cEEG for prognostication in this setting, especially in resource-limited environments.

Declaration of competing interests

Authors declare no conflict of interest.

Ethics approval and consent to participate

This study was approved by the ethic committee of each participating center (leader: Commission cantonale d'éthique de la recherche sur l'être humain 2017–00268).). Recruited patients (or their proxy or guardians) gave their written informed consent.

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