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Neurostimulant use is associated with improved survival in comatose patients after cardiac arrest regardless of electroencephalographic substrate☆

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ABSTRACT

Aim: Identify EEG patterns that predict or preclude favorable response in comatose post-arrest patients receiving neurostimulants.
Methods: We examined a retrospective cohort of consecutive electroencephalography (EEG)-monitored comatose post-arrest patients. We classified the last day of EEG recording before neurostimulant administration based on continuity (continuous/discontinuous), reactivity (yes/no) and malignant patterns (periodic discharges, suppression burst, myoclonic status epilepticus or seizures; yes/no). In subjects who did not receive neurostimulants, we examined the last 24 h of available recording. For our primary analysis, we used logistic regression to identify EEG predictors of favorable response to treatment (awakening).
Results: In 585 subjects, mean (SD) age was 57 (17) years and 227 (39%) were female. Forty-seven patients (8%) received a neurostimulant. Neurostimulant administration independently predicted improved survival to hospital discharge in the overall cohort (adjusted odds ratio (aOR) 4.00, 95% CI 1.68–9.52) although functionally favorable survival did not differ. No EEG characteristic predicted favorable response to neurostimulants. In each subgroup of unfavorable EEG characteristics, neurostimulants were associated with increased survival to hospital discharge (discontinuous background: 44% vs 7%, P = 0.004; non-reactive background: 56% vs 6%, P < 0.001; malignant patterns: 63% vs 5%, P < 0.001).
Conclusion: EEG patterns described as ominous after cardiac arrest did not preclude survival or awakening after neurostimulant administration. These data are limited by their observational nature and potential for selection bias, but suggest that EEG patterns alone should not affect consideration of neurostimulant use.

Introduction

Over 500,000 Americans suffer cardiac arrest annually [1]. Most patients hospitalized after return of spontaneous circulation are comatose, and withdrawal of life-sustaining therapy because of perceived poor neurological prognosis is the most common cause of death in this group [2]. Neurostimulant medications may promote wakefulness in comatose patients with acute brain injury [3]. In comatose post-arrest patients, Reynolds et al. reported higher rates of awakening and survival among patients treated with either methylphenidate or amantadine [4]. However, stimulants are not without potential toxicities. Amantadine withdrawal may cause neuroleptic malignant syndrome and methylphenidate has been associated with hypertension, tachycardia, insomnia, and headaches [5,6]. Currently, clinicians have little evidence with which to make informed decisions about an individual patient's potential risk and benefit profiles, and clinicians may be cautious about using stimulant drugs in patients with seizure tendencies.

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One potentially appealing tool to inform patient selection for neurostimulant treatment is electroencephalography (EEG). EEG is used widely for both prognostication after cardiac arrest and for seizure detection [7–12]. EEG characteristics also might identify patients likely to be responsive to neurostimulant treatment. A reactive and continuous EEG background, for example, likely requires intact thalamocortical connectivity and so might suggests the presence of substrate necessary for neurostimulant responsiveness. Conversely, a suppressed or burst-suppressed EEG suggests neocortical damage or deafferentation, and might predict less responsiveness to neurostimulants [9,13,14]. We sought to test whether characteristics of the EEG substrate predict or preclude awakening, survival, and/or functionally favorable recovery after neurostimulant use in a large cohort of comatose post-arrest patients.

Methods

Patients and setting

The University of Pittsburgh Institutional Review Board approved all aspects of this study. We performed a retrospective, observational cohort study including comatose adults ≥18 years of age treated at a single academic medical center after cardiac arrest from August 2009 to October 2014. We identified eligible patients from our prospective, quality improvement registry, which captures consecutive post-arrest patients with high sensitivity [15]. We excluded patients who arrested secondary to trauma or neurological catastrophe, re-arrested or had limitations of care within 6 h of presentation, or who were awake shortly after resuscitation and so did not require EEG. At our facility, an established Post-Cardiac Arrest Service (PCAS) coordinates care through the entire post-arrest course including initial resuscitation and diagnostic workup, intensive care and inpatient care, neurological prognostication in comatose patients, detailed neurocognitive testing in patients who have awakened, secondary prevention and rehabilitation services. We have previously described roles of the service in detail [16,17], including our standardized bundle of sedation and antiepileptic drug therapy [18]. During the study period, it was our standard practice to manage temperature of all patients meeting the inclusion and exclusion criteria described above to 33 °C (prior to November 2013) or either 33 °C or 36 °C (after November 2014) for 24 h. Thereafter, patients were rewarmed at 0.25 °C/hr to normothermia. We actively maintained normothermia until 72 h post-arrest or until signs of awakening from coma, whichever came first. it was our institutional practice to monitor all comatose post-arrest patients with continuous EEG (cEEG) until awakening, death or approximately 48 h without actionable findings. We treated potentially "malignant" EEG patterns (periodic discharges, suppression burst, seizures and myoclonic status epilepticus) with an aggressive regimen of antiepileptic drugs, as we have previously described [9]. With regard to neurological prognostication and withdrawal of life-sustaining therapy, it is our standard practice to consider clinical neurological examination unreliable for at least 72 h after arrest, and to base withdrawal decisions on multiple modalities of testing, which may include daily neurological examination, initial brain imaging, continuous EEG monitoring, somatosensory evoked potentials, and magnetic resonance imaging of the brain [10,11,19–21].

EEG monitoring and classification

For the present study, we considered only the 24 h of EEG recording immediately prior to neurostimulant administration. If the patient did not get a neurostimulant, we reviewed the final 24 h of EEG recording. We applied 22 gold-plated cup electrodes according to the standard 10–20 International System of Electrode Placement and recorded EEG data using XLTech Natus Neuroworks digital video/EEG systems (Natus Medical, Inc.). A board certified epileptologist study coauthor (MB, NZ and AU) reviewed the clinical EEG recording for the purposes of this analyses and coded the EEG background's continuity and presence of any malignant patterns. Reactivity was assessed and documented clinically at the time of the initial EEG recording using a standardized daily stimulation protocol as well as unplanned patient care-related stimulation. We did not re-adjudicate reactivity for study purposes because video recording were not archived along with the EEG tracings, precluding us from reliably identifying periods of stimulation. Per ACNS terminology, we considered the background to be discontinuous when at least 10–49% of the recording consisting of attenuation or suppression below a threshold of 10 μV [22]. We considered an EEG to be reactive if there was any change in amplitude or frequency in response to stimulation. The routine EEG monitoring protocol in our institution includes once daily neurological assessments performed by EEG technicians or PCAS. These assessments include auditory and noxious stimulation in unresponsive patients. We did not consider EEG stimulus induced rhythmic, period or ictal discharges (SIRPDS) or isolated muscle artifact to be reactive. We considered periodic epileptiform discharges (generalized or lateralized), suppression burst, seizures and status epilepticus to be "malignant" patterns, and used standard definitions to define status epilepticus [22,23].

Data collection and outcome measures

We abstracted demographic and clinical data from our prospective registry. These variables included gender, location of cardiac arrest (in-hospital vs out-of-hospital), initial cardiac rhythm (ventricular tachycardia/ventricular fibrillation, pulseless electrical activity, asystole, or unknown), median nerve somatosensory evoked potential (SSEP) results (bilaterally absent N20 cortical response vs any other result) and Pittsburgh Cardiac Arrest Category (PCAC) a validated measure of post-arrest illness severity [19,24]. Briefly, PCAC stratifies patients based on their severity of initial brain injury and cardiopulmonary failure as follows: PCAC 1: awake and following commands; PCAC II: coma with preserved brainstem reflexes and little or no cardiopulmonary failure; PCAC III: coma with preserved brainstem reflexes and severe cardiopulmonary failure; and PCAC IV: coma with loss of some or all brainstem reflexes. We also abstracted patient outcomes at hospital discharge including date and time of awakening, which we defined as following verbal commands, survival to hospital discharge, and functionally favorable recovery at hospital discharge, which we defined as discharge to home or acute rehabilitation, as previously described [25]. Finally, we queried the electronic medical record to obtain a report of all medications each patient received including administration time, dose and route. From this, we determined if each patient had received one or more of the following neurostimulant medications prior to awakening: amantadine, bromocriptine, methylphenidate or modafinil.

Statistical analysis

We used descriptive statistics to summarize population characteristics. Next, we performed unadjusted and adjusted logistic regression to test whether neurostimulant exposure was independently associated with outcome. We included unadjusted predictors significant at a threshold of $p \leq 0.1$ in these adjusted models. We used logistic regression to test EEG predictors of subsequent awakening after stratifying the cohort by neurostimulant exposure. Because of the relatively small number of subjects who