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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 24h 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.

Keywords

Critical Care medicine; Drugs; Electrophysiology; Outcome; Post resuscitation care

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.

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 suggest 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 hours 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 hours. Thereafter, patients were rewarmed at 0.25°C/hr to normothermia. We actively maintained normothermia until 72 hours 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 hours 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 72h 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 hours of EEG recording immediately prior to neurostimulant administration. If the patient did not get a neurostimulant, we reviewed the final 24 hours 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 10µV.[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 $p < 0.1$ 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 received neurostimulants and subsequently awakened, we could not perform adjusted modeling of this association. Instead, we used propensity-score matching to estimate the average treatment effect of neurostimulant use on survival and good outcome after adjusting for baseline differences. For this adjustment, we considered patients eligible for treatment, all of whom were initially comatose in our cohort, from the date of arrest until awakening from coma, death, or discharge from the hospital, whichever came first. Our logit model predicting neurostimulant use included age, arrest location, initial arrest rhythm, as well as EEG continuity, reactivity, and presence of malignant patterns. It was our *a priori* plan to also include PCAC, but this variable was excluded for because of collinearity with other predictors. In the subgroups of subjects with discontinuous, non-reactive or malignant EEGs, we compared survival between those treated with neurostimulants and those who were not treated using Fisher's Exact tests. Finally, in a post hoc analysis we compared median nerve SSEP test results between groups. We performed all statistical analysis using Stata v14.2 (StataCorp, College Station, TX).

Results

Overall, 585 comatose patients were treated after cardiac arrest and underwent EEG monitoring. Mean (SD) age was 57 (17) years and 227 (39%) were female (Table 1). A majority of subjects (77%) arrested out-of-hospital, 177 (31%) had a shockable arrest rhythm and most (59%) patients were PCAC IV. These baseline characteristics did not differ by neurostimulant exposure. Overall, 47 (8%) patients received a neurostimulant prior to

awakening. Thirty-six patients received amantadine (100mg twice daily at 7am and noon), 7 received methylphenidate (5–10mg daily), and 4 received modafinil (100mg twice daily at 7am and noon). All neurostimulants were administered enterically, and treatment was initiated a median of 6 (IQR 5 – 9) days post-arrest. Patients who received neurostimulants were more likely to have continuous EEGs (81% vs 36%, $p < 0.001$) and reactive EEGs (70% vs 32%, $p < 0.001$) (Table 1). There was no difference in the frequency of malignant patterns (34% vs 40%, $p = 0.46$). The analyzed EEGs were obtained a median of 3 [IQR 2–5] days post-arrest among neurostimulant-treated patients and significantly earlier (2 [IQR 1–3] days post-arrest, $P = 0.001$) among untreated patients. Overall, 97 subjects (17%) had SSEPs performed, 16 (34%) in the neurostimulant group and 81 (15%) in unexposed patients ($P = 0.001$). Among tested patients, those treated with neurostimulants were less likely to have bilaterally absent N20 cortical responses (31% vs 72%, $P = 0.002$).

Neurostimulant administration independently predicted improved survival to hospital discharge (adjusted odds ratio (aOR) 4.00, 95% CI 1.68 – 9.52), although functionally favorable survival did not differ (Table 2). As previously reported, patients with continuous and reactive EEGs had better outcomes, while malignant EEG patterns predicted worse outcomes (Table 2). In the subgroup of patients with discontinuous EEGs, survival was better in those treated with neurostimulants than those who were not treated (44% vs 7%, $p = 0.004$). In patients with non-reactive EEGs, survival was better among those treated with neurostimulants (56% vs 6%, $p < 0.001$). Finally, among patients with malignant EEGs, survival was better among those treated with neurostimulants (63% vs 5%, $p < 0.001$). Our propensity-score matching analysis included 508 of 585 subjects. Neurostimulant use was associated with improved survival (average treatment effect (ATE) coefficient 0.29, 95% confidence interval (CI) 0.06 – 0.52, $p = 0.01$), but was not associated with good outcome (ATE coefficient 0.07, 95%CI –0.11 – 0.26, $p = 0.77$).

No EEG feature was a significant predictor of awakening after neurostimulant administration, nor did any EEG feature preclude subsequent awakening (Table 3). Of the 14 patients awakening after neurostimulant administration, 2 had discontinuous backgrounds, 1 had absent reactivity, and 4 had malignant patterns. Of these, 5 patients had favorable functional recoveries at hospital discharge (one patient with a discontinuous background and all 4 with malignant patterns). Two neurostimulant treated patients had bilaterally absent N20 cortical responses on SSEPs and survived to discharge, but neither awakened from coma prior to discharge.

Follow-up EEGs from two patients with malignant patterns prior to treatment were available for review. One patient had generalized periodic discharges (GPDs) before the neurostimulant. Five months later, a repeat EEG no longer had GPDs but instead had rare sharp waves. Another patient initially had periodic pattern consisting of suppression burst with embedded polyspikes prior to treatment. Continuous EEG for two days after starting the neurostimulant showed no deterioration in the EEG or seizures.

Discussion

In this large cohort of comatose patients treated after resuscitation from cardiac arrest, no unfavorable electroencephalographic characteristics precluded awakening, survival or functionally favorable recovery among patients treated with neurostimulants. Given our results, ominous EEG patterns should not preclude the use of neurostimulants. Furthermore, neurostimulant use was independently associated with a 5-fold improvement in the odds of survival to hospital discharge, although not with improved odds of functionally favorable outcome at discharge. This association with survival held when we restricted analysis to subgroups with unfavorable EEG characteristics such as discontinuity, lack of reactivity, and presence of malignant patterns.

Overall, our study supports that neurostimulants can be considered in comatose patients even if a malignant EEG pattern is present. It is important to highlight that although neurostimulant use was a strong independent predictor of survival, it did not predict functionally favorable outcome. We note that, in our system of healthcare, patients are often discharged from their acute hospitalization around the time when they recover to a CPC of 3 and are deemed ready for rehabilitation or subacute care. The functional status of many of these patients continues to improve after hospital discharge,[26] making CPC at discharge a somewhat artificial metric of quality of recovery. Additionally, CPC is a rather crude measure of quality of recovery after neurological injury, variably incorporating domains of function, participation and neurological deficits across levels, and may be poorly calibrated to detect clinically meaningful changes in outcomes.[25, 27, 28]

Our findings supporting a possible benefit to neurostimulant treatment after cardiac arrest is consistent with studies in other acutely brain-injured populations. As a therapeutic class, neurostimulants increase levels of dopamine, serotonin and/or acetylcholine and may promote neuroplasticity.[29–31] After stroke, high-level evidence indicates that fluoxetine improves motor recovery, while smaller studies suggest that levodopa improves gait velocity and dexterity.[32, 33] In patient that have suffered traumatic brain injury (TBI) with persistent vegetative state or minimally conscious state, amantadine accelerates functional recovery and improves level of consciousness.[34] Smaller studies suggest similar benefits to treatment with zolpidem, methylphenidate and pramipexole in patients with TBI and disorders of consciousness.[3, 35–37]

When determining patients most likely to benefit from neurostimulants, there are several tests that may help define a viable phenotype. These may include patients with intact thalamocortical function, evidenced by withdrawing from painful stimuli or an intact N20 response on SSEP. A continuous or reactive EEG may also represent neuronal substrate amenable to neurostimulants. As an effect may require days to weeks to manifest, families should be willing to provide ongoing aggressive support during a neurostimulant trial. This may require tracheostomy and feeding tube placement. Finally, facilities should offer brain focused rehabilitation for these patients, further enhancing the chance of functional recovery.

Our study has several limitations. First, the single center design may limit the generalizability of our results to other settings. Second, because our work was observational,

unmeasured confounders might have affected the observed association between neurostimulant use and outcome and we cannot assert causality between neurostimulant treatment and improved outcomes. Specifically, providers are more likely to initiate neurostimulant treatment in patients who appeared likely to recover, and withhold treatment in cases with no perceived potential for recovery, resulting in confounding by indication. The presence of such an effect is supported by the relatively small number of treated patients overall, although propensity-adjusted analyses are well suited to minimize this bias in observational studies and support causal inference.[38] Moreover, since most deaths after cardiac arrest occur after withdrawal of life-sustaining treatments for perceived neurological prognosis,[2] the association of neurostimulant treatment with survival might have occurred or been magnified by a tendency of providers to delay prognostication and withdrawal after treatment was initiated. Additionally, included EEG patterns may be altered by co-medication (sedation or antiepileptic drug treatment) or other concomitant care (temperature management). Although we have previously describe the prognostic role of many of these markers holds irrespective of co-medication,[18] these and other unmeasured confounders may still bias our results. Finally, our work does not confirm safety of neurostimulant use in this population nor was our sample size sufficient to analyze pharmacologically different neurostimulants independently, precluding exploration of the optimal agent in this population.

Conclusion

Our results suggest that EEG patterns typically viewed as ominous after cardiac arrest do not preclude survival or awakening after neurostimulant administration. Overall, and in each subgroup of ominous EEG findings, neurostimulants were associated with improved survival. We conclude that EEG patterns alone should not affect consideration of neurostimulant use.

Acknowledgments

Conflicts of Interest

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Table 1:

Baseline clinical and electroencephalographic characteristics and outcomes.

Characteristic	Overall (n = 585)	Did not receive neurostimulant (n = 538)	Received neurostimulant (n = 47)
Age, years	57 (17)	58 (17)	53 (15)
Female sex	227 (39)	209 (39)	18 (38)
Out-of-hospital arrest	452 (77)	413 (77)	39 (83)
Shockable rhythm	177 (31)	164 (31)	13 (28)
Pittsburgh Cardiac Arrest Category*			
II	138 (24)	127 (24)	11 (23)
III	78 (13)	67 (12)	11 (23)
IV	319 (55)	298 (55)	21 (45)
Unknown	50 (9)	46 (9)	4 (9)
Features of final EEG recording			
Continuous background	223 (38)	187 (35)	36 (77)
Reactive background	208 (36)	175 (33)	33 (70)
Malignant patterns	227 (39)	211 (39)	16 (34)
Outcomes			
Awakened from coma	163 (28)	114 (27)	19 (40)
Survived to discharge	173 (30)	142 (26)	31 (67)
Functionally favorable survival	91 (16)	81 (15)	10 (21)
Mode of Death			
Rearrested, intractable shock, or multisystem organ failure	69 (17)	67 (17)	2 (12)
Brain Death	39 (10)	39 (10)	0 (0)
Withdrawal for non-neurologic reasons	40 (10)	39 (10)	1 (6)
Withdrawal for perceived poor neurologic prognosis	265 (64)	251 (6)	14 (82)

Data are presented as mean (standard deviation) or raw number with corresponding percentages.

Table 2:

Adjusted predictors of survival and functionally favorable survival at hospital discharge

Predictor	Survival aOR (95%CI)	Favorable outcome aOR (95%CI)
Neurostimulant use	4.00 (1.68 – 9.52)	0.840 (0.33 – 2.11)
Out-of-hospital arrest	1.89 (0.99 – 3.59)	5.42 (2.42 – 12.1)
Shockable rhythm	2.63 (1.47 – 4.71)	2.12 (1.12 – 4.02)
Pittsburgh Cardiac Arrest Category*		
II	Ref	Ref
III	0.58 (0.26 – 1.24)	0.46 (0.20 – 1.06)
IV	0.10 (0.05 – 0.19)	0.12 (0.06 – 0.27)
Unknown	0.77 (0.32 – 1.84)	0.58 (0.22 – 1.57)
Features of final EEG recording		
Continuous background	3.75 (1.87 – 7.53)	7.17 (2.68 – 19.22)
Reactive background	2.89 (1.49 – 5.59)	1.51 (0.66 – 3.45)
Malignant patterns	0.20 (0.10 – 0.39)	0.04 (0.01 – 0.18)

Table 3:

Electroencephalographic predictors of awakening

Predictor	Awakened	Did not awaken	OR (95% CI)
Received neurostimulants	(n = 17)	(n = 30)	
Continuous background	15 (88)	23 (76)	2.28 (0.42 – 12.5)
Reactive background	14 (82)	19 (63)	4.03 (0.89 – 18.3)
Malignant patterns	4 (24)	12 (40)	0.48 (0.16 – 0.51)
Did not receive neurostimulants	(n = 144)	(n = 394)	
Continuous background	124 (86)	68 (17)	29.7 (17.3 – 51.0)
Reactive background	111 (77)	64 (16)	45.9 (27.0 – 78)
Malignant patterns	6 (4)	211 (54)	0.15 (0.10 – 0.23)

Data are presented as raw number with corresponding percentages.