Amantadine to Speed Awakening After Cardiac Arrest (AWAKE)

NCT02486211

June 28, 2019

4. RESEARCH DESIGN AND METHODS

4.1 Design

We will conduct a single-center randomized, controlled, double-blinded trial to determine the effect of amantadine administration in patients resuscitated from cardiac arrest who remain comatose at hospital day 3. The primary outcome will be the rate of awakening (defined as following commands) during hospitalization.

4.2 Recruitment and Informed Consent:

The Post-Cardiac Arrest Service treats over 90% of patients successfully resuscitated from cardiac arrest at UPMC Presbyterian Hospital, ensuring that the PI will care for all potential candidates as part of his clinical duties. Potential subjects who remain comatose for 48 hours will be unable to provide informed consent. Therefore, the investigators will approach family or legally authorized representatives to provide consent as a proxy for the subject. The investigators will already have a relationship with these proxies, and we have previously recruited 50% of potentially eligible subjects into studies in this setting. [**30, 31**]

4.3 Inclusion and Exclusion Criteria are listed in **Table 2**.

Table 2. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Non-traumatic cardiac arrest	Written do not attempt resuscitation (DNAR) reported to providers before randomization
Age 18 years or more	Known prisoner or pregnancy
Defibrillation and/or chest compressions by healthcare providers	Lack of motor response to pain and absent N20 response on SSEP prior to randomization.
Return of spontaneous circulation	Initial CT demonstrating brain edema (defined as grey white ratio <1.2)
	Presence of malignant pattern on EEG at time of randomization.
	Next of kin unwilling to provide supportive care for at least one week after enrollment.
	Creatinine clearance <50mL/min
	Presently using other dopaminergic agent

4.4 Randomization

After informed consent, subjects will be randomly assigned to either amantadine or placebo. For intention-to-treat analysis, subjects will be considered to be randomized as soon as an assignment in made. For per-protocol analyses, subjects will be considered to be randomized after receiving the first dose of study medication. The Investigational Drug Service (IDS) at the University of Pittsburgh will prepare and dispense study drug and maintain the block randomization list. At randomization, subjects will be stratified by PCAC strata and presence of early malignant patterns on EEG recording (these EEG patterns must have stopped by time of randomization, because continued malignant EEG is an exclusion). Both of these have been associated with outcome. [**2, 16, 32, 3.C.1.b**]

4.5 Intervention

Subjects assigned to the intervention arm will receive a dose of 100mg of amantadine, administered twice daily (at 6 am and 12 noon) for up to 7 days. The timing selected reflects the standard times used in our neurologic intensive care unit for this medication. **Subjects assigned to the placebo arm** will receive a dose of placebo that will appear identical to the amantadine. The amantadine and placebo will be made by the University of Pittsburgh IDS.

4.6 Allocation Concealment

Amantadine and placebo will appear identical. Drugs will be only have numerical identifiers when handled by the treating nurse and team. Unblinding can be provided to the treating team by the IDS only after consultation with the principle investigator or in predefined emergency situations. These

situations include severe allergic reactions not attributable to any other drug or unexplained tachydysrhythmia requiring cardioversion.

4.7 Justification for Timing of Intervention

One side effect of temperature management is a decrease in gastrointestinal motility. This returns to normal in the majority of patients after rewarming is completed. This will occur by 72 hours. As amantadine is only available in an oral form, decreased gastrointestinal motility could affect absorption. As noted in the preliminary data above, development and persistence of malignant EEG patterns is associated with poor neurologic outcome independent of initial illness severity. [**Section 3.C.1.b**] This design will allow these patients to be diagnosed with persistent malignant EEG patterns and excluded from the study.

4.8 Pharmacokinetic Measurements

Plasma concentrations of amantadine will be determined using solid phase extraction and a validated ultra-high performance liquid chromatography tandem mass spectrometry adapted from Arndt et al. [33] A 5 ml sample of blood will be obtained in citrated tubes, centrifuged (1000*g* x 15 minutes), decanted, and plasma frozen at -80ºC until assay. Sampling will occur at 8 time points; daily "peak" levels 1-2 h following the afternoon dose on days 1-4 and "trough" levels immediately prior to 6 AM dose on days 2-5. This sampling strategy is designed to both confirm enteral absorption and to permit post-hoc analyses of any differential effect of amantadine based on plasma levels achieved in the study. The 4 days of sampling will capture steady-state levels (amantadine half-live is ~17 h) and also spans the period of greatest vulnerability for hypothermia-induced changes in drug pharmacokinetics if they should occur.

4.9 Monitoring of Compliance:

Dr. Rittenberger leads a unique Post-Cardiac Arrest Service that has cared for this population since 2007. This ensures standardization of prognostic workup and clinical care outside of the care delineated in this study protocol. At enrollment, a trained research assistant will prospectively record pertinent information on the subject. The research assistant will also facilitate obtaining study drug from IDS to ensure drug administration in a timely fashion. The PI will perform random data spot checks, audits and will oversee the database and maintain quality.

Table 3. EEG and seizure definitions. MSE- myoclonic status epilepticus, GPEDs- generalized periodic epileptiform discharges, NCSE- nonconvulsive status epilepticus, EDs- epileptiform discharges.

Interpretation	Definition
Electrographic seizure	Repetitive generalized or focal spikes, sharp waves, spike-and-wave or sharp-slow wave complexes at ≥ 3Hz or sequential rhythmic, periodic or quasi-periodic waves at ≥ 1Hz with unequivocal evolution in frequency, morphology, or location lasting at least 10 seconds.
NCSE	Impaired consciousness with: 1. A continuous single electrographic seizure lasting 30 minutes or greater or recurrent electrographic seizures lasting for over 30 minutes. 2. Presence of GPEDs lasting at least 30 minutes at a rate ≥2.5 Hz. 3. Presence of GPEDs lasting at least 30 minutes at a rate of ≥1 Hz with unequivocal evolution in frequency, morphology, or location over time.
MSE	More than 30-minute period of myoclonic jerks or subtle facial movements locked in with bursts in a burst-suppression pattern or associated with GPEDs.
Interictal GPEDs	GPEDs at a rate of < 2.5 Hz not satisfying criteria 3
EDs	Spikes, polyspikes, sharp waves, spike-and wave or sharp-slow waves occurring independently, periodically (GPEDs) or during burst-suppression.

4.10 Ancillary Care

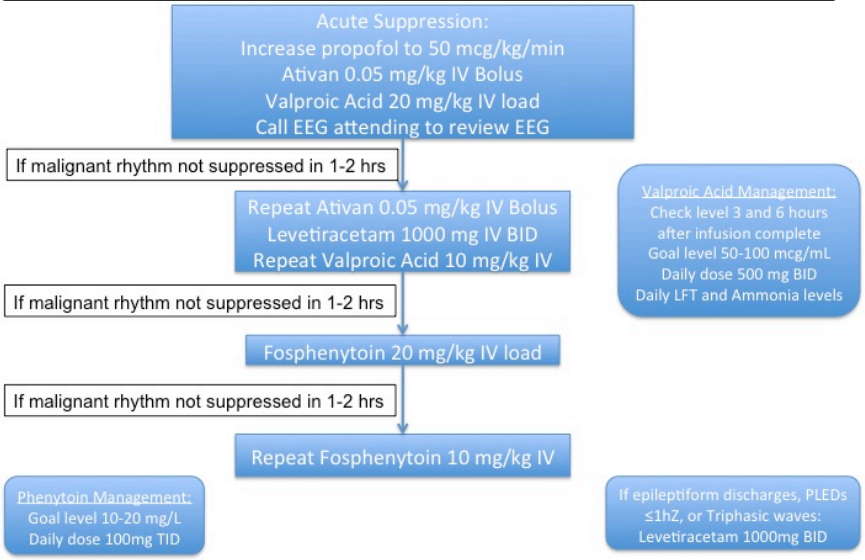
It is critical to control for potential effect modifiers that occur when a patient is hospitalized after resuscitation from cardiac arrest.

Experts have recommended a standardized approach that includes targeted temperature management to optimize outcomes following cardiac arrest. [4, **8,** 17] Our prior work has demonstrated that initial critical care management of the post-cardiac arrest patient has a large influence on neurological recovery and survival. [**5, 26**] Case control studies have reported improved outcomes in patients receiving combinations of hospital-based treatments compared to historical controls. [**5**, 24] We have shown that early use of coronary angiography and primary PCI is associated with good neurologic prognosis. [**6, 8, 34**] Our work through the ROC cardiac arrest registry has demonstrated that patients who were treated to a receiving hospital that had a coronary catheterization laboratory had better outcomes compared to those who were not. [**8**] Collectively, these studies demonstrate that hospital-based care of those resuscitated from cardiac arrest impacts patient outcomes and may modify the effect of interventions for cardiac arrest. We have addressed this issue for all subjects will be cared for by the Post Cardiac Arrest Service at UPMC-Presbyterian and receive standardized post arrest care delivered by the Post Cardiac Arrest Service.

4.11 EEG Protocol

We obtain a 22-channel digital EEG with simultaneous video recording on all patients resuscitated from cardiac arrest in our facility. This permits correlation of motor activity with electrographic findings and allows for accurate diagnosis of malignant EEG patterns. Contemporaneous interpretation is provided by the Department of Neurology. Subjects will be classified as demonstrating a malignant pattern or not using standard definitions. [**Table 3**] Locally, the PCAC II illness severity phenotype with malignant EEG patterns has a markedly reduced survival when compared to PCAC II illness severity without malignant EEG patterns. Thus, subjects will be stratified on PCAC and (in the PCAC II illness severity subjects) presence of malignant EEG pattern prior to randomization. If malignant patterns do develop, we will provide therapy to suppress the EEG and any clinical evidence of seizures. [**Figure 3**] This ensures a standard approach to all subjects in the study. Importantly, subjects with malignant EEG patterns that persist beyond 48 hours are excluded from the study and will not be enrolled.

Figure 3. Standardized antiepileptic treatment algorithm for malignant EEG patterns. (Malignant= GPED's, MSE, NCSE)



4.12 Justification for Outcome Measures

We have chosen the rate of awakening as the primary outcome in this study. This short-term outcome is appropriate to determine if a potential for benefit exists. [35] Awakening is a prerequisite for a good neurologic outcome. [17] Persistent coma is the most common reason for withdrawal of care (56%) while multiple organ failure is the etiology of death in a minority (17%) of patients. [**2**]. Prior literature is hindered by withdrawal of support in patients who remain comatose. Achievement of awakening will likely increase the family's interest in continuing supportive care for this population. Consequently it is **critical** to evaluate rate of awakening and time to awakening in both an intervention and placebo group as delaying time to withdrawal may independently increase the rate of awakening.

Awakening is an appropriate short-term outcome as subjects who awaken survive and comprise all good outcomes by definition of CPC or mRS. Most tend to improve in functional status over the year after hospitalization. [**19**] Two-thirds of patients who awaken but do not survive to discharge die from multiple organ failure. This investigation proposes an early neurologic intervention that is unlikely to improve other organ failure. Thus, we have chosen a short-term neurologic outcome to maximize detection of a neurologic benefit to this intervention. If the rate of awakening is higher in the treatment arm, the face value of awakening would probably prompt clinicians to adopt the treatment. Furthermore, a larger trial powered to evaluate a treatment effect on long-term functional outcomes might be justified.

Table 4. Clinical Examination of Comatose Post-Arrest Patients

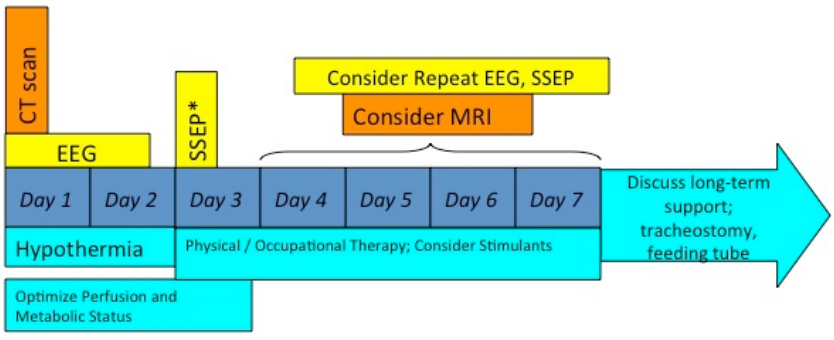
Reflex	Method to Elicit	Potential Responses
Pupil Response	Light stimulus into each pupil for 5 seconds in a darkened room. A positive response will consist of any pupillary response to the light stimulus.	0- Absent 1- Present
Corneal Response	3 drops of sterile saline will be dropped onto the cornea from a distance of 5cm. If this does not elicit a corneal response, sterile gauze will gently be used to stimulate the cornea. Any blink response will be considered a positive response.	0- Absent 1- Present
Gag Response	A Yankauer catheter will be used to suction the posterior pharynx and tonsilar pillars. Gagging will be considered a positive response.	0- Absent 1- Present
Motor Response	Supraorbital pressure, pectoral pinch, and stimulation of the nailbeds with pressure exerted by forceps will be used to elicit a response. The best motor response will be recorded.	0- No response or myoclonus 1- Decorticate posturing 2- Decerebrate posturing or withdraw to pain 3- Localization 4- Following commands

4.13 Daily Examinations

A study physician will complete a neurologic examination upon hospital arrival and again once the subject has rewarmed to a core temperature of >36°C. [**Table 4]** The initial examination is used to determine the category of initial illness severity. [**2**] Daily examinations will not be performed until sedative medications have been discontinued for at least 40 minutes. [36] Our facility uses propofol for the majority of patients. In subjects receiving continuous infusion of midazolam, the midazolam will be discontinued for 60 minutes before examination. In the rare instance of neuromuscular blockade use, examinations will not be completed until the train of four monitor reads 4/4. Following rewarming, this examination will be completed daily. Prior literature has demonstrated that individual findings are less predictive for outcome in the modern era, thus, no one finding will result in cessation of support. [**7**, 37, 38]

4.14 Prognostic Evaluation

Figure 4. Timeline and testing for neurologic prognostication. EEG- electroencephalogram; SSEP- somatosensory evoked potential; MRI- magnetic resonance imaging.



Prior literature has demonstrated that individual physical exam or test findings are insufficient to preclude a good outcome. Therefore, no single finding will result in cessation of support. [**7,** 37, 38] A multimodal workup will be employed to predict neurologic outcome. This includes clinical examination, continuous EEG monitoring, computerized tomography, somatosensory evoked potentials, and magnetic resonance imaging. [**Figure 4**] The clinical examination is described in **Table 4**. Continuous EEG monitoring is described above.

4.14.a Computerized tomography of the brain- Loss of grey-white differentiation (gray-white ratio of Hounsfeld Units <1.2) on initial CT of the brain predicts survival and neurologic outcome following cardiac arrest. [**39-**41] Subjects with a grey-white ratio <1.2 will be excluded from the study.

4.14.b Somatosensory evoked potentials- Subjects without a motor response to painful stimuli (GCS Motor=1) at 72 hours following cardiac arrest will have SSEP's obtained as part of the standard protocol. A lack of N20 response bilaterally remains predictive for a poor neurologic outcome following cardiac arrest. [42]

4.14.c Magnetic Resonance Imaging- Subjects who remain unconscious for >72 hours after cardiac arrest may receive MRI of the brain. Whole brain ADC mapping <750 $x10^{-6}$ mm^2/sec has been associated with a mRS of >3 in prior work. [43]

4.14.d Neuronal Specific Enolase/S100B- These are not available clinically in our local facilities and have varying associations with neurologic outcome. [7, 42, **44**]

4.15 Statistical Analysis

4.15.a Random Assignment

Those eligible for the study will be randomly assigned with equal probability to the experimental condition (amantadine) or the control condition (placebo). Random assignment will be stratified by cardiac arrest category (PCAC) and presence of malignant EEG patters (only in those with PCAC II), resulting in four strata: PCAC IV, PCAC III, PCAC II with malignant EEG patterns, and PCAC II without malignant EEG patterns. Survival markedly differs between these strata. [**Section 3.C.1.b**]

To maximize the probability of a balanced design, assignments will occur in block of two and four within each stratum. To ensure that the research team will be masked to the next treatment assignment, the size of the block will be randomly generated.

Random assignment will occur through the University of Pittsburgh Investigational Drug Service (IDS). Study staff will contact the IDS pharmacist, provide the necessary information (e.g., stratum) and the random assignment will be delivered. Given the volume of clinical studies at the University of Pittsburgh, IDS pharmacy medications and randomization are available 24/7.

4.15.b Data Analysis

The data analysis will begin by describing the baseline characteristics of the population. Summary statistics, such as means, standard deviations and frequencies will be generated. Graphical techniques, such as scatter plots and box plots will be used to evaluate the distribution of the baseline characteristics.

The balance of the baseline characteristics across treatment group will be compared. For discrete characteristics a chi-square tests or Fisher's exact test will be used to compare the proportions across treatment group. For continuous measures, either t-tests or Wilcoxon tests will be used to compare the characteristics across treatment group.

Aim 1, Hypothesis 1: Administration of amantadine after cardiac arrest will decrease time to awakening when compared to placebo during the 7 days of treatment.

Kaplan-Meier curves will be generated for time-to-awakening for each treatment group and a log-rank statistic will be used to compare the cumulative probability of awakening across treatment groups. Those participants who are not awake by treatment day 7 will be considered censored observations. A Cox proportional hazards regression model will be used to compare time-to-awakening by treatment group controlling for baseline characteristics that are not balanced through random assignment and stratification variables. The assumptions of the Cox proportional hazards model will be evaluated (proportionality of the hazards model) and if violated, a split analysis will be conducted.

Aim 1, Hypothesis 2: A larger proportion of subjects will awaken during the first 7 days of treatment after administration of amantadine when compared to placebo.

A chi-square test will be used to compare the proportion of participants that are awake at day 7 between the two treatment groups. Logistic regression model will be used to compare the proportions by treatment group controlling for baseline characteristics that are not balanced through random assignment and stratification variables.

Aim 2: Determine if the number of serious adverse events differ between subjects randomized to amantadine and subjects randomized to placebo.

It is anticipated that given the severe critical state of those enrolled in the study, each study participant will have multiple serious adverse events. A t-test (or Wilcoxon test) will be used to compare the means number of serious adverse events that occurred during the 7 days after treatment initiation. A regression model will be used to compare the means after controlling for baseline characteristics that are not balanced through random assignment and stratification variables. The type of regression model will depend in the distribution of the number of serious adverse events and could be a linear regression model, negative binomial model, or Poisson model.

4.15.c Sample Size

The sample size calculations are based on the analysis approach for the primary hypothesis (Aim 1, Hypothesis 1) with a type I error rate of 0.05, a two-sided alternative hypothesis, and 80% power. Based on these assumptions, a sample of 120 (60 per treatment group) will be sufficient to detect a difference of awakening of 30% in the control group and 50% in the active treatment group.