Clinical Trial Protocol/Statistical Analysis Plan

Continuous Neuromuscular Blockade following Successful Resuscitation from Cardiac Arrest: A Randomized Controlled Trial

Clinical Trial Identifier: NCT02260258

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Funded By:
The American Heart Association
The National Institutes of Health

Revision History:
v1: May 30th, 2019
v2: June 7th, 2019

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Background and Rationale

Two randomized trials published in 2002 found improved mortality and neurologic morbidity among out-of-hospital cardiac arrest (OHCA) victims with initial shockable rhythms (pulseless ventricular tachycardia and ventricular fibrillation) treated with therapeutic hypothermia targeting a temperature of 32℃-33℃ as compared to placebo.[1,2] A more recent, larger randomized trial comparing temperature controlled to 33℃ vs 36℃ did not demonstrate a significant difference in outcomes.[3] In the earlier therapeutic hypothermia studies, neuromuscular blockade (NMB) was administered throughout the cooling period in the intervention group but not the control group. In contrast, paralytic use was minimized in both groups in the more recent study comparing 33℃ to 36℃. Thus, the use of NMB is a potential unrecognized confounder from the earlier hypothermia studies.

Multicenter observational data has previously demonstrated that continuous NMB following cardiac arrest may be associated with improved lactate clearance and reduced mortality.[4] NMB may improve post-cardiac arrest outcomes through a number of mechanisms including the reduction of global oxygen consumption, prevention of patient-ventilator dyssynchrony, reduction of metabolic demand, reduction of inflammation, or other unidentified pathways.[5] The presently reported phase II trial, in addition to a similar phase II trial published by an affiliated cardiac arrest clinical trials group in South Korea[6], tested the hypothesis that early, continuous neuromuscular blockade following cardiac arrest will improve blood lactate levels and potentially clinical outcomes as compared to usual care.

Study Overview

Study Design and Setting

This was a phase II, multi-center, randomized trial of continuous neuromuscular blockade using rocuronium vs. usual care in patients who had sustained return of spontaneous circulation (ROSC) but remained unresponsive after cardiac arrest. Enrolling sites were five urban tertiary care centers in the United States. The trial coordinating center gathered and analyzed the data, and vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Written informed consent was obtained from the legally authorized representatives of all patients.

Trial Participants

Adult patients (aged ≥18 years) who experienced a cardiac arrest and subsequently had sustained ROSC (≥20 minutes) but remained comatose (i.e. not following commands) and were undergoing TTM targeting between 32℃ and 36℃ were enrolled in the study. An additional inclusion criterion of a minimum serum lactate level of ≥2mmol/L was added after the 42nd patient was enrolled. Patients were excluded if they had a traumatic etiology of cardiac arrest, were already receiving continuous neuromuscular blockade for clinical purposes, were not expected by the physician team to survive 24-hours, had been undergoing TTM for ≥6 hours, had a pre-arrest modified Rankin scale score of 4 or higher, or were members of a protected population (including prisoners, pregnant patients, and the developmentally disabled). Patients who had received a single-dose of a neuromuscular blocking agent, most commonly during

tracheal intubation, could be enrolled in the study so long as the drug had worn off and there were no immediate plans for additional neuromuscular blockade administration.

Patient flow through the trial will be displayed in a CONSORT diagram (see Appendix Figure 1 for shell figure).

Randomization and Intervention
Patients were randomized to continuous NMB or usual care in blocks of four and in a 1:1 ratio. The randomization was stratified by study site and by the presence of shock, defined as the use of any vasopressor at the time of randomization. The random sequence was generated by an independent statistician who was not involved in the conduct of the study. The site-specific allocation sequences were maintained by the research pharmacies at each site for the duration of the study.

Patients in the continuous NMB arm received a rocuronium bolus of 1.0mg/kg followed by a continuous infusion of rocuronium for a total of 24-hours. The infusion of rocuronium was titrated to 1-2 out of 4 twitches on a train-of-four peripheral nerve stimulator. To minimize any difference in the time between randomization and receipt of the study drug between the two groups, patients in the usual care arm were administered a small volume of normal saline to mark the 0-hour time point. All patients undergoing TTM, including those who received continuous NMB, were deeply sedated per local site protocol. Use of the Columbia anti-shivering protocol was recommended to clinical teams, but adherence was not mandated.[7]

Study Registration and Monitoring
The trial was registered at clinicaltrials.gov (NCT02260258) and was approved by the institutional review boards of all enrolling institutions.

A Data Safety and Monitoring Board (DSMB) evaluated and monitored the trial for safety. There were no pre-specified stopping rules for futility or efficacy. No statistical interim analyses were performed.

Outcomes and Definitions

Primary Outcome and Sample Size Estimation
The primary outcome of the study is change in serum lactate level measured between 0-hours and 24-hours after the receipt of study drug. This outcome was chosen as lactate is a continuous variable which is highly correlated with hospital survival in cardiac arrest patients.[8] The 24-hour time point was selected as it was drawn after completion of the rocuronium infusion but not so late that a significant proportion of patients may have already died. Based on conservative estimates drawn from observational data[4], a sample size of 80 patients was specified to detect a predicted mean difference in 24-hour lactate of 2.0mmol/L (±3.2mmol/L) with 80% power assuming a two-sided test and an alpha of 0.05.

Secondary Outcomes
- Lactate change between 0- and 12-hours after administration of study drug
- Lactate change between 0- and 36-hours after administration of study drug
- Shock-free days
    - Shock-free days measured as days alive and free of shock (<6 hours receiving a vasopressor) over the first 7 days after enrollment.

- Ventilator-free days
    - Ventilator-free days measured as days alive and free of invasive mechanical ventilation (<6 hours with an endotracheal tube) over the first 7 days after enrollment.
- Length of initial Intensive Care Unit (ICU) stay truncated at 28-days
    - Includes only the initial stay in the ICU and does not include ICU readmission
- Length of initial hospital stay truncated at 28-days
    - Includes only the initial hospital stay and does not include any readmissions
- Survival to hospital discharge
- Neurologic outcome at hospital discharge
    - As defined using the Modified Rankin Scale
- Biomarker measures (available at 0-hours and 24-hours)
    - Interleukin (IL)-1β, IL-6, IL-8, IL-10, and TNF-α
    - Neuron specific enolase [NSE]
    - S100 calcium-binding protein B (S100B)
- Muscle weakness assessed using a modified Medical Research Council scale

A table of outcomes by treatment group will be included (see Appendix Table 3).

Statistical Analysis

General Principles

All initial analyses will be performed in a modified intention-to-treat (modified ITT) population, defined as all randomly assigned subjects who received any study drug (rocuronium or the saline time marker). The primary analysis for the outcome of lactate at 24-hours will be repeated in the per-protocol population including only those patients who were alive at 24-hours and received either 24-hours of continuous rocuronium (if so assigned) compared to those who received usual care without any neuromuscular blockade medication after the time 0-hour point.

Baseline Characteristics

A description of the baseline characteristics will be presented by treatment group (see Appendix Table 1). Categorical variables will be summarized by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Continuous variables will be summarized using means (standard deviations, SD) or medians (interquartile range, IQR). Statistical tests will not be used to compare baseline characteristics between groups. A table describing sedative and off-protocol paralytic use in each arm will be included (Appendix Table 2)

Analysis of Primary Outcome

The primary outcome is lactate change between 0-hours and 24-hours after enrollment. The group difference in change from the time of study drug administration (0-hours) to 24-hours will be assessed using a linear mixed effects model. Lactate values will be log-transformed for this analysis if they are not approximately normally distributed. Fixed effects will include the allocated treatment, shock stratification, time point (0-hour, 12-hour, and 24-hour), and the interaction between treatment and time point. Study site will be included as a random intercept. The usual care group will be the reference variable for group, and baseline (0-hour) will be the

reference variable for time. Means and 95% confidence intervals of lactate over time will be presented, by treatment, using longitudinal plots (see appendix Figure 2)

Analysis of Secondary Outcomes
The following outcomes will be summarized using mean ± SD or median (IQR) and linear regression using the above described linear mixed model will be performed to assess the differences between treatment groups.

- ICU length of stay
- Hospital length of stay
- Time to shock reversal
- Time to liberation from mechanical ventilation
- Biomarker measures (regression controlled for baseline level of each biomarker)
- Muscle weakness score

The following outcomes will be summarized using frequencies and percentages and logistic regression will be performed to assess the differences between treatment groups.

- Neurologic outcome at hospital discharge
- Survival to hospital discharge

Subgroup Analyses

The primary outcome analysis will be additionally performed in each of the below subgroups.

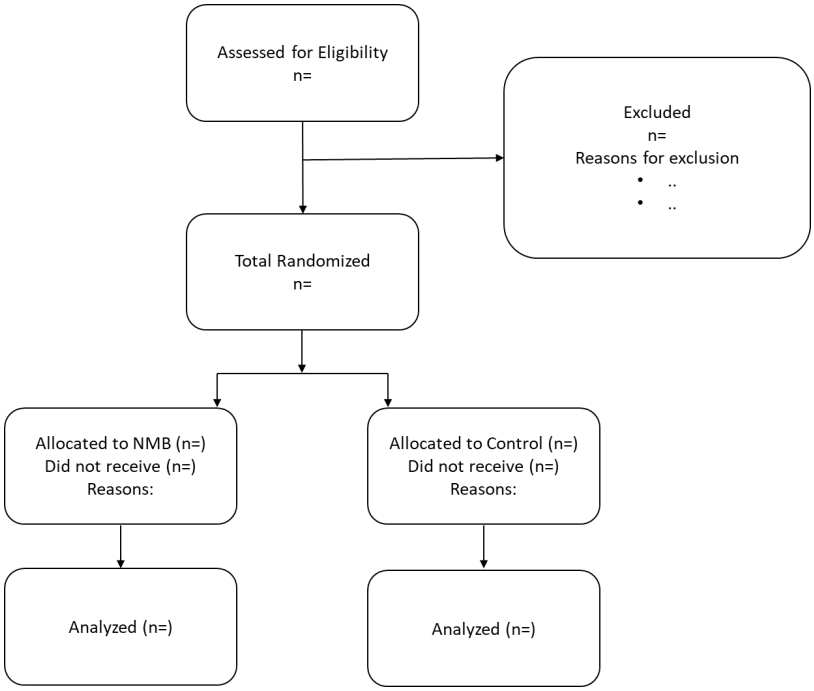
- Shock and non-shock stratification groups
- Shockable and non-shockable initial rhythms
- Cardiac arrest location

Additional Planned Analyses
Additional planned analyses of total body oxygen consumption and cellular oxygen consumption for those patients in whom these variables are available will be performed.

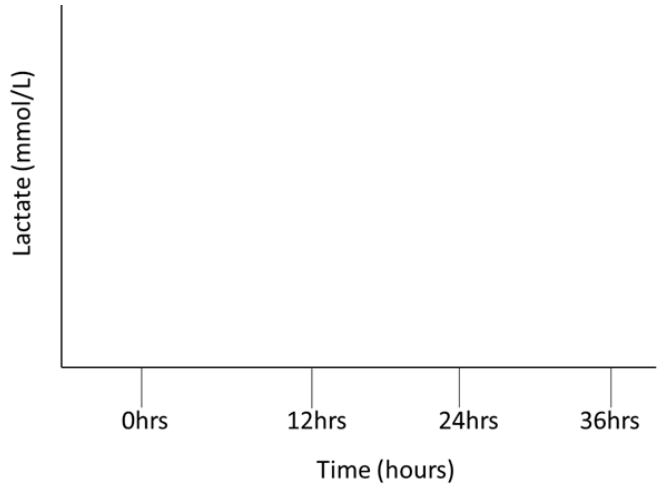
Statistical Software
Stata (version 14, StataCorp, College Station, Tx) will be used for all analyses.

Appendix

Appendix Figure 1



Appendix Figure 2 - Change in Lactate over Time



Appendix Table 1 - Cohort Characteristics

Variable	**NMB**	**Usual Care**
Demographics		
Age (Median, IQR)		
Sex (%Female)		
Race (%White)		

Past Medical History		
Congestive heart failure		
Atrial fibrillation		
Coronary artery disease		
Prior cardiac arrest		
Chronic pulmonary disease		
Kidney disease		
Active malignancy		
Arrest Characteristics		
Location (%OHCA)		
Initial Rhythm (% Non-shockable)		
Estimated no-flow time (median, IQR)		
Estimated low-flow time (median, IQR)		
Arrest duration (minutes, median, IQR)		
Witnessed (%yes)		
Bystander CPR provided (%yes)		
Arrest etiology (%cardiac)		
Characteristics at Enrollment		
pH (median, IQR)		
pCO2 (median, IQR)		
pO2 (median, IQR)		
Shock stratification (% shock)		
STEMI present (%yes)		
Target temperature (median, IQR)		

Received any paralytic prior to enrollment (%yes)		

Appendix Table 2 - Sedatives and Off-Protocol Paralytics

Variable	**NMB**				**Usual Care**			
Sedation and Analgesia (% receiving)	0hr	12hr	24hr	36hr	0hr	12hr	24hr	36hr
Propofol								
Midazolam								
Lorazepam								
Dexmedetomidine								
Fentanyl								
Paralytic (% receiving)								
Bolus Rocuronium								
Continuous Rocuronium								
Bolus Cisatracurium								
Continuous Cisatracurium								

Appendix Table 3 – Outcomes

Variable	**NMB**	**Usual Care**	**Effect estimate (95% confidence interval)**
Lactate Level (mmol/L, median, IQR)			
0-hour			
12-hour			
24-hour			
36-hour			
Clinical Outcomes			
ICU LOS (days, median, IQR)			

Hospital LOS (days, median, IQR)			
Discharge CPC ≤2 (%)			
Muscle Weakness Score (median, IQR)			
Hospital Survival (% survived)			

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