Thiamine as a Metabolic Resuscitator After Cardiac Arrest: Study protocol and statistical analysis plan

NCT03450707

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Introduction

The study protocol for Thiamine as a Metabolic Resuscitator After Cardiac Arrest is summarized in the original posting for the trial on clinicaltrials.gov, NCT03450707. Additional details on the protocol and the statistical analysis plan are included in this document, which is being submitted for posting prior to initiation of any data analysis.

Methods

Trial Design

This is a randomized, double-blind, placebo controlled to investigate the effect of intravenous thiamine (vitamin B1) on lactate, cellular oxygen consumption, global oxygen consumption and biomarkers of neurologic injury in patients who achieve return of spontaneous circulation (ROSC) after an out-of-hospital cardiac arrest (OHCA).

Intervention:

Thiamine 500mg in 100mL 0.9% saline IV every 12 hours for 5 doses, with initial dose given within 4.5 hours of ROSC. Control arm will receive 0.9% saline of the same volume and frequency.

Consent/Exception from Informed Consent (EFIC):

This trial will be conducted under EFIC, as approved by the FDA and the Beth Israel Deaconess Medical Center Internal Review Board (IRB) following completion of community consultation and dissemination of information about the trial, including provision of the opportunity to opt out. EFIC will be utilized due to the need to enroll patients within 4.5 hours of ROSC. In line with the EFIC process, if the patient's legally authorized representative (LAR) is present, the research team will approach them for informed consent and the patient will be enrolled if the LAR consents. If the LAR is not present at the time of eligibility, the research team will make an attempt to contact them and provide them the opportunity to opt out of the trial. If the LAR is not reachable but a family member/next of kin is present or can be reached, that person will be provided the opportunity to opt out. If the LAR or family member does not opt out or if no LAR or next of kin can be reached, the patient will be enrolled in the trial. If a patient is enrolled under EFIC, the patient or the LAR will be approached for continuing consent as soon as this is possible.

Patient Population

Inclusion Criteria:

- Adult patient (age ≥ 18 years)

- Cardiac arrest occurring with sustained (> 20 minutes) return of spontaneous circulation (ROSC)
- Lactate ≥3
- Within 4.5 hours of cardiac arrest event

Exclusion Criteria:

- Clinical indication for thiamine administration (alcoholism, known or highly suspected deficiency) or treatment with thiamine beyond the amount found in a standard multivitamin within the last 10 days
- Traumatic etiology of arrest
- Comfort measures only or anticipated withdrawal of support within 24 hours
- Protected populations (pregnant women, prisoners)
- Known allergy to thiamine

Randomization and blinding

Randomization: The randomization, completed by an independent statistician, will be generated using a random number generator via the use of the Statistical Analysis System (SAS) version 9.2 software, function RANUNI. Randomization will be 1:1, in blocks of 4. This function generates a random number between 0 and 1 from a uniform distribution function with parameter 0 and 1. If the random number is less than or equal to 0.5, the assignment is to the treatment group (coded A). If the random number is larger than 0.5, then the assignment is to the control group (coded B).

The research pharmacy, following the randomization list as above, will prepare and release study drug for each enrolled patient. Intravenous thiamine is odorless and colorless, and will be mixed in a 100mL bag of normal saline (NS). Patients assigned to the placebo arm will receive an identical volume of NS. Thiamine is odorless and colorless, and it is not possible to tell the difference between thiamine and placebo using this method. All study personnel with the exception of the research pharmacist will be blinded to the intervention. Unblinding will take place in the unlikely event of a case of suspected anaphylaxis or other severe reaction to study drug

Study Registration and Monitoring

The trial was registered at clinicaltrials.gov (NCT03450707) on March 1, 2018, prior to study start. Adverse events will be monitored by the PI and reported to the IRB and FDA as required. A Data Safety and Monitoring Board (DSMB) has been convened for this trial as required for any trial conducted under EFIC. DSMB meetings will occur at pre-planned

intervals of one year. There are no pre-specified stopping rules for futility or efficacy. No statistical interim analyses were planned.

Protocol:

Intervention: Thiamine 500mg IV in 100ml 0.9% saline every 12 hours for 48 hours (5 doses)
Placebo: 100ml 0.9% saline IV every 12 hours for 48 hours (5 doses)
Blood collection: Blood will be drawn at enrollment/time 0 (prior to study drug administration), 6 hours, 12 hours, 24 hours, 72, and 168 hours. Blood for all study labs will be collected by the patient's clinical nurse, using an existing intravenous or arterial line if present. Nursing or phlebotomy will perform a peripheral stick to obtain research blood only if no line is available for use. Research assistants will take all blood for immediate processing per the requirements of each lab test. Lactate and labs for SOFA score calculation will be processed in the BIDMC clinical lab. All other research assays (see list of secondary outcomes) will be completed in the BIDMC Center for Resuscitation Science Lab.
VO_2 monitoring: All patients meeting criteria for metabolic data collection (FiO_2 60% or less and positive end expiratory pressure (PEEP) 15cm H_2O or less) will be connected the the VO_2 monitor at enrollment or as soon as the ventilator criteria are met, if still within 48 hours of enrollment. The monitor is made by General Electric, monitor version B650 with gas exchange module, and attaches in-line to the ventilator tube, between the endotracheal tube and the Y-connector. All connections and disconnections of the monitor will be done by a trained respiratory therapist, with study staff present at the bedside. The tubing is attached to sensors that collect data breath-by-breath and that data is continuously recorded while connected to a laptop with dedicated software for this purpose. At the end of the study protocol all data will be downloaded and stored in a secure CSV file.
Cerebral Performance Category (CPC) and Cerebral Performance Category-Extended (CPC-E) score assessments: CPC and CPC-E will be assessed just prior to hospital discharge, at 30 and 90 days. Research staff will approach patients for assessment of CPC-E prior to hospital discharge. The CPC-E includes several questions testing logical thinking, attention and memory. The outpatient portion, which will be assessed in addition to the inpatient portion after hospital discharge/at 30 and 90 days, also includes questions about functional status and return to work. The CPC score will also be assessed by research staff prior to discharge. Phone calls to the patient will be made at 30 and 90 days (if the patient is no longer in the hospital).

Outcome Measures

Primary Outcome: Lactate change

The primary outcome is change in lactate over 24 hours following enrollment.

Secondary Outcomes:

1. Absolute level and change in VO_2 over 48 hours
2. Absolute level of lactate over 72 hours
3. Absolute level and the change in pyruvate dehydrogenase (PDH) quantity, activity and specific activity over 72 hours
4. Absolute level and the change in S100 levels over 72 hours
5. Absolute level and the change in neuron-specific enolase (NSE) levels over 72 hours
6. Mortality (hospital discharge, 30 and 90 days)
7. Cerebral Performance Category (CPC) score (hospital discharge, 30 and 90 days)
8. Cerebral Performance Category-Extended (CPC-E) (hospital discharge, 30 and 90 days)
9. Absolute level and the change in Sequential Organ Failure Assessment (SOFA) Score SOFA over 72 hours
10. Acute renal failure during first 7 days following arrest
11. Absolute level and change in cellular oxygen consumption rate over 72 hours
12. Absolute level and the change in creatinine over 72 hours

Sample Size Calculations:

The analysis method for the primary endpoint will be linear mixed-effects modeling (LMM). This type of modeling is used in longitudinal or repeated-measures studies to take into account the correlation of within-subject measurements and can optimize the power. In this case, each subject will have lactate measurements at multiple time points, which are correlated. Since LMM will be used for the analysis, we have also used LMM for power analysis for this endpoint. We evaluated approximately 61 post-arrest patients in our databases for which we had lactate measurements over 24 hours and that matched the inclusion/exclusion criteria for the current proposal. We observed that the post-CA patients have a mean lactate of 3.8±2.2 mmol/L at 6 hours, 3.5±2.2 at 12-hours, and 2.9±2 at 24-hours. We took a conservative position to assume that the potential effect size (the mean difference of lactate between the two groups) will be 33%. That is, we assumed that the mean lactate level at the three different time points were 2.55, 2.35, and 1.94. We then simulated the longitudinal data with the assumption that the variance-covariance structure of the lactate data followed a compound-symmetry structure with between-subject variance of 2.07. The linear-mixed effects model was used on the simulated data to obtain the estimated F statistic, numerator, and denominator degrees of freedom. From these estimates, the non-centrality parameter was computed and used to obtain the power. To obtain 80% power, with type-I error of 0.05, 66 subjects (33 thiamine, 33 placebo) will be needed to detect the stated difference over 6, 12, and 24-hours. We

secondarily performed calculations using the difference in means approach at the time point of 6 hours where we anticipate maximal effect of thiamine. At this time point, a reduction by 33% yields a power of 80% with a total sample size of 92. To be conservative we will use the larger sample size of 92 patients to ensure adequate power. With this sample size, the linear-mixed model will have 92% power to detect differences between groups with the same assumptions.

Statistical Analysis

General Principles

The statistical analyses and reporting will adhere to the CONSORT guidelines. All tests will be two-sided, a p-value <0.05 will be considered significant, and all confidence intervals will have 95% coverage. All analyses will be conducted on a modified intention-to-treat basis only including participants receiving at least the first dose of the study medication. In a double-blind trial, this approach is unbiased while increasing precision**.** Analyses will not be adjusted for covariates unless there are significant differences in baseline characteristics between study arms.

Baseline Characteristics

A description of the baseline characteristics will be presented by treatment arm. 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 mean+/-standard deviation or median (interquartile range) based on the distribution of the data.

Analysis of Primary Outcome

We will compare repeated measures of lactate levels at each time point (0h, 6h, 12h, 24h) between arms using a linear mixed-effects model with an independent variance–covariance matrix to account for the correlation of within-patient repeated measures. Covariates in the model include treatment arm, time (as a categorical variable with four levels, defined as baseline, 6 hours, 12 hours, and 24 hours), and the interaction between treatment arm and time. Linear contrasts will be used to estimate the mean difference between treatment arms for each time point. If a patient dies before 24 hours, levels will be imputed by carrying forward the last known value before the event with a 20% penalty. A sensitivity analysis will be performed in which patients who die before 24 hours are assigned the last known value before the event without a penalty.

Analysis of Secondary Outcomes

Lactate levels over 72 hours

To test for a difference in absolute lactate level values, we will compare means or medians, as appropriate, between arms using either a Student's t-test or a Wilcoxon rank-sum test, respectively, at 6, 12, 24 and 72 hours.

Change in oxygen consumption (VO_2) over 48 hours

Prior to unblinding or analysis, oxygen consumption data will be cleaned using an algorithm designed by our research team in R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). This automated algorithm excludes VO_2 data (and the corresponding value for carbon dioxide production, or VCO_2) if one or more of the following criteria is met: all values recorded in the 10 min following a change in FiO_2 of 10%, all values recorded while FiO_2 is >61% (61% used in order to capture all situations when the ventilator is set for an FiO_2 of 60% or less, as the monitor reports this number to two decimal places and a set number of 60% may be recorded as 60.54%), all values deviating 15% or more from the mean of the previous five values and the next five values (i.e, deviating 15% from the mean of the ten neighboring data points), and all VO_2 values out of physiologic range unless these are persistent for more than 30 minutes, as these measurements are considered artifacts. Values that will be considered out of physiologic range are VO_2<80 mL/kg/min or VO_2>800 mL/kg/min. We allow these values if they persist for at least 30 min and if they are not excluded per the algorithm for other reasons, as critically ill post-arrest patients can sometimes have values well outside of standard normal range, due to temperature, medication use such as sedatives and neuromuscular blockade and/or alterations in metabolic function. The respiratory quotient (RQ) is calculated as the ratio of VCO_2/VO_2 at each time point. After data is run through the algorithm and still prior to unblinding, there is a final visual review of a graphical print-out of all data points for each patient to provide a secondary confirmation that values were kept or dropped appropriately.

To investigate the association between treatment and gas metabolism data (VO_2, VCO_2 and RQ) in the first 48 hours after ROSC, we will compare the area under the curve (AUC) for each oxygen consumption variable between the treatment arms. The AUCs for the oxygen consumption variables are influenced by the number of minutes of data available, which varies between patients. To account for this, AUCs for each patient will be adjusted by dividing by the number of minutes of oxygen consumption data available for that patient. Additionally, the AUCs for the VO_2 and VCO_2 variables are influenced by the weight of the patient, and thus will also be adjusted by dividing by the bodyweight of the patient, in kilograms. The median AUCs will be compared between treatment groups using the univariate Wilcoxon rank-sum test. To

control for the known effect of temperature on oxygen consumption, we will use quantile regression to compare median AUCs between patients using the treatment assignment as the predictor and average temperature as a covariate. To examine the association between treatment and the VO_2:Lactate Ratio, we will use a linear quantile mixed model (LQMM) with the VO_2:Lactate Ratio as the outcome variable, treatment as the predictor variable and temperature as the covariate. To account for clustering of VO_2:Lactate Ratio and temperature measurements within patients, we will add a random intercept for each patient to the LQMM. We will not control for vasopressor use or sedation in the above analyses unless use of these agents is significantly imbalanced between arms.

Pyruvate dehydrogenase (PDH), S100, NSE, SOFA score, creatinine, and cellular oxygen consumption rate levels over 72 hours

To test change over time, we will compare repeated measures of each outcome listed above at each time point (0h, 24h, 72h) between arms using a linear mixed-effects model with an independent variance–covariance matrix to account for the correlation of within-patient repeated measures. Covariates in the model include treatment arm, time, and the interaction between treatment arm and time. Linear contrasts will be used to estimate the mean difference between treatment arms for each time point. To test for a difference in absolute values between arms, we will compare means or medians, as appropriate, using either a Student's t-test or a Wilcoxon rank-sum test, respectively, at 24 and 72 hours.

Mortality, Cerebral Performance Category (CPC) Score, and Cerebral Performance Category-Extended (CPC-E) Score at hospital discharge, 30 days, and 90 days

Proportions of patients who do not survive to hospital discharge, 30 days, and 90 days will be compared between treatment arms using Fisher's exact test. Fisher's exact test will also be used to compare the proportion of patients who have a favorable CPC score at the same time points, with favorable CPC score defined as a score of 1-2 and unfavorable a CPC of 3-5. CPC-E will be analyzed between treatment arms as a continuous variable in survivors to the time point of interest using either a Student's t-test or a Wilcoxon rank-sum test, based on the distribution of the data.

Acute renal failure in the first 7 days after study drug initiation

Acute renal failure in the first 7 days after study drug initiation will be determined using the Kidney Disease Improving Global Outcomes (KDIGO) criteria for Stage 3 acute kidney injury/kidney failure. These criteria are as follows:

1. An increase in creatinine to ≥ 3 x baseline (baseline defined as enrollment [post-arrest pre-study drug] creatinine value) OR
2. An increase in creatinine by ≥ 0.3mg/dL from baseline to ≥ 4mg/dL OR
3. Initiation of renal replacement therapy

Patients who die before 7 days and who do not meet the above criteria before death or transition to comfort measures only status will be classified as not having acute renal failure. Proportions of patients who have renal failure will be compared between groups using Fisher's exact test. Patients who already have end-stage renal disease (defined as being on dialysis/renal replacement therapy prior to arrest) will be excluded from the acute renal failure analysis.

Additional Planned Analyses

Pre-planned subanalyses of the primary outcome and of the secondary outcomes of mortality and VO_2 will be performed stratified by arrest duration, dichotomized into <15 minutes and >=15 minutes and in the group of patients with baseline thiamine deficiency (plasma vitamin B1 level <=7 nmol/L). Based on feedback from the DSMB, we will also perform subanalyses based on 0 hour lactate, stratified by <=5 and >5.

Analysis of Adverse Events

Rates of serious expected and unexpected adverse events will be reported by arm assignment. Proportions of patients with adverse events will be compared between the treatment arms using Fisher's exact test.

Statistical Software

Stata (version 17, StataCorp, College Station, Tx) & R (version 4.1.1, R Foundation for Statistical Computing, Vienna, Austria) will be used for all analyses and graphics.