Thiamine vs. Placebo to Increase Oxygen Consumption After Cardiac Arrest: Study protocol and statistical analysis plan

NCT02974257

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Introduction

The study protocol for Thiamine vs. Placebo to Increase Oxygen Consumption After Cardiac Arrest is summarized in the original posting for the trial on clinicaltrials.gov, NCT02974257. Additional details on the protocol and the statistical analysis plan are included in this document, which is being submitted for posting prior to unblinding or initiation of any data analysis.

Methods

Trial Design:

This is a randomized, double-blind, placebo-controlled trial of high-dose intravenous thiamine to decrease lactate and increase global oxygen consumption (VO_2) in patients who achieve return of spontaneous circulation (ROSC) after an in-hospital cardiac arrest (IHCA).

Consent:

Eligible patients will be intubated and sedated at the time of eligibility. Therefore, the legally authorized representative (LAR) will be approached by the research team, and written informed consent will be obtained prior to beginning the study protocol. If patients improve to the point of being consentable, they will be approached for consent for continuing participation.

Intervention:

Thiamine 500mg in 100mL 0.9% saline IV every 12 hours for 48 hours, with initial dose given within 12 hours of ROSC. Control arm will receive 0.9% saline of the same volume and frequency.

Patient Population

Inclusion Criteria:

- Adult patient (age ≥ 18 years)
- Cardiac arrest occurring while admitted to the hospital, with sustained (>20 minutes) return of spontaneous circulation (ROSC)
- Mechanically ventilated at the time of enrollment
- Within 12 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

- Comfort measures only or anticipated withdrawal of support within 24 hours
- Severe agitation
- Protected populations (pregnant women, prisoners)

Randomization and blinding

The randomization will be done in a 1:1 ratio between treatment and control arms in blocks of four. Random assignments will be generated by computer, and a randomization list will be provided to and kept in the research pharmacy. A sealed envelope with arm assignment will be placed in each patient's chart for the unexpected and rare occurrence of the need to un-blind the study. Randomization will be stratified by screening lactate value, with stratification groups of lactate > 5 or ≤ 5.

The research pharmacy, following the randomization list as above, will 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. It is not possible to tell the difference between thiamine and placebo using this method, and 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 (NCT02974257) on November 18, 2016, prior to study start. Adverse events were monitored by the PI. There were no pre-specified stopping rules for futility or efficacy. No statistical interim analyses were planned. This trial was approved by the Internal Review Board (IRB) at Beth Israel Deaconess Medical Center.

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 and 48 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 creatinine will be processed in the BIDMC clinical lab, and other clinical labs that will be obtained from the patient record include platelet levels and total bilirubin (for SOFA score calculation). 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 to 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 tubing, 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

Note: At the time of trial start, the primary outcome was change in oxygen consumption (VO_2) over 48 hours and change in lactate was a secondary outcome. After the first year, however, the primary outcome was changed to lactate, and VO_2 was changed to secondary. This change was made due to too many patients not meeting the ventilator criteria to allow collection of VO_2 data for at least the initial several hours of the study protocol, and enrollments therefore lagging behind. This change in primary outcome was posted at that time on clinicaltrials.gov and was submitted and approved by our Internal Review Board (IRB).

Prespecified Secondary Outcomes:

1. Change in VO_2 over 48 hours
2. Absolute level of lactate over 48 hours
3. absolute level and the change in oxygen consumption over 48 hours

4. absolute level and the change in pyruvate dehydrogenase (PDH) activity, quantity and specific activity over 48 hours
5. absolute level and change in creatinine over 48 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 48 hours
10. renal failure during first 7 days following arrest
11. absolute level and change in cellular oxygen consumption rate over 48 hours

Sample Size Calculations:

Lactate: The analysis method for lactate will be linear mixed-effects modeling (LMM). This type of modeling is used in longitudinal or repeated-measures studies to consider the correlation of within-subject measurements and can optimize the power. In this case, we also want to include the interaction between arm (thiamine or placebo) and time, as our hypothesis is that the change of lactate over time will vary by arm. 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, with similar characteristics to patients who will be included in this study, for whom we had lactate measurements over 24 hours. 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 arms) will be 33%. That is, we assumed that the mean lactate level at the three different time points in the thiamine arm would be 2.55, 2.35, and 1.94. Using LMM, accounting for an interaction between arm and time, and assuming a within-subject correlation of 0.7 with no decay in correlation over time, we will need 58 subjects (29 in each arm) to obtain >80% power with type-I error of 0.05 for detecting a difference in the change in lactate over 24 hours between arms. We assumed an average baseline (time 0) lactate of 4, and a standard deviation of 2. Our inclusion criteria restricts the patients population to those with a lactate >/=3, which is why we made our standard deviation slightly smaller. We also conducted a sample size calculation using the ANCOVA method for one baseline and 3 follow up lactate measurements. For this method we used the 24 hour means of 2.9 (+/- 2) and 1.9(+/-1.5), assumed a within-subject correlation of 0.7 between time points, and obtained target number of 54 patients (27 in each arm) to achieve 90% power with a type-I error of 0.05. To be conservative we will plan to enroll 60 patients, to account for possible drop out.

VO_2: Prior to our pilot study, there was no data on the effect of thiamine on VO_2 in hospitalized patients. We have therefore relied on our pilot data for the sample size calculation. In critically ill patients with preserved cardiac index (>2.4L/min/m^2), the average increase in VO_2 after thiamine administration was 35mL/min. Using the average change in VO_2 of 35mL/min and the average standard deviation of 45mL/min, we will need to enroll 28 patients in each arm to achieve a power of 0.8 with a Type I error of 0.05. We have chosen to enroll 30 in each arm to allow some room for drop out.

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 arm differences in baseline characteristics.

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, 48h) 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 five levels, defined as baseline, 6 hours, 12 hours, 24 hours, and 48 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 48 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 48 hours are assigned the last known value before the event without a penalty.

Analysis of Secondary Outcomes

Lactate levels over 48 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 48 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), creatinine, SOFA score, and cellular oxygen consumption rate levels over 48 hours

To test change over time, we will compare repeated measures of each outcome listed above at each time point (0h, 24h, 48h) 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 48 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 or transition to comfort measures only 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

A pre-planned subanalysis of the primary outcome will be performed stratified by arrest duration, dichotomized into <15 minutes and >=15 minutes. Two additional sub-analyses will focus only on the patients with baseline thiamine deficiency (plasma vitamin B1 level <=7 nmol/L), one looking at the primary outcome of change in lactate and the other on the secondary outcome of change in VO_2 (provided sufficient data are available).

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.