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Mild Hypothermia to prevent Acute kidney injury in Liver Transplantation (MHALT) Trial - Statistical Analysis Plan for the Interim Analysis, v1.0

Michael Bokoch¹, Claus Niemann¹, Dieter Adelman¹, Rishi Kothari¹¹University of California, San Francisco

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UCSF Transplant Anesthesia Research Group (TARG)



Michael Bokoch

University of California, San Francisco

ABSTRACT

Acute kidney injury (AKI), or worsening kidney function, is a common complication after liver transplantation (20-90% in published studies). Patients who experience AKI after liver transplantation have higher mortality, increased graft loss, longer hospital and intensive care unit stays, and more progression to chronic kidney disease compared with those who do not. In this study, half of the participants will have their body temperature cooled to slightly lower than normal (mild hypothermia) for a portion of the liver transplant operation, while the other half will have their body temperature maintained at normal. The study will evaluate if mild hypothermia protects from AKI during liver transplantation.

This study is a single-blinded, randomized controlled trial of mild hypothermia during liver transplantation to provide protection from AKI. Participants will be randomized to normothermia (36.5-37.5 °C) versus mild hypothermia (34-35 °C) during a portion of the liver transplant operation. The protocol is based on preliminary data from rodent models showing that hypothermia protects the kidneys from ischemia-reperfusion injury, as well as studies in deceased organ donors showing that cooling improves post-transplant organ function. Temperature will be maintained with standard techniques plus a minimally-invasive esophageal cooling device that is approved by the U.S. Food and Drug Administration. The investigators hypothesize that mild hypothermia will reduce the incidence and severity of AKI after LTx. Standard surrogates (e.g., change in serum creatinine, need for initiation of dialysis) and biomarkers will be used to assess the severity of kidney injury.

STATISTICAL CONSIDERATIONS

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Statistical Analysis Plan for the Interim Analysis

[NCT03534141](https://clinicaltrials.gov/ct2/show/study/NCT03534141)

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1.1 Analysis Populations

The following populations will be used for the summaries and analyses of the study data. These populations are defined as follows:

- **Randomized:** The Randomized population will consist of all subjects who are randomized to a treatment group
- **Intention-to-treat (ITT):** The ITT population will consist of all randomized subjects not withdrawn from the study. The interim efficacy analysis will be based on the ITT population.

- **Per-Protocol (PP):** The PP population will consist of all ITT subjects who complete liver transplant, received the full randomized study treatment, and complete 72 hours of study follow up. Analyses of the PP population will be performed in the final statistical analysis.

Adjustments may be made to refine the definition of the above populations prior to database lock for the final statistical analysis. The final definition of these populations will be documented in a prospectively developed final statistical analysis plan (final SAP) published on Protocols.io. The final SAP must be finalized and approved prior to database lock and unblinding.

1.2 Statistical Hypotheses

The null (H_0) hypothesis and the alternative (H_1) hypothesis to be tested for the primary endpoint are that:

$$H_0: p_1 = p_2 \text{ versus } H_1: p_1 \neq p_2$$

Where p_1 is the proportion of the ITT population meeting the primary outcome in the Control Arm (Normothermia), and p_2 is the proportion of the ITT population meeting the primary outcome in the Experimental Treatment Arm (Mild Hypothermia).

1.3 Demographic and Baseline Characteristics

For the final statistical analysis, demographic and relevant baseline characteristics will be presented and summarized descriptively by treatment for the Randomized, ITT, and the PP populations. These characteristics will not be included for the interim statistical analysis for efficacy, as they have been summarized and reported elsewhere to the Data Safety Monitoring Board (DSMB). Additional summary of demographic and baseline characteristics may be specified in the final SAP, if deemed necessary.

1.4 Sample Size Justification and Power Analysis

Considering one interim analysis for efficacy, and given the incidence of acute kidney injury (AKI) in liver transplantation (LTx) patients at UCSF (68%), we estimate a sample size of 101 subjects per arm ($n = 202$ total) is needed to detect a 30% reduction in AKI with 80% power at overall alpha = 0.05 (two-tailed).

We will aim to enroll 230 total subjects to allow for just over a 10% drop-out rate, since some subjects may not be able to complete the protocol and be withdrawn from the study.

STATISTICAL ANALYSES



1.5 1.5.1. Interim Analysis for Efficacy

A single interim analysis for efficacy is planned for this study after 50% of the required patients (101 of the 202 estimated by the power calculation) are accrued after accounting for withdrawn subjects. Based on the O'Brien-Fleming approach to calculate alpha spending, during the interim analysis step, if the p value is < 0.0054 , the study will be stopped as the desired efficacy will have been achieved; if not, then we will continue the study. If the final p value after 100% enrollment is < 0.0492 , then we will declare that the AKI status is different between the two arms.

1.5.2. Analyses of Primary Efficacy Endpoint

The primary efficacy endpoint is the incidence of AKI within 72 hours after LTx. The International Club for Ascites (ICA) 2015 criteria, a revision of the Kidney Disease Improving Global Outcomes (KDIGO) criteria for patients with cirrhosis, will be used to define AKI (Angeli et al., 2015). The definitions are as follows:

- **AKI:** increase in serum creatinine (sCr) ≥ 0.3 mg/dL within a 48-hour time window, or a percentage increase $\geq 50\%$ from baseline, or initiation of renal replacement therapy (RRT)
- **Baseline sCr:** the most recent value of sCr prior to LTx

The primary outcome (presence or absence AKI) will be compared between the two arms by a two-sample test of proportions (Fisher's exact test or chi-square, as appropriate).

To determine whether a subject met the primary outcome, the following procedure is followed in order:

Step #1. Need for renal replacement therapy

If the patient had RRT within 72 hrs from the End of Surgery ("postop_rrt_72h" = yes), the primary outcome is met (subject had AKI).

Step #2. Calculation of the fold-increase in sCr

The interim analysis database will contain four sCr values:

- creat_0** = Baseline sCr (most recent prior to Surgery)
- creat_24h** = Highest sCr, 0-24 hrs from End of Surgery
- creat_48h** = Highest sCr, 24-48 hrs from End of Surgery
- creat_72h** = Highest sCr, 48-72 hrs from End of Surgery

The highest of these values (*b-d*) will be used to calculate the following:

$$\text{Fold increase in sCr} = \text{Maximum of \{creat_24h, creat_48h, creat_72h\}} / \text{creat_0}$$

If the Fold increase in sCr is ≥ 1.5 , the primary outcome is met (subject had AKI).

Step #3. Calculation of the difference in sCr

The following calculation should be performed:

$$\Delta \text{sCr}_{\text{max}} = \text{Maximum of \{creat_24h, creat_48h, creat_72h\}} - \text{Minimum of \{creat_0, creat_24h, creat_48h\}}$$

If $\Delta \text{sCr}_{\text{max}} < 0.3$ mg/dL, the primary outcome is NOT met (subject DOES NOT have AKI).

If $\Delta \text{sCr}_{\text{max}} \geq 0.3$ mg/dL, but the patient does not meet either of the criteria described in **Step #1 (RRT)** or **Step #2 (Fold increase)**, additional timing information may be required to determine if the subject had AKI. According to KDIGO criteria, the sCr must increase by ≥ 0.3 mg/dL within a 48 hour time window to diagnose AKI (i.e., if the sCr increased by 0.3 mg/dL over 72 h, this is not necessarily AKI) (Kellum et al., 2012). In this situation, the following calculations should be performed:

$$\begin{aligned} \Delta_1 &= \text{creat_24h} - \text{creat_0} \\ \Delta_2 &= \text{creat_48h} - \text{creat_0} \\ * \Delta_3 &= \text{creat_48h} - \text{creat_24h} \\ \Delta_4 &= \text{creat_72h} - \text{creat_24h} \\ * \Delta_5 &= \text{creat_72h} - \text{creat_48h} \end{aligned}$$

* indicates a time interval that is unambiguous (definitively less than 48 h)

If either Δ_3 or Δ_5 is ≥ 0.3 mg/dL, the timing is unambiguous (< 48 h window). The primary outcome is met (subject has AKI).

If any of Δ_1 , Δ_2 , or Δ_4 is ≥ 0.3 mg/dL, the timing is ambiguous and further information is required to determine AKI status. The Data Management Team will provide the Statistician with the exact times and dates of collection for the relevant sCr values.

- The time interval (Δt) between sCr collections should be calculated for each $\Delta_1, 2, \text{ or } 4$ that is ≥ 0.3 mg/dL.
- If any Δt is ≤ 48 h, the primary outcome is met (subject has AKI).
- If all $\Delta t > 48$ h, the primary outcome is NOT met (subject DOES NOT have AKI).

Step #4. Death of a subject prior to 72 hours from the End of Surgery

If a subject died < 72 h from the end of surgery, the subject is defined as having met the primary outcome (subject has AKI). This agrees with the definition of Major Adverse Kidney Events recommended for clinical trials (Kellum et al., 2017).

1.5.3. Analyses of Secondary Endpoints

Analyses of secondary endpoints are not included in the interim analysis for this study. A detailed analysis of the frequencies and distribution of KDIGO stages of AKI is an important component of the final statistical analysis.

1.5.4. Analyses of Safety Endpoints

Analyses of safety endpoints are not included in the interim analysis for this study.

1.6 Stopping Rule

This study does not have a formal stopping rule that is based on statistical testing.

1.7 Handling of Missing Data

Subjects with missing primary outcome data will be excluded from the interim analysis.

1.8 References

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