

Remote Ischemic Conditioning (RIC) in Recipients of Brain Death Donor Livers –

A Feasibility and Safety Study

NCT02635347

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RIC Liver Recipients – Data Analysis Plan

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Available Data

- RECIPIENT Baseline Characteristics
 - Study Group
 - Hospital Days (#)
 - Post-Transplant Hospital Days (#)
 - Age, years
 - Gender
 - Ethnicity
 - American Indian/Alaska Native
 - Asian
 - Native Hawaiian
 - African American
 - Hispanic/Latino
 - White
 - More than 1 race
 - Unknown/not reported
 - Height
 - Weight
 - BMI
 - Beta blockers at transplant (y/n)
 - CCB at transplant (y/n)
 - Primary Etiology, Secondary etiology
 - EtOH
 - HBV
 - HCV
 - Cryptogenic/NAFLD
 - AIH
 - PBC
 - PSC
 - Budd-Chiari
 - Wilson's
 - Alpha-1 Antitrypsin
 - Biliary atresia
 - Other
 - HCC (y/n) – based on path report
 - HTN
 - CAD
 - Hx of MI
 - Peripheral vascular disease

- Peripheral neuropathy
- HIV
- Asthma
- COPD
- PNA
- Current smoker
- DM
- CKD
- On dialysis at time of Tx
- Serum creatinine
- eGFR
- Total Bilirubin
- INR
- MELD
- Pressors (y/n)
- Hypertonic saline (y/n)
- Mechanical ventilation (y/n)
- Days of mechanical ventilation
- Donor Baseline Characteristics
 - Age, years
 - Gender
 - Race
 - White
 - African American
 - Hispanic/Latino
 - Asian
 - Native American
 - Other
 - Height
 - Weight
 - BMI
 - Cause of death
 - Hospital days
 - OPO
 - Local
 - Regional
 - National
 - Donor receiving glucocorticoids
 - Donor on sulfonylureas
 - Pre-recovery biopsy performed
 - Macrosteatosis
 - Microsteatosis

- DRI
- Operative Variables
 - Anesthesia Maintenance agent (each y/n)
 - Sevo
 - Iso
 - Des
 - Other
 - Propofol used for induction (y/n)
 - Surgery length (min)
 - CIT (min)
 - WIT (min)
 - Veno-venous bypass used (y/n)
 - Piggypack or bicaval
 - Crystalloid (liters)
 - Albumin (liters)
 - RBC (units)
 - FFP (units)
 - Platelets (units)
 - Cryo (units)
 - Other fluid (likely nothing in this field)
 - UOP (liters)
 - EBL (liters)
 - Post-implantation biopsy (y/n)
 - Fields exist for %macro and %microsteatosis but these are all empty because the slides have not been reviewed.
- POST-Operative Variables
 - Propofol for sedation POST-OP (y/n)
 - ICU LOS (days)
 - POD 0-7 (8 values total)
 - AST
 - ALT
 - Total Bilirubin
 - INR
 - Creatinine (if not on HD to begin with and if not already in stage III AKI pretransplant)
 - Time to extubation
 - Reintubated within 7 days (y/n)
 - Early allograft dysfunction – EAD (y/n)
 - Prolonged respiratory insufficiency – PRI (y/n)
 - Stage 2 AKI (y/n)
 - Stage 3 AKI (y/n)
 - Pre- and post-transplant dialysis and whether or not it was discontinued in the hospital

- Time to dialysis discontinuation
- Clavien Dindo – all for 30 day complications
 - 3b (y/n)
 - 4a (y/n)
 - 4b (y/n)
 - 5, ie. Death (y/n)
 - Highest complication grade
 - Any complication greater than or equal to 3b (y/n)
 - Number of 3b or higher complications
- Survival PATIENT – 90 days
 - (y/n) and number of days
- Survival GRAFT – 90 days
 - (y/n) and number of days
- Dialysis – 90 days
- Creatinine at 90 days if not on dialysis
- eGFR at 90 days
- Completed study (y/n)

Statistical Analysis Plan

No comparison (one group)

- All feasibility data
 - Proportion of all patients who tolerated all 6 interventions
 - Proportion of patients who were intubated for all 6 interventions
 - Proportion of patients who were extubated for at least one intervention and tolerated all 6 interventions
 - For extubated patients: number of interventions tolerated while extubated. Break down into those who tolerated all 6 vs those who didn't tolerate all 6.
 - Mean/median pain score for patients receiving an intervention
 - Present as mean/median plus/minus STDEV/IQR for pain scores and number of interventions. Also histograms would be useful for these as the pain scores are likely going to end up being bimodally distributed.
 - Present as proportions with confidence intervals for all others.

Bivariate analyses – categorical data

Chi-squared or Fisher's exact tests.

- Recipient baseline characteristics
 - Gender, beta blockers at transplant (y/n), CCB at transplant (y/n), HCC (y/n) – based on path report, HTN, CAD, Hx of MI, Peripheral vascular disease, Peripheral neuropathy, HIV, Asthma, COPD, PNA, Current smoker, DM, CKD, On dialysis at time of Tx, Pressors (y/n), Hypertonic saline (y/n), Mechanical ventilation (y/n)
- Donor baseline characteristics
 - Gender, Donor receiving glucocorticoids, Donor on sulfonylureas, Pre-recovery biopsy performed (y/n)
- Operative Variables
 - Propofol used for induction (y/n), Veno-venous bypass used (y/n), Piggypack or bicaval, Post-implantation biopsy (y/n)
- POST-operative Variables
 - Propofol for sedation POST-OP (y/n), Reintubated within 7 days (y/n), **Early allograft dysfunction – EAD (y/n), Prolonged respiratory insufficiency – PRI (y/n)**, Pre- and post-transplant dialysis and whether or not it was discontinued in the hospital
 - Stage 2 AKI (y/n)
 - Stage 3 AKI (y/n)
 - These need to be discussed. The ideal method for comparison would be as an ordinal variable, using a CMH test. However, numbers may end up being low. Alternatively, can analyze as one y/n (ie. Stage 2 or 3 AKI) or using exact chi-squared.
- Clavien Dindo – all for 30 day complications

- 3b (y/n), 4a (y/n), 4b (y/n), 5 ie. Death (y/n)
 - These need to be discussed. We can analyze each individual complication grade using a 2x2 table. Analysis using an ordinal scale doesn't make sense, unless we take only the highest grade, for example.
 - Death also needs to be discussed. Later, we have 90 day mortality data (yes/no) as well as data regarding number of days survived. So we need to decide (a) if we are including death here at all, (b) if we end up analyzing 2x2 tables, is there any point to analyzing 30 day death separately from 90 days, I think no.
- Any complication greater than or equal to 3b (y/n)
- Other data
 - 90 day patient survival (y/n)
 - Can also analyze using Kaplan-Meier estimates
 - Should we consider gathering the data past 90 days? Our protocol does not say we would do this.
 - 90 day graft survival (y/n)
 - Can also analyze using Kaplan-Meier estimates
 - Patient on dialysis at 90 days (y/n)

Chi-squared or Exact Chi-squared tests (categorical variables with more than two levels for the outcome).

- Recipient baseline characteristics
 - Ethnicity, Primary/secondary etiology of cirrhosis,
- Donor baseline characteristics
 - Ethnicity, OPO (local/regional/national), Cause of Death,
- Operative variables
 - Anesthesia type
- POST-operative variables
 - Stage 2 / Stage 3 AKI (see discussion above)
- Clavien-Dindo
 - Complication grades (see discussion above)

Cochran–Mantel–Haenszel test for Ordinal Data

- Stage 2/3 AKI, Complication grades (see discussion above)

Bivariate analyses – Continuous Data

Student's T-Test vs Mann-Whitney U test

- Recipient baseline characteristics

- Hospital Days (#), Post-Transplant Hospital Days (#), Age years, Height, Weight, BMI, Serum creatinine, eGFR, Total Bilirubin, INR, MELD, Days of mechanical ventilation
- Donor baseline characteristics
 - Age years, Height, Weight, BMI, Hospital days, Macrosteatosis, Microsteatosis, DRI
- Operative variables
 - Surgery length (min), CIT (min), WIT (min), Crystalloid (liters), Albumin (liters), RBC (units), FFP (units), Platelets (units), Cryo (units), Other fluid (likely nothing in this field), UOP (liters), EBL (liters)
 - Macro/microsteatosis if data become available
- POST-op variables
 - ICU LOS (days)
 - POD 0-7 (8 values total)
 - AST, ALT, Total Bilirubin, INR, Creatinine (if not on HD to begin with and if not already in stage III AKI pretransplant)
 - Here, we need to decide how the data will be analyzed. There are three options: day-by-day comparisons, an omnibus test such as a factorial ANOVA (there will be a problem with missing data if we do this), and bivariate longitudinal linear regression (my personal preference, this accounts for correlation between observations within a subject on different days but at the same time uses all the data)
 - Time to extubation
 - Time to dialysis discontinuation
- Clavien-Dindo
 - Number of 3b or higher complications
- Creatinine at 90 days, eGFR at 90 days.

Multivariate regression analysis

- Logistic regression
 - EAD, PRI, Stage 2/3 AKI
- Longitudinal linear regression
 - AST, ALT, Total bilirubin, INR, Creatinine