Beta-Adrenergic Blockade for **Attenuation** of Catecholamine Surge Following Traumatic Brain Injury: A Randomized Pilot Trial

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Methods

A single-center prospective randomized controlled pilot trial was conducted at the Presley Regional Trauma Center at Regional One Health in Memphis, TN from 1/1/16 to 12/13/17. This hospital is the only trauma center in Memphis, serves as the only trauma center in the Mid-South area, and is a major teaching facility for the University of Tennessee Health Science Center. The Mid-South is a geographic area of approximately 3,500 square miles surrounding Memphis including western Tennessee, eastern Arkansas, northern Mississippi, and small portions of Missouri and Kentucky. The trial is registered on clinicaltrials.gov (NCT02957331). After informed consent was obtained by one of the investigators or research nurses from the patient or legally authorized representative (LAR), patients were randomly assigned to either the treatment (PRO) or control arm using block randomization in groups of 4 to ensure equal group size. This sequence was generated using SAS version 9.4 (SAS Institute, Cary, NC). The study was not blinded due to the treatment effects and need for titration of the medication on physiologic parameters.

The primary outcome was in-hospital mortality. The secondary outcome was to examine the interaction between beta-blockade and catecholamines by measuring urinary catecholamines. A power analysis was performed using literature review to determine probable effect size. Utilizing a 15% difference in mortality between groups, a sample of 99 patients per group would be required to power the study at 0.80. This sample size would not be feasible at a single center. Therefore, in lieu of performing a multi-center study with limited resources, we elected to perform a pilot study to determine study

safety, feasibility, and effect size over a one-year period. The enrollment was re-assessed after one year and still short of the goal, so the study was extended an additional year.

Eligible patients for screening were 18 years or older with a TBI as determined by Glasgow Coma Scale score (GCS) less than 12 on admission and documented brain injury on head computed tomography scan. Qualifying patients were randomized within 72 hours of injury. Exclusion criteria included patients with a significant injury in another body region (Abbreviated Injury **Scale score** >3), incarceration or gravidity, hepatic disease, home beta-blocker use, ongoing resuscitation or vasoactive medications, active acute coronary syndrome, and **non-survivable injury as determined by neurosurgery review of imaging**. Data were extracted from the electronic medical record (Sorian, Cerner, Kansas City, MO) and the local trauma registry (NTRACS version 3.0, Digital Innovations, Forest Hill, MD). Patients assigned to the PRO arm were dosed with propranolol starting at 20 mg three times daily (TID) by mouth or per feeding tube. The dose of propranolol was increased daily in 20 mg TID increments (60 mg/day total) until heart rate (HR) was less than 100 beats per minute (bpm) with maximum dose of 640 mg/day. Parameters for holding the medication included HR less then 60 bpm or systolic blood pressure less than 100 mm Hg. Patients assigned to the control arm were managed per institutional standard for TBI based on the Brain Trauma Foundation guidelines.[27] Neither arm had additional beta-blockers withheld if the care team deemed that class of medication necessary for appropriate care. Treatment duration for active study intervention was 14 days with a 48-hour taper of propranolol after the study period ended in the PRO arm. Patients were followed during the hospital stay until death or discharge.

Variables collected included demographics, severity of injury, severity of illness scores, physiologic parameters, operative interventions, hospital length of stay (LOS), intensive care unit length of stay (ICU LOS), discharge disposition, infectious morbidity, urinary catecholamines, and mortality. Urinary catecholamines were collected from discarded urine at study enrollment and then at study day (SD) 2, SD-5, SD-7, SD-10, and at the end of the study period (SD-14) or when the patient came off study. The samples were stabilized with hydrochloric acid (HCl) and sent to a standard lab. Timely acid stabilization of the urine specimens was required prior to shipping to the central lab for processing. If HCl was not added to the specimen, unpredictable results were obtained that were not physiologically possible *in vivo*. These values were excluded from analysis. Patients in the PRO arm were compared to the control **using intent to treat analysis.**

Statistical analyses for categorical variables were compared using *Chi*-square tests or Fisher's exact tests where appropriate. Normally distributed continuous variables were compared using *Student's* t-tests and non-normally distributed continuous variables were compared using Wilcoxon Rank Sums tests. Effect size for mortality was calculated using the absolute difference between treatment groups. A two-way mixed model III Analysis of the Variance (ANOVA) with repeated measures was used to estimate differences between the two treatment arms over time. Using planned contrasts, the mean for each follow-up measurement was compared to SD-1 (i.e., randomization) for *within-group* contrasts and means at each assessment time were compared for *between-group* contrasts. Because these contrasts were planned, no correction was made for multiple comparisons. Output for the ANOVA is reported as Least Square Means

(LSMeans) with standard error (±SE). Finally, Kaplan-Meier survival analysis was performed to further examine mortality over time between groups. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). The University of Tennessee Health Science Center and Regional One Health Institutional Review Boards approved the study. A p value of less than 0.05 was considered significant.