Esmolol to Treat the Hemodynamic Effects of Septic Shock

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Statistical Analyses

Preliminary observational data on a cohort of septic shock patients indicated a mean norepinephrine equivalent dose was 0.15 ± 0.09 mcg/kg/min at the 6 hour time point. We anticipated a 33% reduction in mean norepinephrine dose to 0.10 ± 0.09 mcg/kg/min after 6 hours of continuous treatment with esmolol. Based on these estimates, for a two-sample t-test with a power of 80% and a type I error of 0.05, we estimated that a total of 104 patients would be required to show a statistically significant difference between treatment and control groups.

Descriptive statistics are provided for baseline and outcome variables. Continuous variables are presented as means with standard deviations or medians with interquartile ranges (IQR), based on the distribution of the data. Categorical variables are presented as counts with percentages. In univariate analysis, continuous variables were analyzed using a Student's t-test if normally distributed and a Wilcoxon ranked sum test if non-normal. Categorical variables were analyzed using a Fisher's exact test.

The association between continuous infusion of esmolol and need for vasopressor support was assessed by comparing the median 6 hour norepinephrine equivalent dose (NED) between groups using a Wilcoxon rank-sum test. No patients expired prior to 6 hours after enrollment. To analyze the difference in vasopressor dose between groups at 12 hours and over time, we compared NED (recorded hourly for 12 hours) over time between groups using linear mixed effect models accounting for repeated measures and adjusting for pre-intervention NED. The appropriate variance-covariance structure was selected based on Akaike information criterion. Using this model, we tested whether NED was different at 12 hours and for differences in the overall trend over time. A similar analysis was used to assess the difference in heart rate between groups over the first 12 hours and lactate between groups over the first 24 hours; however, in the heart rate analysis, we tested for mean differences at 6 hours, 12 hours and for differences in the overall trend over time, and in the lactate analysis, we used a log-transformed lactate value to test for mean differences at 12 and 24 hours and for differences in the overall trend over time. We compared the median number of shock free days, defined as cessation of all vasopressors during the first 7 days, between the two groups.

To characterize the effects of esmolol infusion on VO_2, we limited the analysis to patients who were mechanically ventilated during the study period. The VO_2 values were cleaned based on a custom algorithm that eliminated points that met any of the following four criteria: 1) VO_2 value corresponding to a Fraction of Inspired Oxygen (FiO_2) value above 61%. 2) VO_2 value within 10 minutes of a 10-unit change in FiO_2. 3) VO_2 value above 800 mL/kg/min or below 80 mL/kg/min that is not sustained for at least 30 consecutive minutes. 4) VO_2 value that is 15% higher or lower than the average of the VO_2 values 5 minutes before and after the point in question.

To analyze the difference in oxygen consumption between groups at 12 hours, 24 hours and over time for patients who were on mechanical ventilation at enrollment, we compared VO2 measurements (standardized by bodyweight in kilograms) over time (recorded every minute

from the time of study drug administration over a period of at least 24 hours) between groups using mixed linear model accounting for repeated measures (n = 15). We did not adjust for pre-intervention VO2 measurements. Using this model, we tested for mean differences at 12 hours, 24 hours and for differences in the overall trend over time. The appropriate variance-covariance structure was selected based on Akaike information criterion. Additionally, a figure was created by first computing the mean of all the VO2 observations for a patient by timepoint, and then computing the mean of the means for each timepoint by treatment group.

To characterize effects of esmolol on inflammatory markers in patients with vasopressor-dependent septic shock, we compared log-transformed values of biomarkers at 12 and 24 hours and over time between groups using mixed linear model accounting for repeated measures and adjusting for pre-intervention biomarkers. The appropriate variance-covariance structure was selected based on Akaike information criterion.

In-hospital mortality was compared between groups using the Fisher's Exact test. Baseline covariates appeared to be balanced, so we did not adjust for any additional covariates. Length of hospital and ICU stay was compared between groups using a Wilcoxon ranked sum test and stratified based on hospital survival. To characterize effects of esmolol on SOFA score over the first 24 hours, we compared SOFA at 6, 12, and 24 hours and over time between groups using a mixed linear model accounting for repeated measures and adjusting for pre-intervention SOFA.

All analyses were conducted using Stata 14.2 (College Station, TX) and a p-value of <0.05 was considered significant.