NCT03196167

Sugammadex and Decreased Time to Extubation

SAP

6/19/2020

Study Protocol:

Subject Recruitment: Subjects will be consented in the collaborating surgeons offices or in pre-admission testing. Every effort will be made to consent subjects prior to day of surgery. If a patient is referred or identified any time after those visits, they may be consented in the preoperative area.

Anesthetic management per protocol: For enrolled patients, anesthetic management will be left to the discretion of the attending anesthesiology provider. As per our usual clinical practice, Rocuronium or vecuronium will be used as the non-depolarizing NMB and that where sedation is desired and appropriate, The patients will be transferred to the CTICU intubated and on a propofol infusion and/or dexmedetomidine per our usual clinical practice.

Upon CTICU arrival, determination of continued eligibility will be determined. If the decision is made to continue on a fast-track extubation pathway, eligible patients will be randomized, investigational pharmacy will be contacted for study drug. 30 minutes after the ICU admission, propofol will be discontinued. Precedex may be continued per clinical discretion. The participant will be randomized to either receive Sugammadex or placebo. A qualitative train-of-four measurement will be obtained. The administration of the study and placebo compounds will be performed by CTICU nurses who will receive the drugs in a blinded fashion from the departmental research pharmacy. The level of neuromuscular blockade will be measured by accelerometer before and after the drug/placebo administration by the research coordinator. This will be done by placing a sheet over the limb being tested, so that the clinical team remains blinded to the results of the drug /placebo administration. The study drug will be supplied by Merck. Patients will be initiated on SIMV with 40% FiO2, tidal volumes 8-10 ml/kg and PEEP of 5.

Ten minutes after the drug administration, if the patient is able to lift head and remains hemodynamically stable, the patient will be switched to CPAP mode of ventilation for 30 minutes. At the end of the CPAP trial tidal volumes, Rapid Shallow Breathing Index (RSBI) and ABG will be assessed. The patient will be extubated if he/she is not hypoxic/ hypercarbic, has RSBI<100 and has TV >300 cc. The final clinical decision to extubate the patients will be taken by the CTICU team.

If a patient fails the 30 minute CPAP criteria, the ICU intensivist will be immediately notified. Every attempt will be made to correct the underlying cause of CPAP failure, and a prompt reassessment will be made as deemed appropriate by the intensivist to reattempt CPAP versus continuing controlled mechanical ventilation.

It is estimated conservatively that the study personnel will randomize 3 patients per week allowing for data collection to be completed within 1 year of study commencement. Data analysis and dissemination of findings will be conducted over the subsequent 6 months by the study institution investigators per the publication plan below.

Blinded analyses of the data will be performed by the study investigators along with the departmental statistician in the Department of Anesthesiology at the Yale School of Medicine.

Variables/Time Points of Interest: The primary outcome is the time to extubation, which will be the duration from arrival to the ICU to the extubation time. Participants' blood pressure, heart rate, and chest tube output will be tracked from arrival to the CTICU until extubation per ICU protocol.

Statistical Methods: Baseline comparability. We expect that the randomization process will produce reasonably comparable groups. However, the adequacy of the randomization will be assessed by comparing the distribution of baseline demographic and clinical characteristics among the intervention groups. Comparability for continuous variables will be examined graphically and by summary statistics (means, medians, quartiles, etc.). Categorical variables will be examined by calculating frequency distributions.

Proposed statistical test/analysis: Positively skewed variables will be log-transformed prior to hypothesis testing. For the primary outcome, a two-sided Student's t-test will be used to compare the time to extubation between the two groups. If necessary, covariate adjustment will be made using the multiple linear regression analysis method. Differences between means and 95% confidence intervals will be estimated to describe the magnitude of intervention difference between the two groups. As part of sensitivity analyses, the time-to-extubation outcome will be also analyzed by the Cox regression model. To compare the categorical adverse events between two groups, chi-square test or Fisher's exact test will be used.

Missing Data: Prevention is the most obvious and effective manner to control bias and loss of power from missing data. Therefore, several strategies (e.g., timely data entry and daily missing data report) will be imposed to limit the likelihood that missing data will occur during this study. This protocol will follow the intention to treat principle, requiring follow-up of all subjects randomized regardless of the actual treatment received.

Power analysis: Our 'in-house' historical data (n = 73) showed that after excluding outliers greater than the 80th percentile, patients undergoing isolated CABG demonstrated a mean of 8.39 hours to extubation (SD 2.89). Although we anticipate a Hawthorne effect demonstrating reduced time to extubation in both the active and placebo arms of the present study, we have conservatively chosen to maintain power based on historical data. We therefore estimate that 45 subjects per group will give us 90% power to detect a clinically relevant effect size of 2-hours difference between active and placebo groups at an alpha value of 0.05 using a two-sided two-sample t-test. To allow for post consent, pre-randomization study drop out, we will aim to enroll a total of 110 (90 + 20 = 110) subjects.

Per-protocol Sensitivity Analysis: In parallel with the primary analysis, if exclusions above occur post randomization but prior to drug administration, the investigators will conduct a parallel "per-protocol" sensitivity analysis.

Drug supplies will be supplied by the sponsor.

Adverse Experience Reporting: Throughout the duration of the study, researchers will adhere to good clinical practice and the guidelines of the institution. Patient vitals will be continuously monitored during and after the administration of the test drug. A data and safety monitoring board (DSMB) consisting of the head nurse and a senior critical care staff will meet monthly to discuss any serious events. Any incidence of anaphylaxis or unexplained hypotension requiring initiation of pressors or cardiac pacing within 5 minutes of drug administration will be reported an evaluated. Increases in chest tube output considered clinically significant by the critical care team will be noted. Any of these adverse events will trigger an analysis by the DSMB. If the DSMB determines that study drug may be causing an increase in adverse events, the study will be suspended until the DSMB is able to fully review the events and make a recommendation in consultation with the Yale Human Investigations Committee. The local Merck research

representative will also be notified about the events. If the data monitoring board and/or institutional review board (IRB) view that the study is unsafe, the study will be discontinued.

Specific Safety Events to Be Reported During Manuscript Preparation: For manuscript preparation, the rates of hypotension, anaphylaxis, and bleeding (i.e. Chest Tube output) will be reported and compared between active and placebo groups.

Protocol Amendments:

Three changes were made to the protocol within the first year of initiation to generalize the inclusion criteria due to slow recruitment rates:

1. Originally the trial's inclusion criteria was patients undergoing isolated coronary artery bypass grafting. It was expanded to allow for coronary artery bypass grafting (CABG), aortic valve replacement (AVR) or coronary artery bypass grafting and aortic valve replacement (CABG and AVR).
2. The exclusion criteria for postoperative temperature was changed from 36.2° C to 35.5° C.
3. Low dose pressors infusion was allowed as long as it did not preclude fast track protocol as adjudicated by the clinical team that was blinded to the arm allocation.