Sugammadex versus Neostigmine for Reversal of Rocuronium-Induced Neuromuscular Blockade: A Study of Thoracic Surgical Patients

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This will be a prospective, randomized, double-blinded study of thoracic surgical patients that seeks to determine if reversal of rocuronium-induced neuromuscular blockade with sugammadex versus neostigmine results in a decreased incidence of hypoxia in the early postoperative period.

Study Procedures:

Screening and Informed Consent

A member of the research team will use a screening form to look for surgical patients that meet all of the inclusion and exclusion criteria. He/she will approach potential subjects during pre-anesthesia evaluation clinic (PAEC). Patients who are unable to be consented in PAEC will be approached in the preoperative area and the study will be explained in detail in a private room. Patients will be informed that they will receive no compensation for participating in the study and there will be no adverse consequences if they choose not to participate. If the subjects agree to participate, informed written consent will be obtained prior to any study procedures and this document will be sent to pmhresearchparticipants@phhs.org, for inclusion in the patient's medical record, per Parkland regulations. The study duration is approximately 72 hours, from the start of anesthesia to postoperative day 3.

Baseline Subjective Measures

In the preoperative area, patients will be asked to complete a baseline assessment in 3 domains (Appendix 1. Preoperative Questionnaire):

1. Physiological factors
2. Nociceptive factors
3. Emotional factors

Anesthesia Protocol

The anesthesia team that will be caring for the subject during surgery will be given the protocol for the study, which standardizes the general anesthetic technique. All patients will receive 0.6 mg/kg of rocuronium for neuromuscular paralysis during induction. Additional rocuronium will be given in 0.15 mg/kg increments to keep the patient at a neuromuscular depth of 1 twitch throughout the surgery.

Maintenance of anesthesia will be with sevoflurane in 70% oxygen, titrated to keep the bispectral index (BIS) between 40-60. All patients will have a forced air warming device (e.g., Bair Hugger, 3M, Maplewood, MN) used to maintain normothermia throughout the surgery. Subjects will be randomized to receive blinded study drug: <u>either</u> neostigmine or sugammadex for reversal of neuromuscular blockade, which will be administered intravenously at the beginning of skin closure. The anesthesia team will be blinded. The blinded study drug (reversal agent(s)) will be prepared into a 10 mL syringe by a pharmacist in Investigational Drug Service (IDS) Pharmacy and labeled in a blinded fashion as "sugammadex or neostigmine/glycopyrrolate." Any volume of blinded study drug (reversal agent(s)) that is less than 10 mL will be supplemented with 0.9% normal saline solution, preservation-free so that all syringes contain a volume of 10 mL and appear identical in order to preserve blinding. The remaining aspects of the anesthetic will be standardized and not differ from the standard of care and will be similar for all patients.

Randomization & Dosing:

Patients will be randomized to one of two groups for reversal of neuromuscular paralysis:

1. **Group 1**- neostigmine (NEO group)
    a. Neostigmine 50 mcg/kg of IBW, maximum 5 mg
    b. Glycopyrrolate, 8 mcg/kg of IBW, maximum 1 mg

2. **Group 2**- sugammadex (SUG group).
    a. Sugammadex 2 mg/kg

PACU Assessment
A blinded, trained research assistant will observe and record all parameters from the time the patient arrives in the PACU until they are discharged. All episodes of hypoxia will be recorded and any use of supplemental oxygen will be recorded. All vital signs will be extracted from the EMR. Any drugs given in the PACU will be recorded.

Statististical Analysis Plan
The sample size was calculated so that the study would have 80% power to detect an absolute difference of 25% between the incidence of hypoxia, assuming 30% of subjects in the neostigmine group and 5% of subjects in the sugammadex group would have hypoxia within the first 90 minutes postoperatively. Assuming a 15% loss of outcomes due to non-completion, 92 subjects were randomized in a 1:1 ratio to the two study groups.

All analyses were performed on an intent to treat basis, which consisted of all randomized subjects who received sugammadex or neostigmine. Standardized differences were calculated for the baseline demographic data on the two groups.17 To determine whether reversal of rocuronium-induced neuromuscular blockade with sugammadex versus neostigmine results in a decreased incidence of hypoxia, the proportion of patients with hypoxia for the neostigmine versus sugammadex groups were compared using Fisher's exact test with a two-sided level of significance of 0.05. Categorical variables were summarized using frequencies and percentages and compared between arms using the chi square test and Fisher's exact test. Continuous variables were summarized using the median and interquartile range, and then compared using the Kruskal-Wallis test. Boxplots were created to visualize the distributions of variables by treatment arm. Kaplan-Meier plots and the log rank test were used to visualize and assess time to achieve recovery from neuromuscular blockade. The number of hypoxic episodes was compared between treatment using a negative binomial regression model. Statistical significance is indicated by $p < 0.05$. All statistical analysis was conducted using R project software (R version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria).

<u>Treatment of data when rescue medication has been administered:</u>
Occasionally, a participant will not achieve sufficient reversal of neuromuscular block for extubation following administration of study medication. In this situation, caregivers might administer open-label sugammadex as a rescue medication. This constitutes a protocol deviation, as the protocol does not specify actions for this situation. In this case, all data collected up to the time of rescue administration will be treated in the assigned treatment group (neostigmine or sugammadex). Demographic statistics will include such patients' data as will all outcomes measured prior to rescue reversal administration. All data collected subsequent to the time of rescue administration will be censored for the main analyses.

Caregivers administer rescue reversal medication in this situation because they fear post-operative complications from incomplete reversal; however, giving rescue medication prevents the trial from detecting those occurrences. Accordingly, sensitivity analyses of appropriate outcome variables will include these participants, using an imputed result consistent with achieving the complication, e.g. hypoxemia in PACU.

In the event that 8 or more participants receive rescue medication requiring imputation of the primary outcome, the trial will enroll additional participants to preserve the power of the trial to answer the primary hypothesis.