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Sugammadex versus neostigmine for reversal of rocuronium neuromuscular block in patients having catheter-based neurointerventional procedures

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Study Summary

Title	Sugammadex versus neostigmine for reversal of rocuronium neuromuscular block in patients having catheter-based neurointerventional procedures
Principal Investigator	Ehab Farag, MD
Primary Objectives	The aim of this study is test the hypothesis the use of Sugammadex for reversing the neuromuscular blocking effects of rocuronium during neurointerventional procedures speeds recovery of neuromuscular function to TOF ratio more than 0.9 as primary outcome. Secondarily, we will test the hypothesis that use of Sugammadex reduces the extubation time of the trachea, returns the diaphragmatic contractility to baseline faster than neostigmine and associated with less incidence of postoperative pneumonia.
Primary Endpoints	- Time in minutes to reach TOF ratio ≥ 0.9 after the administration of reversal agent.
Secondary Objectives	- Time in minutes from the administration of reversal agent to tracheal extubation. - Diaphragmatic function excursion in centimeters measurement and speed (slope) in both groups shortly after recovery from general anesthesia. - Postoperative pulmonary infections. - Economic analysis from the hospital perspective, considering drug costs and the time required between the end of surgery and extubation. -
Study Design	A single institution study
Inclusion Criteria	**1-** Age ≥ 18 years; **2-** ASA physical status 1-3; **3-** Scheduled for catheter-based neurointervential procedures including coiling and stent insertion; **4-** General anesthesia.
Exclusion Criteria	**1-** Suspected difficult intubation; **2-** Neuromuscular disorder; **3-** Renal impairment creatinine ≥ 2 mg /dl; **4-** Hepatic dysfunction; **5-** History of malignant hyperthermia; **6-** Allergy to neuromuscular blocking drugs, Sugammadex, neostigmine or glycopyrrolate;

	7- Perioperative respiratory infections and/or pneumonia; **8-** Intubated or unresponsive; **9-** Pregnancy or breast-feeding.
Expected Sample Size	50 Patients
Statistical Methodology	We will assess the primary hypothesis that patients who receive sugammadex for reversing the neuromuscular blocking effects of rocuronium during neurointerventional procedures will have quick recovery of neuromuscular function to TOF ratio ≥ 0.9 as compared with patients who receive neostigmine. The primary outcome of time to reach TOF ratio ≥ 0.9 will be measured in continuous manner every 12 seconds from the administration of the reversal drug. The effect of sugammadex on time to reach TOF ratio ≥ 0.9 will be assessed using student t-test or multivariable linear regression adjusting for imbalanced variable, if any. Missing outcome will be imputed based on observed other recovery data from the same patients such as time to TOF ratio ≥ 0.7. Logarithmic transformation will be used to meet the normality assumption if needed. As a sensitivity analysis, we will compare the two groups on TOF ratio by 90 minutes after administration of the reversal drug. For patients who fail to reach TOF ratio ≥ 0.9 by 90 minutes, the outcome will be censored at 90 minutes in the analysis. The effect of sugammadex on time to reach TOF ratio ≥ 0.9 will be assessed using a multivariable Cox proportional hazards regression, adjusting for imbalanced variables, if any. Secondly, we will compare the randomized groups on time to reach TOF ratio ≥ 0.9, using Kaplan-Meier analysis with the log-rank test. Kaplan-Meier estimates for the two groups with equal precision (EP) 95% confidence bands will be calculated and plotted.

List of Abbreviations

Abbreviation	Definition
DB	Deep Breathing
EP	Equal Precision
MAP	Mean Arterial Blood Pressure
NMBA	Neuromuscular Blocking Agents
PACU	Post Anesthesia Recovery Unit
PORB	Postoperative residual neuromuscular
TOF	Train of four
VS	Voluntary Sniff

Background

Incomplete recovery from neuromuscular blocking agents (NMBAs) residual block after anesthesia and surgery continues to be a common problem in the post anesthesia care (PACU). The routine use of anticholinesterase reversal agents has not guaranteed adequate antagonism of the residual effects of intermediate –acting NMBAs as 20%-40% 0f patients continue to arrive in the PACU with objective evidence of postoperative residual neuromuscular block (PORB), defined as TOF ratio less than 0.9 (1,2).

PORB is associated with impaired pharyngeal function, increased aspiration risk, upper airway muscle weakness, and partial upper airway obstruction. These symptoms have been observed among patients with TOF ratios between 0.7 and 0.9 (3). Therefore, those patients with residual neuromuscular blocking effects are prone to impaired breathing or diminished protective airway reflexes, which are essential in order to avoid respiratory complications (4). A recent retrospective analysis showed that intraoperative use of intermediate nondepolarizing NMBAs is associated with postoperative pneumonia, and that nonreversal augmented risk (2).

Neostigmine remains the most common acetylcholinesterase inhibitor in the United States. However, use of neostigmine for reversal of NMBAs is not without complications. Administration of the drug significantly impairs genioglossus muscle activity when administered after full recovery from neuromuscular block. Moreover, the high doses of neostigmine more than 0.06 mg/kg increases the risk of respiratory complications independent of NMBAs effects (1, 5).

Sugammadex is a modified γ-cyclodextrin that rapidly reverses that effect of the steroidal nondepolarizing NMBAs rocuronium and vecuronium. Sugammadex forms a stable, inactive 1:1 complex with rocuronium or vecuronium; this reducing the amount of free NMBA available to bind to nicotinic acetylcholine receptors at the neuromuscular junction, resulting in reversal of neuromuscular blockade (6). Unlike neostigmine, sugammadex completely reverses even dense neuromuscular blocks.

Neurointerventional procedures have become the mainstay for the management of neurovascular pathologies like cerebral aneurysms, venous arterial malformation, management of cerebral vasospasm after subarachnoid hemorrhage, intra-arterial thrombolysis of cerebral thrombosis and management of cerebral vessels stenosis. The anesthetic management for neurointerventional procedures requires the patients to completely relax to avoid coughing or movement during the procedure. Either can cause serious complications including cerebral hemorrhage from perforation of cerebral vessel by the guide wire or mis-placement of stents or coils. Consequently, patients having catheter-based neurointerventional procedures are

keep deeply anesthetized and fully paralyzed. Unlike routine surgery there is usually no warning of when the procedure will finish. Consequently, it is common to find patients nearly completely paralyzed at the end of neurointerventional procedures, and have a markedly delayed emergence while waiting for muscle function to recover sufficiently to safely antagonize with neostigmine.

The aim of this study is test the hypothesis the use of Sugammadex for reversing the neuromuscular blocking effects of rocuronium during neurointerventional procedures speeds recovery of neuromuscular function to TOF ratio more than 0.9 as primary outcome. Secondarily, we will test the hypothesis that use of Sugammadex reduces the extubation time of the trachea, returns the diaphragmatic contractility to baseline faster than neostigmine and associated with less incidence of postoperative pneumonia.

Primary Outcomes

1- Time in minutes to reach TOF ratio ≥ 0.9 after the administration of reversal agent.

Secondary Outcomes

1- Time in minutes from the administration of reversal agent to tracheal extubation.
2- Diaphragmatic function excursion in centimeters measurement and speed (slope) in both groups shortly after recovery from general anesthesia.
3- Postoperative pulmonary infections.
4- Economic analysis from the hospital perspective, considering drug costs and the time required between the end of surgery and extubation.

Methodology

Inclusion criteria:

1. Age ≥ 18 years;
2. ASA physical status 1-3;
3. Scheduled for catheter-based neurointervential procedures including coiling and stent insertion;
4. General anesthesia.

Exclusion Criteria:

1. Suspected difficult intubation;
2. Neuromuscular disorder;
3. Renal impairment creatinine ≥ 2 mg /dl;
4. Hepatic dysfunction;
5. History of malignant hyperthermia;

6. Allergy to neuromuscular blocking drugs, Sugammadex, neostigmine or glycopyrrolate;
7. Perioperative respiratory infections and/or pneumonia;
8. Intubated or unresponsive;
9. Pregnancy or breast-feeding.

Anesthetic Management

Patients will be randomly assigned to either Sugammadex 4 mg/kg or neostigmine 0. 07 mg/kg with glycopyrrolate 0.01 mg/kg with ceiling dose of 5 mg neostigmine with 1 mg of glycopyrrolate. Randomization (1:1 without stratification) will be based on computer-generated codes (SAS Institute, Cary, NC, USA), which will be accessed via a secure web system a few minutes before the start of anesthesia start. Consequently, allocation will remain concealed until the last practical moment.

Anesthesia will be induced using propofol and rocuronium (0.6 mg/kg) in both groups. The anesthesia will be maintained using sevoflurane (inspired concentration 2.5%) in both groups. Inspired oxygen concentrations will 50% in air. The mean arterial blood pressure (MAP) will be kept within 10% of preoperative value. Narcotics use will be according to the anesthesiologist discretion.

Rocuronium will be given in infusion in the dose of 3-10 μg/kg (lean body weight = ideal + 20% in morbidly obese patients) to maintain one twitch of the train of four (TOF) in the neostigmine group (moderate block) or at a post-tetanic count of 1-2 of sugammadex group (deep neuromuscular block) till the end of the procedure.

At the end of procedure, depending on randomized assignments, patients will be given: 1) neostigmine 0.0 7 mg/kg with 0.01mg of glycopyrrolate with ceiling dose of 5 mg of neostigmine with 1 mg of glycopyrrolate with TOF of two twitches; or, 2) sugammadex 4 mg/kg at the post-tetanic count of two (7,8).
In case of neostigmine group if the patient has only one twitch of TOF, we will wait till the patient will have two twitches before reversal by neostigmine. However, in sugammadex group if the patient has one twitch in the TOF at the end of the procedure the patient will be kept in the sugammadex group and we do a conventional intention-to treat analysis.
The endotracheal tube will be removed when patients are awake and fulfilling the criteria for extubation according to the managing anesthesia team.

Measurements

1- The time for extubation in minutes after administration of reversal agents.

2- The TOF ratio twitches ≥ 0.9 will be measured in continuous manner every 12 seconds from the administration of the reversal drug. The TOF ratio will be measured by the acceleromygraphy of the force developed in the adductor pollicis muscle using the TOF scan (new acceleromygraphy monitor). The patients will be monitored for the TOF ratio for 90 minutes after endotracheal extubation.
3- The amount of vasopressors used during the procedure to maintain the MAP within the required range in both groups.
4- The number of patients who will fail extubation due to unsuccessful reversal of the neuromuscular agents will be considered in the following conditions: a- Failure to maintain good tidal volume, b- hypoxia c- hypercarbia, d- reintubation, e- continuation of postoperative mechanical ventilation due to weak motor power tested by TOF twitches.
5- Pneumonia will defined according to NSQIP criteria for pneumonia as the presence of at least one definite chest radiologic examination and at least one sign of pneumonia (fever, leukopenia, leukocytosis, or altered mental status with no other cause), as well as at least one microbiologic laboratory finding (positive cultures from blood, bronchoalveolar lavage, or pleural fluid specimens) or at least two symptoms (new onset of purulent sputum, new onset of or worsening, cough, dyspnea or tachypnea, ales or rhonchi breath sounds, or worsening gas exchange).

Diaphragmatic Function Measurement

Diaphragmatic function will be measured using M-mode ultrasonography. With the patient in semi sitting position with the head elevated approximately 30 degrees, 4 –MHz curvilinear ultrasound probe in the b-mode will used to scan subcostally between the midclavicular and anterior axillary lines, using liver as an acoustic window. The probe will be directed medially, cephalad, and dorsally such as the beam focuses on the posterior third of the right hemidiaphragm. When optimal images will be obtained, the ultrasound machine will be set to M-mode. In M-mode, the diaphragm appears as a crisp white, hyperechoic line slowly undulating through the respiratory cycle.

Patients will be asked to perform 2 discrete breathing maneuvers: the first will “voluntary sniff” [VS] test, for which patients will be asked to forcefully inhale through the nose in sniffing fashion. In the M –mode the slope (speed cm/s) of diaphragmatic contraction will be calculated, as diaphragmatic excursion in cm and the inspiratory time in seconds will be measured as well. Diaphragmatic excursion from baseline will be measured in centimeters using digital calipers on the ultrasound machine. Two measurements will be performed and the average will be taken. Second patients will be asked to perform a “deep breathing” (DB) maneuver, inhaling deeply through the mouth up to vital capacity and then slowly exhaling. The test will be performed twice and the average

will be taken (9, 10, and 11). Diaphragmatic function will be measured at baseline before the procedure and before discharging from the post anesthesia recovery unit (PACU).

Data analysis

Randomized groups will be compared for balance on baseline variables using standard summary statistics (i.e., mean ± standard deviation, median [Q1, Q3], or N (%) as appropriate). Balance will be assessed using the standardized difference (i.e., the difference in means or proportions divided by the pooled standard deviation). Any covariable with a standardized difference greater than 0.2 in absolute value will be regarded as a potential confounder, and will be adjusted for when comparing sugammadex and neostigmine on all the outcomes. All analyses will be on the modified intention-to-treat basis; all patients who receive any treatment will be included in the analysis

Primary analysis.

We will assess the primary hypothesis that patients who receive sugammadex for reversing the neuromuscular blocking effects of rocuronium during neurointerventional procedures will have quick recovery of neuromuscular function to TOF ratio ≥ 0.9 as compared with patients who receive neostigmine. The primary outcome of time to reach TOF ratio ≥ 0.9 will be measured in continuous manner every 12 seconds from the administration of the reversal drug. The effect of sugammadex on time to reach TOF ratio ≥ 0.9 will be assessed using student t-test or multivariable linear regression adjusting for imbalanced variable, if any. Missing outcome will be imputed based on observed other recovery data from the same patients such as time to TOF ratio ≥ 0.7. Logarithmic transformation will be used to meet the normality assumption if needed.

As a sensitivity analysis, we will compare the two groups on TOF ratio by 90 minutes after administration of the reversal drug. For patients who fail to reach TOF ratio ≥ 0.9 by 90 minutes, the outcome will be censored at 90 minutes in the analysis. The effect of sugammadex on time to reach TOF ratio ≥ 0.9 will be assessed using a multivariable Cox proportional hazards regression, adjusting for imbalanced variables, if any. Secondly, we will compare the randomized groups on time to reach TOF ratio ≥ 0.9, using Kaplan-Meier analysis with the log-rank test. Kaplan-Meier estimates for the two groups with equal precision (EP) 95% confidence bands will be calculated and plotted.

Secondary analyses.

We will assess the effect of sugammadex on the following 4 secondary outcomes are (1) time from administration of reversal agent to tracheal extubation, (2) diaphragmatic function before discharging from PACU, (3) postoperative pulmonary

infection, and (4) drug costs and the time required from end of surgery to extubation. The neostigmine will be spilt among the patients according to our pharmacy rules as well as the glycopyrrolate. However, the sugammadex will not be split. The Holm Bonferroni correction will be used to control the hypothesis-wise 2-sided type I error for the secondary outcomes at 0.05

We will compare the randomized groups on time from administration of reversal agent to tracheal extubation, using a multivariable Cox proportional hazards regression. Outcome for patients who fail extubation due to unsuccessful reversal of the neuromuscular agents will be censored at the maximum observed time, and labeled as a failure in the analysis.

We will assess the difference between the sugammadex and the neostigmine groups on diaphragmatic function before discharging from PACU, using multivariable liner regression adjusting for diaphragmatic function at baseline before the procedure and imbalanced covariables, if any. Logarithm transformation on the outcome will be made, if necessary.

Incidence of postoperative pulmonary infection will be compared between the randomized groups, using Chi-square test or Fisher exact test, or multivariable logistic regression, as appropriate.

A cost-effectiveness analysis will be conducted to determine the optimal strategy for economic outcomes related to recovery of neuromuscular function. In a cost-effectiveness analysis, costs are measured in monetary terms and benefits are measured in a unit of effect. For this study, the costs will be considered from the perspective of the hospital. The benefits will be evaluated on the cost to decrease the recovery time. For this cost-effectiveness analysis, the incremental difference in costs and effects between interventions being evaluated will determine the optimal strategy of choice.

Sample size considerations.

The sample size consideration was based on the test for the primary hypothesis that patients who receive sugammadex for reversing the neuromuscular blocking effects of rocuronium during neurointerventional procedures will have quick recovery of neuromuscular function to TOF ratio ≥ 0.9 as compared with patients who receive neostigmine.

We would need **46 patients** to have more than 90% power at a 2-sided alpha level of 0.05 to detect a mean difference of 5 minutes or more, assuming a standard deviation of 5 minutes. In addition to the 46 patients, we will enroll **4 pilot patients** to test feasibility of recruitment, protocol adherence, randomization process, and data collection.

SAS software version 9.4 for Windows (SAS Institute, Cary, NC) will be used for all statistical analyses and graphics.

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