Sugammadex in Patients with Myasthenia Gravis

Jennifer A. Madsen

University of Kansas
Title of Proposed Research Project

Rocuronium and Sugammadex versus Rocuronium and Neostigmine in Patients with Myasthenia Gravis Undergoing Thymectomy

Objectives of Study

The aim of this study is to evaluate the neuromuscular blockade reversal effectiveness of sugammadex in comparison to neostigmine in myasthenia gravis patients receiving rocuronium, undergoing video assisted thoracoscopic thymectomy.

Background and Significance to Nurse Anesthesia

Myasthenia gravis is an autoimmune disorder of the neuromuscular junction, manifested by increased skeletal muscle weakness and fatigability upon exertion (Nagelhout & Plaus, 2014). Upon microscopic examination, there is a decrease in the number of functional postsynaptic acetylcholine (ACh) receptors, while the prejunctional ACh pool remains normal. Sixteen percent of patients have only ocular symptoms, however most patients will progress to generalized myasthenia gravis with involvement of bulbar and extremity muscles. The thymus gland produces autoantibodies that cross-react to antigens in the neuromuscular junction, and is found to be hyperplastic in more than half of these patients. Thymectomy is often recommended to improve symptoms of the disease, although the response is relatively unpredictable.

The use of non-depolarizing neuromuscular blocking agents in this patient population remains a controversial topic with concern for incomplete reversal or the development of myasthenia crisis requiring prolonged mechanical ventilation. The introduction of sugammadex may provide a safer way to administer non-depolarizing agents in this patient population. Sugammadex is a γ-cyclodextrin that encapsulates steroidal neuromuscular blocking agents (Palanca et al., 2013). According to previous studies, sugammadex appears to be safe and well
tolerated, causing no central nervous toxicity due to its poor blood-brain barrier penetration (Palanca et al., 2013). A study conducted in 2013 by Ulke et al., concluded that neuromuscular blockade with rocuronium and sugammadex in patients with myasthenia gravis can provide rapid and complete neuromuscular recovery during thoracoscopic thymectomy.

The underlying goal of this study is to expand on previous research while focusing on the myasthenia gravis patient population. This information is critical for anesthesia providers, providing them with guidelines for the safe administration of paralytic agents in this specific patient population.

**Research Questions and Hypothesis**

This study will test the hypothesis that sugammadex provides a quicker and more complete reversal of paralysis compared to neostigmine for myasthenia gravis patients undergoing surgical intervention with neuromuscular blockade.

**Research Design**

**Study design**- This study will be conducted as a double-blind, randomized control trial. Both the anesthetist administering the neuromuscular reversal agent, as well as the study participant will be masked. The pharmacist will prepare appropriate weight-based dosages of the specified reversal agents, and maintain obscurity from the anesthesia provider. Simple randomization will be utilized in order to maintain complete randomness of the assignment of study participants to particular groups. A basic posttest-only design will be implemented upon randomization and completion of the intervention.

Anesthesia in both groups will be induced with propofol 2mg/kg. Utilizing the TOF Watch S monitor, a baseline TOF at the ulnar nerve will be obtained following loss of eyelash reflex. Rocuronium 0.3mg/kg will be given to facilitate intubation. Anesthesia will be maintained with propofol infusion, titrated to effect. Neuromuscular blockade will be monitored
in 15-minute intervals starting at the time of induction until surgical instrumentation is removed.

In the presence of three twitches during the procedure, 5mg rocuronium will be given to maintain paralysis. After surgical instrumentation is removed, the patient will be given assigned reversal agent at the presence of two twitches- sugammadex 2mg/kg or neostigmine 0.03mg/kg. Monitoring will continue every 15 seconds until the TOF Watch S monitor displays a 90% TOF ratio, this timeframe will be documented as reversal time to TOF 0.9. Ability to extubate before leaving the operating room will also be recorded. Extubation criteria will include patient able to open eyes and grip provider’s hand on command, patient spontaneously ventilating and achieving tidal volumes of 4-6 mL/kg, oxygen saturation >94% per pulse oximetry, and blood pressure within 20% of patient’s baseline. If these criteria are not met, the patient will remain intubated.

**Setting**- This study will be conducted in the main operating rooms at the University of Kansas Medical Center, and will only include qualified study participants.

**Study subjects**- Two groups will be included in this study, a control group receiving neostigmine and an experimental group receiving sugammadex. Participants included in both groups will meet the following criteria: diagnosis of myasthenia gravis scheduled to undergo video assisted thoracoscopic thymectomy, between the age of 30 and 60 years, currently receiving cholinesterase inhibitor treatment, and classified as ASA II or III. Exclusion criteria include patients who require mechanical ventilation preoperatively with no plan for extubation postoperatively and patients whose procedure must be converted to open.

**Variables**- The independent variables in this study are neostigmine and sugammadex. The dependent variable is the time after reversal administration to reach TOF ratio of 0.9 per TOF Watch S monitor.
Ethical Issues- Both groups of participants will receive treatment, however it is understood that there are potential adverse effects that could arise from administration of the reversal agents. All information regarding potential complications will be disclosed to participants prior to receiving written, informed consent. Both randomization and masking will be utilized in an effort to minimize bias. If participants in either group require prolonged mechanical ventilation or other interventions detrimental to their health and safety, those interventions will be implemented and it will be determined at a later time if that participant may remain in the study. Participants have the ability to withdraw from the study at any point in time. The sample population is capable of making sound decisions, and as a whole is not considered to be vulnerable. Confidentiality will be ensured and monitored in accordance with the Human Subjects Committee. All anesthesia providers involved in the study will receive extensive training for the use of the TOF Watch S monitor. Data collectors will receive the same extensive training in order to optimize accurate, unbiased data collection.

Data Analysis- T-test of independent samples will be performed in order to determine statistical significance between the mean time, in seconds, that it takes to obtain a TOF value >0.9 after administration of neostigmine or sugammadex. Ability to extubate before leaving the operating room will also be recorded.

Anticipated Limitations- If the video assisted thoracoscopic thymectomy must convert to an open procedure, the patient will be eliminated from the study. Patients undergoing one specific procedure are being studied, this may limit the ability to generalize findings to other surgical procedures. Rocuronium is the only neuromuscular blocking agent under exploration for this study, future studies could address the use of vecuronium with sugammadex. Confounders to consider include total amount of rocuronium received, level of disease progression amongst individuals, and duration of the procedure.
Conclusions

There is concern for recruiting an adequate sample size for the study. While prospective participants may initially show interest to be involved, they may decline after being informed that it is a randomized study. Self-randomization was considered, but there is concern for adequate sample size for the experimental group. The US Food and Drug Administration (FDA) has not approved Sugammadex for use- this could also deter individuals considering participation. While it is not an anticipated outcome due to results from previous studies, there is the possibility of adverse effects from the use of either reversal agent, which could affect sample size or ability to continue the study.
References

