

Date: 09/13/2017  
Version Number: 2  
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Application Number: Review ID 224556  
IRB project number: 2008066

Application Title:

**A Prospective, Randomized, Double-Blind Clinical Trial Evaluating the Speed of Recovery after Reversal of Neuromuscular Blockade with Sugammadex (Bridion™) versus Neostigmine in Geriatric Patients undergoing Spine Surgery**

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## **Protocol**

### **2.1 Objectives:**

This prospective, randomized, double-blind trial will randomize elderly patients undergoing posterior back surgery in the prone position to reversal of neuromuscular blockade (NMB) with either neostigmine or sugammadex

#### Primary Endpoint:

1. Speed of neuromuscular recovery from a moderate NMB with rocuronium in elderly patients measured by recovery of the T4:T1 ratio  $\geq 0.9$  (measured with a TOF-watch)

#### Secondary Endpoints:

1. Time from NMB reversal to tracheal extubation
2. Time from NMB reversal to exit from OR
3. Hemodynamic stability after administration of the neuromuscular reversal agent
4. Vitals and outcomes (nausea, vomiting) in the Postanesthesia Care Unit (PACU)
5. Readiness for PACU discharge (length of PACU stay)
6. Time to first ambulation after the surgery
7. Postoperative patient satisfaction scores
8. Health economic data: OR cost and PACU cost difference between groups

### **2.2 Clinical Hypotheses:**

#### Primary Hypothesis:

We hypothesize that reversal of neuromuscular blockage (NMB) in geriatric patients will be faster with sugammadex than with neostigmine in geriatric patients. As a result, OR efficiency will be improved as measured by time from end of surgery to departure from the OR suite and PACU.

### Exploratory Hypotheses:

We hypothesize that the use of sugammadex (*versus* neostigmine) for NMB reversal will:

1. result in less hemodynamic instability (tachycardia, bradycardia, dysrhythmias) after the administration of NMB reversal
2. improve SpO<sub>2</sub> levels in PACU
3. decrease length of stay in the PACU
4. decrease postoperative pain and the need for postoperative pain medication after surgery
5. decrease postoperative nausea and vomiting
6. improve patient satisfaction levels after surgery
7. decreased OR and PACU costs
8. decrease time to first ambulation after the surgery

### **3.1 Background & Rationale:**

The elderly (age  $\geq 65$  years) population is the fastest growing segment of the American population. Spine surgery is one of the most common operative procedures in the United States and, as the population ages, a larger percentage of geriatric patients will require this procedure. In addition, spinal surgery is often more complex in the elderly population, resulting in longer surgical times.<sup>1</sup> Deyo et al.<sup>1</sup> reported that the rate of complex procedures increased 15-fold in Medicare recipients. Spine surgery is performed in the prone position and neuromuscular blockade (NMB) is maintained until the patient is returned to the supine position at the end of surgery to avoid the risk of patient movement, injury, and inadvertent tracheal extubation while prone. Currently, NMB is reversed with neostigmine immediately after turning the patients back to the supine position at the end of the procedure.

Rocuronium bromide, an intermediate-acting neuromuscular blocking agent (NMBA), is used in approximately 60% of surgical cases in the United States and is commonly used for muscle relaxation during spinal surgery.<sup>2</sup> With aging, the clearance and half-life of rocuronium is prolonged resulting in a wide variability in the duration of action and time to reversal.<sup>3,4</sup> Until recently, the only medication available for the reversal of neuromuscular blockade was neostigmine and postoperative residual neuromuscular block (PRNB) was common, especially in elderly patients. A recent study reported that PRNB occurred in 58% of elderly patients who were maintained at a moderate level (2 twitches in the TOF) of muscle relaxation with rocuronium during elective surgery.<sup>4</sup> As a result, these older adults experienced an increased incidence of airway obstruction, hypoxemic events, muscle weakness, postoperative pulmonary complications, and increased PACU and hospital lengths of stay.<sup>4</sup>

A new neuromuscular reversal agent sugammadex (Bridion®) has the ability to rapidly reverse both moderate and deep rocuronium-induced NMB. McDonagh et al.<sup>5</sup> reported that the mean time to complete reversal (TOF ratio  $\geq 0.9$ ) of a moderate block (2 twitches in the TOF) with sugammadex in geriatric patients was 2.9 minutes, which was only 1 minute longer than in younger patients. Reversal of NMB with neostigmine is much slower and it is reported to take approximately 19 minutes to achieve complete reversal in middle-aged patients.<sup>6</sup> There is little available data on the NMB reversal time in older adults, but it will likely be even longer because the age-related physiologic changes prolong neuromuscular recovery. Thus, sugammadex has the potential to more rapidly reverse NMB in geriatric patients at the end of surgery. As a result, the use of sugammadex should decrease time in the OR and possibly PACU time and result in cost savings.

Neostigmine has cardiac muscarinic effects and, therefore, has to be administered with an anticholinergic agent such as glycopyrrolate to counteract these effects. A previous study found a 16% incidence of cardiac dysrhythmias in elderly patients who received neostigmine/glycopyrrolate NMB reversal.<sup>7</sup> The ability of sugammadex to completely

reverse NMB without the addition of an anticholinesterase agent should result in an improved safety profile in elderly patients.

The goal of this prospective, randomized, double-blinded controlled trial is to test the hypothesis that the reversal of neuromuscular blockage with sugammadex as compared to neostigmine in geriatric patients will provide a shorter time to complete recovery of neuromuscular function, improve the workflow in the operating room and decrease operative costs.

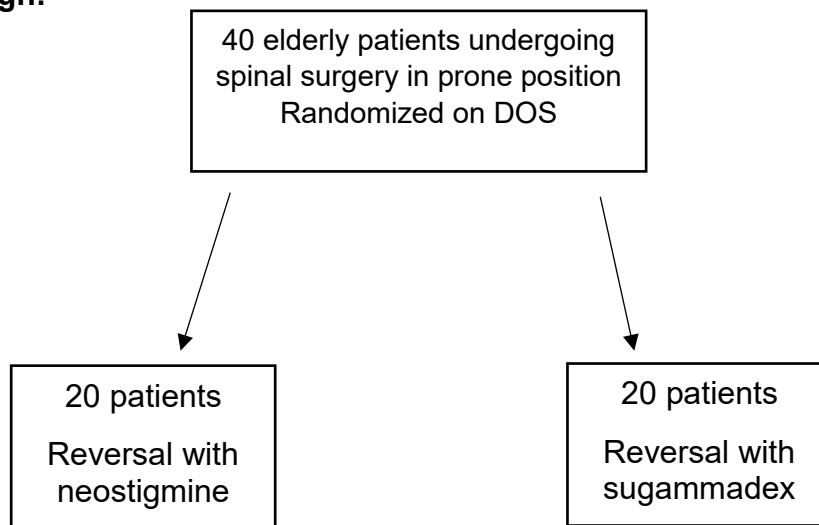
#### **4.1 Study Design:**

Study design: prospective, randomized, double-blinded controlled trial that will be performed at a single academic hospital. The surgeons, anesthesiologists, subjects, and individuals performing the postoperative assessments will be blinded to the study group assignment. All subjects will receive a standardized general anesthetic.

Rocuronium will be administered to facilitate endotracheal intubation and a moderate (reappearance of T1-2 on TOF-watch) NMB will be maintained with a rocuronium infusion for the remainder of the surgical procedure.

After the patient is turned to the supine position at the end of surgery, NMB will be reversed (per a randomization schedule) with either sugammadex, 2 mg/kg, or neostigmine, 50 micrograms/kg (not to exceed 5 mg) and glycopyrrolate, 10 micrograms/kg (not to exceed 1 mg). The reversal agent will be prepared in a blinded fashion. Dosing of reversal agents will be based on actual body weight not ideal body weight. Tracheal extubation will occur when the T4:T1 ratio is  $\geq 0.90$ .

#### 4.2 Study Design:



#### 4.3 Study Procedures:

- I. Patient population: this study will enroll 40 elderly adults undergoing elective posterior lumbar spinal surgery.
- II. Inclusion criteria:
  - a. Age  $\geq 65$  years
  - b. ASA I-III
- III. Exclusion criteria:
  - a. Inability to obtain written informed consent
  - b. Allergy to rocuronium or anesthetic agents used in the protocol
  - c. Known or suspected neuromuscular disorders
  - d. Significant renal disease with a serum creatinine  $\geq 2$  mg/dl
  - e. Significant liver disease
  - f. A family history of malignant hyperthermia
- IV. Randomization: On the day of surgery, patients will be randomized to one of two groups:

- 1.) N group: neostigmine, 50 micrograms/kg (not to exceed 5 mg) and glycopyrrolate, 10 micrograms/kg (not to exceed 1 mg) iv for reversal of NMB; or
- 2.) S group: 2 mg/kg of sugammadex IV for reversal of NMB.

Dosing will be based on actual body weight not ideal body weight.

Randomization will be stratified for the two groups so that the young elderly (65 to 75 years) and the old elderly ( $\geq 75$  years) are equally distributed between the groups.

- V. Blinding: The surgeon, anesthesiologist, operating room staff, patients, personnel in the postanesthesia care unit (PACU) as well as the investigators collecting the postoperative data will be blinded to the group allocation. The rocuronium infusions will be prepared in a standard fashion. The anesthesia providers administering the anesthesia will be unaware of the treatment assignment. The reversal agent will be prepared in a room away from any of the blinded personnel and the syringe will be wrapped in foil.

VI. Anesthetic management

a. Monitoring

1. All patients will be monitored with standard monitors including ECG, non-invasive blood pressure, pulse oximetry, esophageal temperature and capnography.
2. Muscle relaxant monitoring – neuromuscular function will be monitored using acceleromyography with the TOF-Watch® SX (Organon Ireland Ltd, a subsidiary of Merck and Co., Inc., Swords, Co. Dublin, Ireland). The TOF tracing will be stabilized after induction of anesthesia (prior to the administration of muscle relaxant drugs) according to the manufacturer's recommended protocol.

- b. Anesthetic Technique – all patients will receive a standardized general anesthetic technique and all anesthetic medications (with the exception of sugammadex) will be dosed on the ideal body weight rather than actual weight.



1. Premedication – none
  2. Preoxygenation with 100% oxygen for a minimum of 3 minutes
  3. Induction – propofol, 1 mg/kg iv, lidocaine 1 mg/kg iv, and fentanyl, 2 micrograms/kg iv. Additional propofol or fentanyl may be administered at the discretion of the anesthesia provider
  4. Intubation – rocuronium 0.6 mg/kg iv after loss of consciousness to facilitate tracheal intubation
  5. Maintenance – ventilation with air/oxygen to achieve a  $FiO_2 = 0.6$  and inhaled sevoflurane adjusted to maintain a BIS level of 40-60, Additional fentanyl, 25-50 micrograms iv may be administered as determined by the anesthesia provider. The  $FiO_2$  of oxygen can also be increased if determined necessary by the anesthesia provider.
  6. Maintenance of muscle relaxation – a rocuronium infusion will be started at the reappearance of 1 twitch and adjusted to maintain 1-2 twitches throughout the procedure
- c. Reversal of neuromuscular blockade - The rocuronium infusion will be continued until the surgery is completed. At that point, the rocuronium infusion will be discontinued. The patient will be turned prone and the level of NMB will be assessed with the TOF watch. The patients will be reversed with sugammadex or neostigmine after assessment of the TOF ratio (using actual body weight).as described above.
- d. Extubation: Prior to extubation, patients will be following verbal commands (opening eyes, squeezing hands, head lift) and the T4:T1 ratio  $\geq 0.90$ .

## VII. Postoperative Pain Management

- a. Hydromorphone 0.5 mg, IV will be given at the end of the surgery prior to turning patient supine.
- b. Additional doses of hydromorphone 0.2 mg, IV will be given in PACU as needed

- c. Hydromorphone PCA will be started in PACU room and continued for the first 24 – 48 hours after surgery.

#### VIII. Perioperative assessments

- a. Perioperative time variables including the duration of surgery (incision to end of surgery), the duration of anesthesia (intubation to extubation), time from administration of NMB reversal to T4:T1 ratio  $\geq 0.9$ , time from end of surgery to extubation and exit from the OR, time in the PACU, time to the first ambulation and length of hospital stay
- b. Evidence of cardiac dysrhythmias after administration of NMB reversal agents. Criteria for significant dysrhythmias will be defined as: 1.) heart rate  $> 100$  beats per minute or  $< 60$  beats per minute, or increase or decrease of  $\geq 20\%$  in heart rate from the baseline heart rate prior to administration of NMB reversal  
2.) electrocardiographic evidence of a conduction defect not observed prior to administration of reversal, 3.) new atrial or ventricular premature contraction or a three-fold or greater increase in the frequency of any atrial or ventricular premature contraction noted preoperatively<sup>7</sup>
- c. Postoperative opioid requirements will be assessed daily and data collected from the PCA devices. Verbal pain scores (VAS) will also be collected daily until hospital discharge.
- d. Postoperative complications including the need for postoperative mechanical ventilation, re-intubation, residual paralysis, pneumonia, infections, and other adverse events during the hospital stay. The need for ICU admission and length of hospital stay will also be collected.
- e. Patient satisfaction evaluated during an interview on POD1 using the perioperative questionnaire developed by Bauer et al.<sup>8</sup>

#### 4.4 Study Duration:

The Orthopedic Department at the University of Missouri-Columbia performs over 660 posterior spinal surgery procedures per year. About 150 are done in elderly  $\geq 65$  years old. The majority of spine cases are done by Dr. Choma, Dr. Goldstein and Dr. Nourbakhsh. They are co-investigators on the study. We estimate that we can enroll 40 patients in nine months.

We will need an additional 3 months after enrollment is complete for data analysis and abstract/manuscript preparation.

### **5.1 Statistical Analysis and Sample Size Justification:**

The primary endpoint is the time from sugammadex or neostigmine administration to recovery of the T4:T1 ratio to  $\geq 0.9$ . The sample size calculation was based on literature findings that, in geriatric patients, full recovery (T4:T1  $\geq 0.90$ ) from a moderate NMB (2 twitches) occurs in  $2.9 \pm 1.6$  min after sugammadex reversal,<sup>3</sup> Recovery after neostigmine reversal is very variable with reported times from 6 minutes to 20 minutes.<sup>6,9,10</sup>

We are going to enroll 40 subjects (20 per group). Assuming the standard deviations of 50%, with 20 subjects per group we will have power of 90% to detect a significant difference in means of as little as 6 minutes.

In addition, we wanted to have an adequate sample size to show a difference in PACU time. We anticipate that the group reversed with neostigmine will have a PACU stay that is at least 12 minutes longer than the group reversed with sugammadex. For 80% power and alpha of 0.05, a sample size of 20 per group would detect a difference of 12 minutes or greater.

Secondary outcomes will be time to extubation, hemodynamics on emergence of anesthesia (difference heart rate and blood pressure during emergence), PACU readiness/discharge time, total pain medication requirements, time to ambulation and OR cost and PACU cost difference. Data will be analyzed using chi-square and t-tests as appropriate with  $p < 0.05$  considered significant.

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