Use of Sugammadex for Reversal of Paralysis in Microlaryngoscopy

NCT03111121

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Investigator Studies Program (MISP) Protocol Template

Requirements for Submitting a Full Proposal

Section #1 - MISP Protocol Identification

Study Title:	The title of the protocol should include study design, indication and, where applicable, dosage, dosage form, and comparative agent(s). **Use of Sugammadex for Reversal of Paralysis in Microlaryngoscopy**
Request Date:	September 1 2016
Institution Name	West Virginia University
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Section #2- Core Protocol	
2.1 Objectives & Hypotheses	2.1 List the objectives. **<u>Outcome measures measured in the two groups:</u>** **Primary outcome** Time to extubation after end of procedure West Virginia University Hospitals use an electronic medical record (EMR) to chart the end of the procedure. When the surgeon states "We are done", always at withdrawal of the scope, extubation begins. From the time we chart end of procedure to the time of extubation is the extubation time. The start and end times for extubation will be recorded in the EMR. The OR time is billed in 15 minute increments and it is a tremendous cost saving even for every 5 minutes saved. It is anticipated that extubation using sugammadex will provide at least a 5 min reduction in extubation time when compared to the combination of neostigmine and glycopyrrolate (8, 11). This translates to a possible 45.8 % reduction (12, 13, 14). **Secondary outcomes** 1. Subjective interpretation of optimal surgical conditions as evaluated by the surgeon for ease of exposure graded from 1-10 (1 being difficult and 10 being the best surgical conditions) 2. Hemodynamic parameters – intra-op and post-op. Δ in BP, HR and CO2 from base–line and incidence /frequency of 20% change in BP from baseline vitals (baseline= pre-induction vitals) 3. Respiratory parameters – intra op and post op 4. Inhaled anesthetic concentration intra-op 5. Narcotics required intra op and post op 6. Total OR time 7. Time taken to meet ALDRETE criteria in PACU 8. Time to discharge from PACU 9. Any adverse event and severe adverse events such as - hypotension, arrhythmia, hypoxia, stridor and re-intubation will be compared in both groups

	2.1.1 List the clinical hypotheses. **Hypotheses:** **Primary Hypothesis:** Use of Muscle relaxant and reversal with Sugammadex at end of airway procedures will reduce the time to extubation after end of procedure **Secondary Hypotheses:** ➢ Surgeon will report optimal surgical conditions for ease of exposure ➢ Have less hemodynamic changes in the OR and PACU. Δ in BP, HR and CO2 from base–line and incidence /frequency of 20% change in BP from baseline vitals (baseline= pre-induction vitals) ➢ Decrease the amount of inhaled anesthetics ➢ Decreased narcotics needed intra-operatively and post operatively ➢ Decrease the total OR time ➢ Subjects will meet ALDRETE PACU discharge criteria quicker in the PACU ➢ Subject will have less adverse events and severe adverse events such as - hypotension, arrhythmia, hypoxia, stridor and re-intubation.
2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	Microlaryngoscopy and rigid bronchoscopy for vocal cord and tracheal procedures causes an intense sympathetic response during the procedure (1). Abrupt increases in heart rate, blood pressure can be seen in these procedures(1). Patients have to be extremely still for these highly stimulating procedures and hence have to be deeply anesthetized(2) (3). Ideal surgical exposure often depends on relaxation of muscles of mastication. Most of these procedures are done as outpatient procedures and many of these patients have significant co-morbidity. Deeply anesthetizing these patients can cause profound hypotension which can worsen the medical status of the patient and have longer PACU stay and can cause increased post-operative complications. Muscle relaxation with non-depolarizing muscle relaxants are rarely used in these procedures as the duration of action of the muscle relaxant is significantly longer than the actual procedure and time to extubation from end of procedure is significantly longer than without using muscle relaxation or a Succinylcholine drip.(4) Muscle relaxants are synergistic with inhaled anesthetics, and narcotics. Hence, the total amount of anesthetics and narcotics used can be significantly reduced when combined with muscle relaxants if we are able to

	fully reverse the paralysis at the end of the procedure.(5)
2.3 Study Design	This is a prospective, clinical interventional, randomized single blinded single center study. We note that the nurses in PACU will be blinded to whether the subjects were in Group 1 or 2. After IRB approval, subjects will be consented in the clinic by the PI or CO-I for the study. After written consent is obtained and a copy provided to the subject; the following inclusion and exclusion criteria will be reviewed. The subject must meet all inclusion criteria and no exclusion criteria to qualify for the treatment phase. The subject that does not qualify will not be included in this study. Inclusion Criteria: ➢ Age 18 years or older, ➢ ASA physical status I-III ➢ Ability to give written informed consent. Exclusion criteria: ➢ Known or suspected neuromuscular disease/pre-existing weakness, ➢ Creatinine clearance less than 30 ml/min, ➢ Bradycardia of less than 40 beats/min, ➢ Pregnancy, breast feeding women, ➢ Known or suspected allergy to BRIDION® (sugammadex), neostigmine or rocuronium. ➢ Patients with contraindications towards sugammadex, neostigmine or rocuronium ➢ Patients included in another trial within the last 30 days ➢ Patients with legal guardians or surrogate decision making ➢ Patients who refuse to use non-hormonal contraceptive method or back-up method of contraception (such as condoms and spermicides) for the next 7 days if receiving sugammadex. Ref (6) Patients will be randomized, using a block randomization scheme, to one of the two anesthetic groups. The block randomization scheme will use random block sizes varying from 2 to 6 patients per block. Subjects will

	receive a unique study id number (subject 1: i.e. 0001-{3 initial i.e. A-B-C}). The randomization scheme will be developed by the statistician; the master list of study ids and reversal treatment allocations will be held by the PI and research coordinator. Strict adherence to the sequence of treatment allocations will be maintained. Group 1: Inhaled anesthetics: sevoflurane at 1 MAC, remifentanil and intubation with rocuronium at 0.6-1.2 mg/kg (vitals maintained within 20% of baseline). Group 1 will receive reversal with neostigmine (0.04 mg/kg and glycopyrrolate (0.01 mg/kg) Group 2: Inhaled anesthetics: sevoflurane at 1 MAC, remifentanil and intubation with rocuronium at 0.6 -1.2 mg/kg (vitals maintained within 20% of baseline). Group 2 will receive reversal with sugammadex 4mg/kg Both groups will receive standard anti-nausea prophylaxis – Ondansetran and Decadran intraoperative. After induction, the amount of inhaled anesthetic and remifentanil used will be titrated based on hemodynamic parameters (maintained within 20% from baseline) and a BIS monitor. All subjects will have TOF testing done every 5 minutes throughout the procedure and tabulated in the Electronic Medical Record (EMR). At the end of the procedure patient will be extubated when the subject meets the following criteria: Tidal volume : > 5 cc /Kg Respiratory rate: >8 /min O2sat > 95% ON 100% inspired oxygen With vitals at 20% of baseline. Extubation will begin when the surgeon states, “We are done”. This usually coincides with the withdrawal of the scope. The start and end times for extubation will be recorded in the Electronic Medical Record. The PACU nurses will evaluate ALDRETE discharge criteria and make a note in the electronic medical records for the subject discharge time from PACU. The nurses in PACU will be the only evaluators of the subject who will be blinded to the two groups

Independent Data and Safety Committee Monitoring:
Data and safety monitoring is a requirement of our institutional IRB (WVU IRB) and is standard for all clinical studies. Independent Data and Safety Monitoring Committee: Individuals not involved with the study will review the data and make recommendations to **continue or stop** the study to the Principal Investigator.

Following the WVU IRB Independent Data and Safety Monitoring Plan, a quality assurance audit will be performed by the IDSMC when 20% of the patients have been recruited (n=17). This audit will include, but not be limited to, the review of informed consent process, eligibility confirmation, adherence to protocol procedures and treatment plans, pharmacy records and storage, and regulatory documentation. Adverse events and severe adverse events such as - hypotension, arrhythmia, hypoxia, stridor and re-intubation will be compared in both groups.

No analysis related to or involving the primary outcome is required or will be performed at this time.

ADVERSE EVENT ASSESSMENT: any unfavorable and unintended medical occurrence, symptom or disease temporally associated with the use of a medical treatment of the subjects whether or not it is associated related to the medical treatment. The Principal Investigator will identify and make adverse events assessments. Adverse events and severe adverse events such as - hypotension, arrhythmia, hypoxia, stridor and re-intubation will be compared in both groups.

SINGLE BLIND: The nurses in PACU will be the only evaluators of the subject who will be blinded to the two groups. The PACU nurses will evaluate ALDRETE discharge criteria and make a note in the electronic medical records for the subject discharge time from PACU.

Subject total: 84 completed

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify subjects. At most, the Web site will include a summary of the results.

2.4 Study Flowchart

After contract signed and IRB approval

Timetable of Investigation:

	Year 0.25 September 2016 – December 2016	Year 1 January 2017 – December 2017			
	Q4	Q1	Q2	Q3	Q4
IRB approval/ Renewal					
Subject Screening/Enrollment					
Data Collection					
Statistical Analysis					
Writing/Presentation					

2.5 Study Procedures

Screening: After IRB approval, Subjects will be consented in the clinic by the PI or CO-I for the study.

After consenting: The following inclusion and exclusion criteria will be reviewed. The subject must meet all inclusion criteria and no exclusion criteria to qualify for the treatment phase. The subject that does not qualify will not be included in this study.

Inclusion Criteria:

- Age 18 years or older,
- ASA physical status I-III
- Ability to give written informed consent.

Exclusion criteria:

- Known or suspected neuromuscular disease/pre-existing weakness,
- Creatinine clearance less than 30ml/min,
- Bradycardia of less than 40 beats/min,
- Pregnancy, breast feeding women,
- Known or suspected allergy to BRIDION® (sugammadex), neostigmine or rocuronium.
- Patients with contraindications towards sugammadex, neostigmine

or rocuronium,

- Subjects included in another trial within the last 30 days
- Patients with legal guardians or surrogate decision making.
- Patients that refuses to use non-hormonal contraceptive method or back-up method of contraception (such as condoms and spermicides) for the next 7 days if receiving sugammadex

Treatment Phase: **Surgery**

Subjects will receive a unique study id number (subject 1: i.e. 0001-{3 initial i.e. A-B-C}) if surgery is performed.

Patients will be randomized, using a block randomization scheme, to one of the two groups, as outlined in the Study Design section. Strict adherence to the sequence of treatment allocations will be maintained.

Group 1: Inhaled anesthetics: sevoflurane at 1 MAC, remifentanil and intubation with rocuronium at 0.6-1.2 mg/kg (vitals maintained within 20% of baseline). Group 1 will receive reversal with neostigmine (0.04 mg/kg and glycopyrrolate (0.01 mg/kg)

Group 2: Inhaled anesthetics: sevoflurane at 1 MAC, remifentanil and intubation with rocuronium at 0.6 -1.2 mg/kg (vitals maintained within 20% of baseline). Group 2 will receive reversal with sugammadex 4mg/kg

Both groups will receive standard anti-nausea prophylaxis – Ondansetran and Decadran intraoperative.

After induction; amount of inhaled anesthetic and remifentanil used will be titrated based on hemodynamic parameters (maintained within 20% from baseline) and a BIS monitor.

All subjects will have TOF testing done every 5 minutes throughout the procedure and tabulated in the EMR.

Follow-Up: PACU

The PACU nurses will evaluate ALDRETE discharge criteria and make a note in the electronic medical records for the subject discharge time from PACU. The nurses in PACU will be the only evaluators of the subject who will be blinded to the two groups

Adverse events and serious adverse events such as - hypotension, arrhythmia, hypoxia, stridor and re-intubation will be followed until

	resolution or 30 days post treatment by phone call from research coordinator (16). A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify subjects. At most, the Web site will include a summary of the results. **Subject total**: 84 completed
2.6 Study Duration	The estimate time for subject enrollment is 12 months, publication and presentation of data will follow completion of data analysis.
2.7 Statistical Analysis and Sample Size Justification	**Power/Sample Size:** All patients have a clearly defined time at which extubation begins and ends (See Section 2.3, Study Design). There will be no patients with unobserved end points (e.g. no loss to follow-up, attrition, or right censoring). Additionally, the Data and Safety Monitoring does not require the analysis of the primary research question prior to the completion of the study (See Section 2.3, Study Design, Data and Safety Monitoring subsection). Based on these considerations, powering for the primary outcome of extubation time used the log-rank test, Schoenfeld's method, and balanced allocation of patients to each group (9-10). With minimum power of 80%, an alpha-level of 0.05, and an effect size of 0.542, a total of 84 patients are required providing 42 patients per group. The effect size was derived using median times-to-extubation to estimate the hazard ratio. An estimate of the median extubation time for sugammadex is 6.4 minutes (8, 11) with a minimum differential of 5.4 minutes for the combination of neostigmine and glycopyrrolate (i.e. 11.8 min). The 5.4 min differential is twice the differential between sugammadex and pyridostigmine (8), and is motivated by longer extubation times for neostigmine and glycopyrrolate when compared against pyridostigmine (15). The anticipated minimal differential has positive clinical and financial ramifications (Section 2.1 Objective & Hypotheses). **Statistical Analysis:**

	We will use univariate statistics (e.g. mean, median, standard deviation, interquartile range) to summarize the collected data. Balance between the two groups for key patient variables (see Section 2.1 for examples) will be assessed using a two-sided two-sample t-test using unequal variances and the Welch modification to the degrees of freedom. For categorical variables, the Chi-square test will be used. If non-parametric tests or exact methods are required, we will use the Mann-Whitney U test and the Fisher-Freeman-Halton exact test respectively. The primary comparison of extubation time between the two groups will be assessed using the Kaplan-Meier method and log-rank test. Statistical significance will be assessed using a two-sided test with an alpha-level of 0.05. All statistical analysis will be performed using the R software environment for statistical computing and graphics (7).
2.8 Specific Drug Supply Requirements	Phase 4 study: Drug: BRIDION®, sugammadex, will be supplied by Merck: Budget for cost for research in-patient pharmacist to receive drug from Merck, dispense drug, keep research accountability, and keep blind for research study is included at $70/subject.
2.9 Adverse Experience Reporting	Phase 4 study: FDA policy on reporting Form 3500
2.10 Itemized Study Budget	Please see attached budget
2.11 References	(1) Cardiac complications of microsurgery of the larynx: etiology, incidence and prevention. Strong MS, Vaughan CW, Mahler DL, Jaffe DR, Sullivan RC, Laryngoscope. 1974 Jun; 84(6):908-20. (2) Anesthesia for laryngoscopy. Benjamin B. Ann Otol Rhinol Laryngol. 1984 Jul-Aug; 93(4 Pt 1):338-42. (3) Effects of anesthetic technique on the hemodynamic response to microlaryngeal surgery. Ayuso A, Luis M, Sala X, Sánchez J, Traserra J Ann Otol Rhinol Laryngol. 1997 Oct; 106(10 Pt 1):863-8. (4) Assessment of depth of anesthesia and postoperative respiratory recovery after remifentanil- versus alfentanil-based total intravenous anesthesia in patients undergoing ear–nose–throat surgery. Anesthesiology. 2001; 94:211–7.

(5) Basics of Anesthesia–sixth edition Ronald C. Miller page 152 (pharmacodynamics responses)

(6) Package circular for BRIDION (sugammadex) U.S. approval 2015

(7) R Development Core Team (2016): R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, URL http://www.R-project.org, ISBN 3-900051-07-0.

(8) Eui-Seok Park, Byung Gun Lim*, Won-Joon Lee and Il Ok Lee. Sugammadex facilitates early recovery after surgery even in the absence of neuromuscular monitoring in patients undergoing laryngeal microsurgery: a single-center retrospective study. BMC Anesthesiology (2016) 16:48. DOI 10.1186/s12871-016-0221-2

(9) David W. Hosmer, Stanley Lemeshow, Susanne May (2008), Applied Survival Analysis: Regression Modeling of Time-to-Event Data, 2nd Ed. Wiley Series in Probability and Statistics, John Wiley & Sons, Hobooken, NJ, USA. [Section 9.7, pp 340-346]

(10) David Collett (2003), Modelling Survival Data in Medical Research, 2nd Ed. Chapman & Hall/CRC, Boca Raton, Florida, USA. [Section 10.2.1, pp 302-304]

(11) Vymazal T, Krecmerova M, Bicek V, Lischke R. Feasibility of full and rapid neuromuscular blockade recovery with sugammadex in myasthenia gravis patients undergoing surgery – a series of 117 cases. *Therapeutics and Clinical Risk Management*. 2015;11:1593-1596. doi:10.2147/TCRM.S93009.

(12) Paton F1, Paulden M, Chambers D, Heirs M, Duffy S, Hunter JM, Sculpher M, Woolacott N 2010 Oct 8.:Sugammadex compared with neostigmine/glycopyrrolate for routine reversal of neuromuscular block: a systematic review and economic evaluation. Br J Anaesth. 2010 Nov;105(5):558-67. doi: 10.1093/bja/aeq269. Epub

(13) D Chambers, M Paulden, F Paton,M Heirs, S Duffy, D Craig, J Hunter,J Wilson, M Sculpher and N Woolacott: Sugammadex for the reversal of muscle relaxation in general anaesthesia: a systematic review and economic assessment: Health Technology Assessment 2010; Vol. 14: No. 39

(14)Chambers D1, Paulden M, Paton F, Heirs M, Duffy S, Hunter JM, Sculpher M, Woolacott N.:Sugammadex for reversal of neuromuscular block after rapid sequence intubation: a systematic review and economic assessment. Br J Anaesth. 2010 Nov;105(5):568-75. doi: 10.1093/bja/aeq270. Epub 2010

	Oct 11. (15)Edoardo De Robertis,1 Geremia Zito Marinosci,1 Giovanni Marco Romano,1 Ornella Piazza,2 Michele Iannuzzi,1 Fabrizio Cirillo,1 Stefania De Simone,3 and Giuseppe Servillo1The use of sugammadex for bariatric surgery: analysis of recovery time from neuromuscular blockade and possible economic impact: Clinicoecon Outcomes Res. 2016; 8: 317–322. Published online 2016 Jun 29. doi: 10.2147/CEOR.S109951:PMCID: PMC4934482:Table 2 : Pharmacological data and costs of reversal drugs (16)Boon M1, Martini C1, Broens S1, van Rijnsoever E2, van der Zwan T3, Aarts L1, Dahan A4: Improved postoperative oxygenation after antagonism of moderate neuromuscular block with sugammadex versus neostigmine after extubation in 'blinded' conditions: Br J Anaesth. 2016 Sep;117(3):410-1. doi: 10.1093/bja/aew246.
2.12 Publication Plan	Publications in Anesthesiology Journal and presentations at ASA meetings in fall of 2017 and/or Spring 2018
2.13 Curriculum Vitae	Please see Attached in vision tracker
2.13 Protocol Submission for Investigator-Initiated Studies	U.S. protocols should be submitted by US investigators directly or through the Global Research Specialist at www.merckiisp.com Non U.S. protocols should be submitted to the MSD office by the investigators.