Section #1 - Protocol Identification	
Study Title:	The Effect of Intraoperative Neuromuscular Blockade on Postoperative Atelectasis in Patients Undergoing Thoracic Surgery With One Lung Ventilation: Moderate vs. Deep Block
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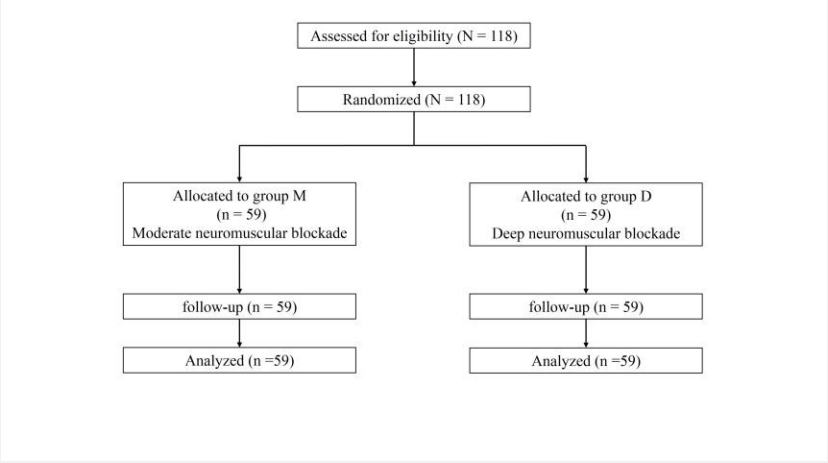
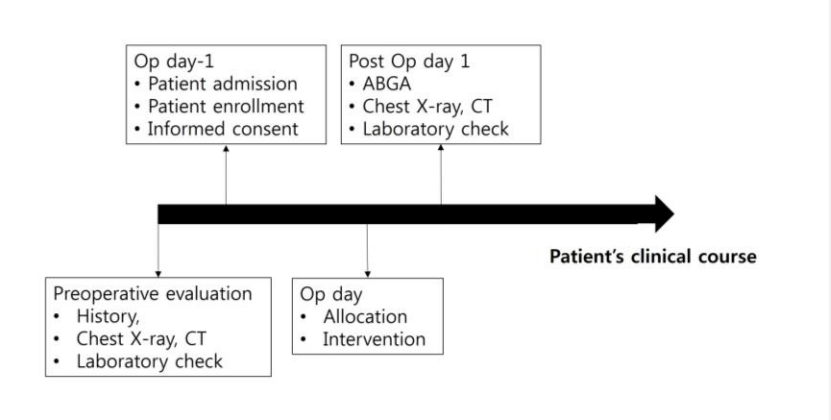
Section #2- Core Protocol	
2.1 Objectives & Hypotheses	2.1.1 Objectives. Primary object is to compare the intensity of neuromuscular blockade on postoperative pulmonary complications. 2.1.2 Clinical hypotheses. Primary hypothesis is that maintaining deep neuromuscular blockade with sugammadex reversal can improve postoperative atelectasis in patients undergoing thoracic surgery with one lung ventilation.
2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	Neuromuscular blocking agents can be used to secure a good surgical field, but it can also cause delayed extubation or postoperative pulmonary complications (Ref 1,2,3) Traditionally, rocuronium which is commonly used non-depolarizing agent are usually reversed by cholinesterase inhibitor such as neostigmine or pyridostigmine. These drugs act by increasing the concentration of acetylcholine at neuromuscular junction (a competing antagonist), not by direct antagonists. Consequently, there is a risk of pulmonary complications when cholinesterase inhibitor is not used appropriately. Use of sugammadex can reverse neuromuscular blockade quickly, thereby being helpful for spontaneous deep breathing postoperatively. In a previous study (Ref 1), moderate NMB was not guaranteed during surgery because intraoperative TOF monitoring was not used and the outcome was focused on the correlation between reversal agent and overall incidence of postoperative pulmonary complications. However, in the present study, we repeatedly measure TOF ratio or PTC during surgery, thereby maintaining the intensity of intraoperative NMB. Moreover, we repeatedly measure lung compliance during surgery and investigate the correlation between the intensity of intraoperative NMB and postoperative atelectasis, which is evaluated by quantitative technique. Particularly in thoracic surgery, one lung ventilation is usually required for surgical procedure. During one lung ventilation, the compliance of ventilated lung is decreased and resistance can be increased, thereby risk of atelectasis being increased. Furthermore, after thoracic surgery, although patients were encouraged to deep breathe, it is difficult to take a deep breath because of various factors. (i.e. pain, chest tube, long retracted time, postoperative interstitial edema, etc.) Therefore, postoperative atelectasis is much more important in patients undergoing thoracic surgery than other type of surgery. For preventing postoperative atelectasis, intraoperative intensity of neuromuscular blockade can be a crucial factor. Because deep neuromuscular blockade provide a good lung compliance during mechanical ventilation, peak inspiratory pressure can be decreased, thereby reducing risk of ventilation induced lung injury, particularly in one lung ventilation situation.(Ref 4) However, there has been still lack of quantitative evidence that deep block is superior to moderate block in the thoracic surgery with one lung ventilation For assessment of postoperative atelectasis, plain chest radiography may be used. However, plain chest radiography can provide only a qualitative assessment of atelectasis. Computed tomography can assess whole lung by density (HU) and enable a quantitative assessment of postoperative atelectasis. Moreover it can indicate the location of atelectasis more clearly than plain chest radiography, thus provide detailed information about postoperative lung state. To assess the effect of maintaining deep block and

	sugammadex reversal on the postoperative atelectasis, using chest CT can provide a much more quantitative and valuable information than conventional chest radiography.
2.3 Study Design	A double blinded, randomized, observational, single center study. The total number of patients was 118 and the randomization was sequenced into blocks of four and six patients using randomization software. Patient population: Patients receiving open or thoracoscopic lobectomy, bi-lobectomy, or sleeve lobectomy. Inclusion criteria: 1. Patients receiving scheduled unilateral lung lobectomy. 2. Patients age ≥19 3. Patients of ASA PS 1 or 2 Exclusion criteria: 1. Patients receiving bilateral lung lobectomy 2. Patients BMI > 35.0 or < 18.5 kg/m^2 3. Patients of contraindicated to epidural patients controlled analgesia 4. Patients with neuromuscular disease (i.e. myasthenia gravis) 5. Patients with major burn (more than 3rd degrees) 6. Patients with compromised cardiopulmonary function. Group description Group M: maintaining moderate neuromuscular blockade (TOF count 1 or 2) during surgery and reversal using sugammadex 2 mg/kg after surgery Group D: maintaining deep neuromuscular blockade (PTC 1 or 2) during surgery and reversal using sugammadex 4 mg/kg after surgery
2.4 Study Flowchart	



2.5 Study Procedures

Anesthesia was induced and maintained with target controlled infusion of propofol and remifentanil. Rocuronium 0.6 mg/kg was used to facilitate tracheal intubation. Neuromuscular blockade (NMB) was monitored by TOF watch and maintained a moderate block status of TOF count 1 or 2 on TOF watch by continuous IV rocuronium infusion until main surgical procedure completed in group M (Moderate block group). In group D (Deep block group), NMB was maintained a deep block status of PTC 1 or 2 on TOF watch.
Pressure controlled mechanical ventilation was performed with peak inspiratory pressure (PIP) 13 cmH2O and 5 cmH2O of positive end-expiratory pressure. Respiratory rate is adjusted between 8 and 17 to maintaining PaCO2 35-40 mmHg. If PaCO2 < 40 mmHg was not obtained when the respiratory rate was more than 17, PIP can be increased. If PaO2 < 80 mmHg or SpO2 < 96% during OLV, increase PIP by 1 cmH2O until 20 cmH2O. When PIP > 20 cmH2O was necessary, FiO_2, which is usually ~0.5, can be increased by 0.1. After the end of surgery, group M was received 2 mg/kg of sugammadex for the reversal of NMBA when a second twitch is present on TOF watch, but in group D, patients are received sugammadex 4 mg/kg. To maintain blindness, each reversal agent was prepared just before general anesthesia induction by an independent nurse who did not participate in the surgery. To make the total volume of 10 ml, each dose of reversal agent was prepared in a 10 ml syringe and the remaining volume was filled with 0.9% NaCl. When TOF ratio reaches 0.9 and spontaneous respiratory movement is well-recovered, patient was extubated and delivered to intensive care unit or PACU. On POD#1, chest CT is checked and pulmonary function test is performed after chest tube is removed.

Blindness

Because the present study was double blind, assigned group of the patient was not revealed to both patient and physicians (including surgeon, attending anesthesioloigist, and radiologist). To maintain blindness, only a study modulator controlled the intensity of NMB during surgery and attending anesthesiologist filled clinical research form without sharing TOF monitoring information. In each patient, the volume of sugammadex was equalized to 10 ml by the remained volume filling with 0.9% NaCl.

Pulmonary complications

1. Atelectasis calculation: (Ref 4)
The lung area was delineated manually. To calculate atelectasis, a region of interest was laid out that encircled the dense part of the lung, excluding large vessels. For further analysis, the lung was divided into four categories: areas with densities ranging from -1000 to -900 Hounsfield units (HU) were classified as overaerated, from -900 to -500 HU as normally aerated, from -500 to -100

	HU as poorly aerated, and from -100 to +100 HU as nonaerated (atelectasis). The proportion of nonaerated lung tissue (-100 to +100 HU) was calculated by dividing the area of the region of interest with the whole lungs. 2. Pneumonia: (Ref 5) Two or more serial chest radiographs with at least one of the following (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease): 1) new or progressive and persistent infiltrates 2) consolidation 3) cavitation; at least one of the following 1) fever (>38.0 C) with no other recognized cause 2) WBC count < 4000/ml or >12,000/ml 3) for adults >70 yr, altered mental status with no other recognized cause; and at least two of the following 1) new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements 2) new onset or worsening cough, or dyspnea, or tachypnea 3) crackles or bronchial breath sounds 4) worsening gas exchange (hypoxaemia, increased oxygen requirement, increased ventilator demand). 3. Pleural effusion : diagnosed on radiograph imaging. 4. Acute Respiratory Distress Syndrome (ARDS): (Ref 5) Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules on chest radiograph or CT scan and Respiratory failure not fully explained by ca rdiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic edema if no risk factor present and PaO2:FIO2 < 300mmHg) with PEEP or CPAP 5 cmH2O. Other measurement parameters: demographics, intraoperative lung compliance (hourly), perioperative ABGA, postoperative WBC, CRP, hospital stay, ICU stay, incidence of desaturation (SpO2 <95% in room air), incidence of re-intubation, pre and postoperative laboratory findings.
2.6 Study Duration	Approximately 18 months, expected.
2.7 Specific Drug Supply Requirements	N/A
2.8 Adverse Experience Reporting	Reporting Procedures for Exchange of Adverse Event Information. (i) For purposes of this Agreement the below terms shall be defined as follows: "Adverse Event" or "AE" shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug regardless of whether or not a causal relationship with the Study Drug exists. By way of example and without limitation, an AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Study Drug. "Device Deficiency" shall mean inadequacy of a Study Drug device related to its identity, quality, durability, reliability, safety or performance, such as

	malfunction, misuse or use error and inadequate labeling. "Incident" shall mean any malfunction or deterioration in the characteristics and/or performance of a Study Drug device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user, or of other persons or to a serious deterioration in the state of health. "Medical Device Event" shall mean any malfunction or deterioration in the characteristics and/or the performance of a Study Drug device, as well as any inadequacy in the labeling or the instructions for use which led to or could have led to an untoward event for the user or any other person. "Serious Adverse Event" or "SAE" shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug that results in death, a life-threatening drug experience, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect, cancer, or is a new cancer if the cancer is the condition of the study, or overdose. Other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes listed previously should also be considered "serious". "Suspected Unexpected Serious Adverse Reaction" or "SUSAR" shall mean any Serious Adverse Event, the nature, severity or frequency of which is not consistent with information in the most current investigator's brochure, or with respect to a marketed product the most current Summary of Product Characteristics (SPC) or Package Insert. (ii) Serious Adverse Event and Suspected Unexpected Serious Adverse Reaction, Medical Device Event, Potential Incident, Device Deficiency or Incident Reporting: Principal Investigator shall forward to MSD's Global Safety ("MSD GS") group, any SAE and SUSAR, Medical Device Event, Device Deficiency or Incident information, including, but not limited to, all initial and follow-up information involving any Study subject in the Study. Notification shall be in the form of a completed CIOMS I/MedWatch (or other mutually agreed upon format) immediately but no later than 1 business day of learning of the information. If learned during a weekend or holiday, report within one business day or no later than three (3) calendar days (whichever is shorter)from the day of learning of the information. This information shall be transmitted to MSD GS using the contact information provided below or such other modified contact information as provided by MSD in writing. All information shall be transmitted in the English language and contain the reporter's name and the Study subject identifier code. SUSAR information will be reported unblinded if the Study Drug has been blinded in the Study. Randomization codes for all other SAEs will be provided to MSD GS at end of Study if the Study Drug has been blinded in the Study. (iii) MSD may define certain Non-Serious Events of Interest. If any Non-Serious Events of Interest are defined, Merck will provide such information in writing to Principal Investigator at the time of Protocol approval, execution of this Agreement or anytime thereafter. Reporting of any defined Non-Serious Events of Interest will be handled in the same manner as SAEs unless mutually agreed otherwise in writing by the parties. (iv) All reports of Study Drug exposure during pregnancy or lactation (including a female partner of a male Study subject using the Study Drug), whether associated with an AE or not, must be reported to MSD GS in

	accordance with the timelines and contact information for an SAE. Principal Investigator shall follow pregnancies to term to obtain the outcome of the pregnancy. The outcome of the pregnancy shall be forwarded to MSD GS. (v) Institution and Principal Investigator shall fully comply with all of their respective reporting obligations to the applicable regulatory authorities with respect to any AE, SAE or SUSAR that arises from the Study. (vi) SAE reports and any other relevant safety information are to be forwarded to MSD GS facsimile number: 215-993-1220.
2.9 References	1. Use of sugammadex in lung cancer patients undergoing video-associated thoracoscopic lobectomy. Cho H.C., Lee J. H, Lee S.C., Park S.Y., Rim J.C. Choi.S.R. Korean J Anesthsiol 2017 70(4):420-425 2. Intermediate acting non-depolarizing neuromuscular blocking agents and risk of postoperative respiratory complications: prospective propensity score matched cohort study. Sundrup M.G., Henneman J.P. et al. BMJ 2012;345:e6329 3. Nondepolarizing neuromuscular blocking agents, reversal, and risk of postoperative pneumonia. Bulka C.M., Terekhov M.A., Martin B.J., Dmochowski R.R., Hayes R.M., Ehrenfeld J.M. Anesthesiology 2016; 125:647-55 4. Prevention of atelectasis in morbidly obese patients during general anesthesia and paralysis. Renius H., Jonsson L., et al. Anesthesiology 2009; 111:979–87 5. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions. Jammer I.B., Wickboldt N., et al. Eur J Anaesthesiol 2015; 32:88–105