Study Title: A Comparison of Surgical Conditions between Deep vs Moderate Neuromuscular Blockade with Rocuronium in patients undergoing Endolaryngeal Procedures

NCT Number: NCT02451202

Document Date: 6 October 2015

Investigator Initiated Trial A full research proposal	
Study Title:	**A Comparison of Surgical Conditions between Deep vs Moderate Neuromuscular Blockade with Rocuronium in patients undergoing Endolaryngeal Procedures.**
ชื่อโครงการวิจัย:	การศึกษาผลการหย่อนกล้ามเนื้อในระดับมาก เปรียบเทียบกับระดับปานกลาง โดยใช้ยารอคคูโรเนียม ในการส่องกล้องผ่าตัดกล่องเสียง
Protocol Approval date:	
Date of Finalization of This Current Version of the Protocol	
Institution Name	**Department of Anesthesiology, Chulalongkorn Hospital, Chulalongkorn University**
Investigator Contact Information: - Full address - Phone No. - Fax No. - e-mail address	**Assoc.Prof. Oraluxna Rodanant,M.D.** Department of Anesthesiology, Chulalongkorn Hospital, Faculty of Medicine, Chulalongkorn University Sirindhron Building, 1873 Rama 4 Road ,Pathumwan , Bangkok Thailand 10330 Phone No. : +662-256 4215, +662-256 4295 e-mail Address: drtuen@yahoo.com
Co-investigators	1. **Dr. Jittiya Watcharotayangul, MD.** Department of Anesthesiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University. 270 Phyathai, Bangkok 10400, Thailand Phone No. +662-2011513 - 23 Fax No.. +662-2-2011569 2. **Dr. Wirat Wasinwong, MD.** Department of Anesthesiology, Faculty of Medicine, Prince Songkla University. 15 Kanrnjanawanit Road, Hatyai Songkhla Thailand 90110 Phone No. +66-7445-1651 3. **Assoc. Prof. Worawut Lapisatepun, MD.** Department of Anesthesiology, Faculty of Medicine, Chiang Mai University. Second Floor, Somboon-Martin Bld., Chiang Mai Hospital. 110 Indhawaroros, Aumpur Maung, Chiang Mai 50200 4. **Dr. Phuriphong Songarj, MD. FRCAT.** Department of Anesthesiology, Faculty of Medicine, Siriraj hospital, Mahidol University. Sayamintr Building 11th Floor Siriraj Hospital 2 Prannok Road Bangkoknoi Bangkok Thailand 10700 Telephone : (662) 419-7995, (662) 419-7993, (662) 419-7989 Fax : (662) 411-3256 5. **Assoc Prof. Mingkwan Wongyingsinn, MD, MSc. (Statistical analysis**

	Plan) Department of Anesthesiology, Faculty of Medicine, Siriraj hospital, Mahidol University. Sayamintr Building 11th Floor Siriraj Hospital 2 Prannok Road Bangkoknoi Bangkok Thailand 10700 Telephone : (662) 419-7995, (662) 419-7993, (662) 419-7989 Fax : (662) 411-3256 **6. Dr. Wimonrat Sriraj, MD.** Department of Anesthesiology, Faculty of Medicine, Khonkhan University. 123 Mittraparp Highway, Muang District, Khon Kaen 40002, Thailand Telephone: +66 (0) 43 363466, +66 (0) 43 363491, +66 (0) 43 363477, +66 (0) 43 363122 Fax: +66 (0) 43 348375

Section #2- Protocol Synopsis

TITLE OF STUDY: A Comparison of Surgical Conditions between Deep vs Moderate Neuromuscular Blockade with Rocuronium in patients undergoing Endolaryngeal Procedures

OBJECTIVES:

Primary Study Objective: To compare the proportion of patients with a score of excellent for surgical conditions of deep Neuromuscular Blockade (NMB) (TOF 0, PTC 1–2) versus moderate NMB (TOF 1–2) using Rocuronium in patients undergoing Endolaryngeal Procedures

Secondary Study Objective:

1. To describe the proportion of patients who are Ready to Discharge from operating room, in both the sugammadex 4 mg/kg after deep Neuromuscular Blockade (NMB) (TOF 0, PTC 1–2) group and sugammadex 2 mg/kg after moderate NMB (TOF 1–2) group .
2. To describe the proportion of patients who are Ready to Discharge from Post Anesthetic Care Unit (PACU), in both the sugammadex 4 mg/kg after deep Neuromuscular Blockade (NMB) (TOF 0, PTC 1–2) group and sugammadex 2 mg/kg after moderate NMB (TOF 1–2) group .
3. To assess frequency of clinical signs of early recovery during Endolargyngeal Procedures both deep NMB and Moderate NMB.

   Clinical signs of early recovery:

   a. Airway pressure alarm
   b. Movement of Vocal cords on Laryngeal Video monitor
   c. Movement of the abdomen
   d. Change of End Tidal CO_2

STUDY DESIGN: Overview: A multi-center, open-label, assessor-blinded, randomized, parallel intervention trial.

Number of Study Centers: This study will be conducted at 6 centers throughout Thailand.

Duration of Participation: Each subject will participate in the study for approximately up to 1 day from the time the subject signs the Informed Consent Form (ICF) through the last data collection point. The subjects will be observed for the post-operative complication for 1 day after study drug cessation.

Duration of Study: The total study duration is 16 months (4 months of institutional review board submission/approval, 8 months of enrollment period, 3 months of study analysis and reporting)

Key Inclusion/Exclusion Criteria:

Inclusion criteria:

1. Male or female aged 18 – 60 years; ASA I-III.
2. Subjects have been planned for elective endolaryngeal Procedures (Direct Laryngoscopy with laser (micro-)surgery in patients with endolaryngeal lesions.

Exclusion criteria:

1. Any renal impairment (CrCL < 80 ml/ min)
2. Any hepatic impairment; Child Pugh A, B or C
3. BMI > 30 kg m2
4. Known or suspected generalized neuromuscular disorders
5. Allergies to Rocuronium, Sugammadex, Sevoflurane, Propofol, fentanyl used during general anesthesia
6. Hypersensitivity to the active substance or to any of the excipients
7. Female patient who are pregnant and breastfeeding.
8. Patient with poor Glasgow Coma Score and mental derangement who is unable to give informed

consent.

9. Patients with tracheostomy tube.

INVESTIGATIONAL PRODUCT, DOSE, MODE OF ADMINISTRATION:

Investigational product:

After initial doses of **0.6 mg** Rocuronium, a continuous infusion can be initiated to maintain 0 responses to train-of-four (TOF) stimulation or 1-2 responses to Post-Tetanic Count (PTC) (Deep NMB). The pump rate will vary and depends on the PTC value. The initial pump rate will be set at 0.5 mg/kg per hour. In case of a deviation from the required PTC value the pump rate can be increased or decreased. This was left to the discretion of the attending anaesthetist. Deep NMB should be maintained throughout the operation.

The infusion of Rocuronium will be discontinued and Sugammadex will be given 4 mg/kg at the end of surgery, which is from deep NMB (PTC = 1-2).

Reference Product:

After evidence of early spontaneous recovery (< 10% of control T1) from initial doses of **0.4 mg** rocuronium, a continuous infusion can be initiated to maintain 1 to 2 responses to train-of-four stimulation (Moderate NMB). The initial pump rate will be set at 0.5 mg/kg per hour. In case of a deviation from the required TOF value the pump rate can be increased or decreased. This was left to the discretion of the attending anaesthesiologist. Moderate paralysis should be maintained throughout an operation.

At the end of surgery, the infusion of Rocuronium will be discontinued and Sugammadex 2 mg/kg via bolus injections will be administered at least reappearance of T2.

STATISTICAL METHODS:

All subjects entered into paper-based Case Report Forms (CRFs) will be considered as part of the enrollment population, and the quality of their data will be assessed for further analyses. The evaluable population will consist of all subjects whose data meet the inclusion criteria. The criteria for exclusion from the evaluable population will be set forth in the Data Analysis Plan prior to commencement of any analyses, and will include such criteria as minimum data points required.

Data Set to be Analyzed:

Baseline Patients Characteristics:
We will describe the data distribution of each collected variable. We will characterize subjects in both groups by demographics, comorbidities, clinical characteristics i.e. neuromuscular weakness grading, and distribution of ASA Classification pattern. Categorical variables will be summarized by frequency and percent while continuous variables will be summarized by the mean, median, standard deviation, and range.

Clinical Outcomes:
The data analysis will be based on the intent-to-treat approach. Categorical variables will be compared using the Fisher's exact test while continuous variables will be compared using the student's t-test or Mann-Whitney U test, depending on the sample distribution.

The level of statistical significance for all analyses is set at 0.05. All comparisons will be made using an alpha level of 0.05.

Sample Size: By using 80% power and 1-sided α=0.05, we performed sample size calculation for the proportional outcome. Based on data from the BLISS study[12], the proportion of patients a with a score of Excellent on the Surgical Rating Score (SRS) among subjects who receive deep NMB with Rocuronium is approximately 99%, while this proportion for patients who received moderate NMB with atacurium followed by mivacurium was lower (82%). The calculated subjects is required 36 subjects per arm. Since we expect 13% of withdrawal from the study[13], we need to inflate the total sample size to 80 subjects (40 subjects per arm)

Efficacy Analysis:

1. **Primary Efficacy endpoints**:
   The Proportion of patients who have a surgical conditions score of excellent (total score = 8-9) will be compared between the Moderate NMB and Deep NMB groups.
2. **Secondary outcome**
   1) The proportion of patients who are ready to be discharged from post- operative care, defined as Modified Aldrete's score ≥ 9, at 0, 15, 30,60, 90 minutes after reach of TOF > 0.9 will be summarized.
   2) The proportion of patients who are ready to be discharged from the operating room, defined as TOF > 0.9 at time of tracheal extubation, at 1, 3, 5, 10 minutes after finish of Procedures will be summarized.
   3) The frequency of patients with clinical signs of early recovery during Endolargyngeal Procedures will be compared between the deep NMB and Moderate NMB arms.

Safety Analysis: This is a post-marketing study of treatment outcomes associated with surgical conditions and readiness of discharge from Post-Operating Care Unit(PACU) with Rocuronium and Sugammadex. Responsibility for clinical follow-up resides with the prescribing physician. Therefore, reporting of AEs and SAEs as they occur in clinical practice should follow the established Procedures for approved, marketed drugs in compliance with applicable laws and regulations. This applies to AEs and SAEs noted by the prescribing physician through clinical observation, clinical monitoring, diagnostic Procedures or other applicable methods.

Interim Analysis: N/A

Section #3- Core Protocol

2.1 Objectives & Hypotheses

2.1.1 List the objectives.

1.1) Primary Efficacy Objective:

1. To compare the proportion of patients with a score of excellent for surgical conditions of deep Neuromuscular Blockade (NMB) (TOF 0, PTC 1–2) versus moderate NMB (TOF 1–2) using Rocuronium in patients undergoing Endolaryngeal Procedures.

   Surgical Conditions will be rated using a four-point surgical condition scale by one dedicated Surgeon from each center.
   - TOF = Train of Four
   - PTC = post-tetanic counts

1.2) Secondary Objective:

1. To describe the proportion of patients who are Ready to Discharge from operating room, in both the sugammadex 4 mg/kg after deep Neuromuscular Blockade (NMB) (TOF 0, PTC 1–2) group and sugammadex 2 mg/kg after moderate NMB (TOF 1–2) group .

**Readiness to discharge:* Readiness to Discharge from operating room, which is defined by train of Four ratio > 0.9 at any time after finish of Procedures.

2. To describe the proportion of patients who are Ready to Discharge from PACU*, in both the sugammadex 4 mg/kg after deep Neuromuscular Blockade (NMB) (TOF 0, PTC 1–2) group and sugammadex 2 mg/kg after moderate NMB (TOF 1–2) group .

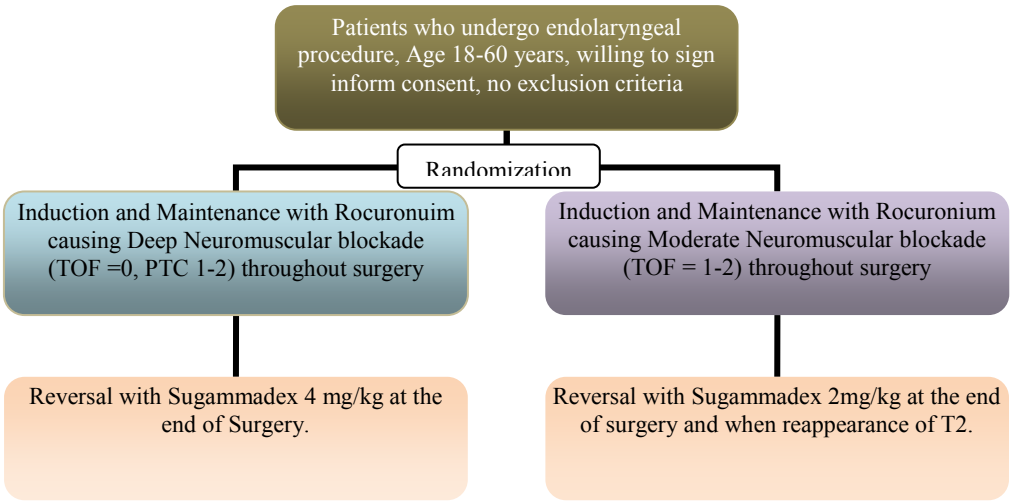
   - *Readiness to discharge from PACU is defined below.
     - Modified Aldrete's scoring system is used for determining when patients can be safely discharged from the postanesthesia care unit (PACU) to either the postsurgical ward or to the second stage (Phase II) recovery area.
     - Modified Aldrete's score: A score ≥ 9 is required for discharge.

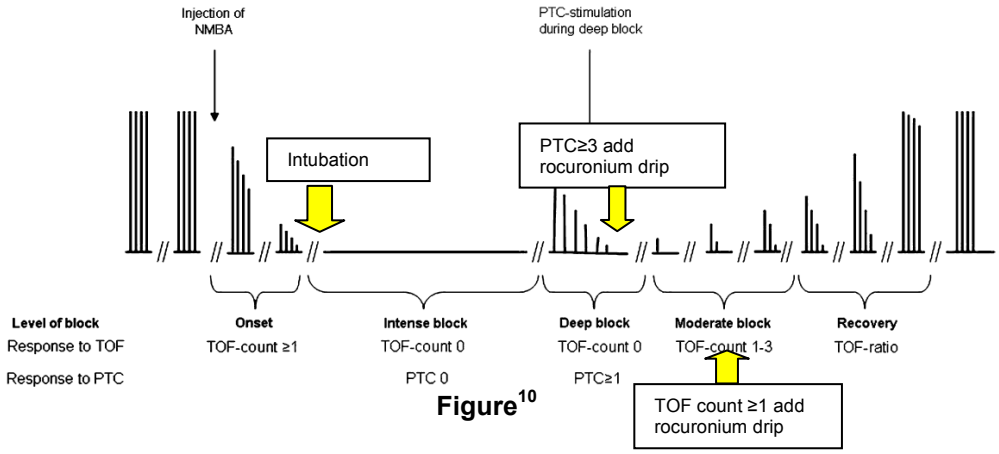
3. To assess frequency of clinical signs of early recovery during Endolargyngeal Procedures both deep NMB and Moderate NMB..

   Clinical signs of early recovery:
   a. Airway pressure alarm
   b. Movement of Vocal cords on Laryngeal Video monitor
   c. Movement of the abdomen
   d. Change of End Tidal CO_2

3) Other objectives: -
- To assess time from the Post-anesthesia Care Unit (PACU) admission to PACU discharge ready
- To assess time readiness to discharge from operating room, which is time from finish of Procedures to train of Four ratio > 0.9.
- To assess Proportion of patients at risk of Post-Operative Residual Curarization (PORC) (definded as TOF < 0.9) at 1,3,5, 10minutes after finish of Procedures and

	at arrival ,15, 30, 60, and 90 minutes during Post-Operative Care Unit stay. - Proportion of patients who have a surgical conditions score in each category (Excellent, good, fair and poor). • Surgical conditions will be rated using a four-point surgical rating scale (SRS) by an anesthesiologist. (not attending physicians) every 15 minutes and every change seen or surgeon's complaint. • The SRS will be also rated by an expert anesthesiologist and expert ENT surgeon from VDO recorder every change seen at a vocal cord. -To assess intubating condition in patients who has endotracheal insertion. This will be assessed by anesthesiologists right after finishing intubation.. **2.1.2 List the clinical hypotheses.** 1. Sustained deep NMB for the duration of surgery in patients undergoing Endolaryngeal Procedures has better surgical conditions compared to those receiving moderate NMB when rated using a four-point surgical rating condition scale (SRS). 2. The frequency of Clinical Signs of Early recovery during an Endolaryngeal Procedures are less frequent in the Deep NMB group compared to the Moderate NMB.
2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	Neuromuscular Blocking (NMB) agents are routinely prescribed in patients who undergo an Endolaryngeal Procedures. Ideally, these Procedures require a short duration of NMB since they are short and fast operations. Sometimes, they may also finish unexpectedly. In Thailand, a short acting NMB is unavailable. The use of intermediate NMBs has many concerns. During the maintenance phase for patients undergoing an Endolaryngeal Procedures under general anesthesia, additional boluses of an NMB agent occurs only in response to Surgeon complaints regarding muscle tension. The main contributing factor is that further doses of muscle relaxants may cause unacceptable delays to extubation. Secondly, there is a lack of data supporting the use of sustained deep NMB throughout Endolaryngeal Procedures. To maintain the same level of stillness, patients without NMB required more anesthetic than patients treated with NMB.[1] A study found that 16 of 19 (84%) patients had hypopnea or apnea after a manually controlled continuous infusion of 0.125 mg/kg/min remifentanil for 2 minutes followed by a continuous infusion of 0.05 mg/kg/min remifentanil.[2] Another study examined the combined effect of propofol and remifentanil and concluded that their effect on respiration was strikingly synergistic, resulting in severe respiratory depression.[3] These data has shown that NMB is required in Balance Anesthesia. Given these considerations, we will conduct a randomized, open-label trial aiming to compare two treatment strategies; Deep neuromuscular Blockade (TOF 0, PTC 1-2) and moderate Neuromuscular Blockade (TOF 1-2) by using Rocuronium 0.6 mg/kg[4] and 0.4 mg/kg[5,6] in deep NMB group and moderate NMB group, respectively, as intubation doses. Usually, neuromuscular block sufficient for intubation is about 80% block or greater. The ED95 is defined as a dose required to produce 95% suppression of the first [T1][7]. In this study, after patients are given rocuronium dose at 0.4 mg/kg (1.3 x ED95) in moderate group and 0.6 mg/kg (2 x ED95) in deep block group, the endotracheal tube will be inserted following the maximal depression T1[6,8]. Since the maximal depression T1 function cannot be expressed on TOF watch, TOF count can be substituted. Twitches suppression of 90% would equate to a TOF

	count of 1 or less[9] (more detail in exhibit A). We hypothesize that deep NMB will offer better surgical conditions. We will also descriptively examine whether the two dose levels of Sugammadex as the reversal agent will provide similar (between the moderate and deep block groups) time of readiness to discharge from Operating room and PACU, which are defined by train of Four ratio > 0.9 and by Modified Aldrete's score ≥ 9 . Consequently, patients would be safely discharged.
2.3 Study Design	**Protocol overview:** We will conduct a multi-center, open-label, assessor-blinded, randomized, parallel intervention trial at University Hospitals in Thailand. The eligible subjects will be randomly allocated to either the deep neuromuscular block group or moderate neuromuscular block group. Details of intervention will be explained in the next section (treatment protocol). Clinical response will be evaluated. **Inclusion criteria:** 1. Male or female aged 18 – 60 years; ASA I-III. 2. Subjects have been planned for elective endolaryngeal. Procedures (Direct Laryngoscopy with laser (micro-)surgery in patients with endolaryngeal lesions **Exclusion criteria:** 1. Any renal impairment (CrCL < 80 ml/ min) 2. Any hepatic impairment; Child Pugh A, B or C 3. BMI > 30 kg m2 4. Known or suspected generalized neuromuscular disorders 5. Allergies to Rocuronium, Sugammadex, Sevoflurane, Propofol, fentanyl used during general anesthesia 6. Hypersensitivity to the active substance or to any of the excipients 7. Female patient who are pregnant and breastfeeding. 8. Patient with poor Glasgow Coma Score and mental derangement who is unable to give informed consent. 9. Patient with Tracheostomy tube.
2.4 Study Flowchart	



Figure[10]

Study flow chart (please see last page)

2.5 Study Procedures

All eligible subjects will be identified through hospital admission for Endolaryngeal Procedures database on daily basis. The investigator will obtain documented consent from each potential subject. Consent must be documented by the subject's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. Depending on local law or review committee requirements such consent may also need to be signed by an impartial witness.

Treatment allocation:

The eligible subjects will be allocated to each study group by randomization. The randomization will be performed by computer-generated block randomization algorithm with allocation concealment. The randomization will be stratified into "Anesthetic Procedures with endotracheal tube" and Anesthetic Procedures without endotracheal tube.

Perioperative protocol:

All patients received balance anesthesia with Propofol, Fentanyl and Rocuronium agents. During the Procedures, routine monitoring is applied [electrocardiography, arterial blood pressure, heart rate, electroencephalographic monitoring, pulse oxymeter)

Study intervention:

1. **Deep Neuromuscular blockade group:**
   - After the enrollment Following induction with Targeting propofol concentrations (TCI) of 4 to 4.5 μg/mL, single bolus injection Fentanyl of 1-2 μg/kg,and single bolus injection rocuronium[4] of 0.6mg/kg will be administered. When following maximal depression of T1 or TOF count 1 [6,9] endotracheal insertion will be initiated in anesthetic procedures with endotracheal tube. Choices of other induction anesthetic agents except NMB agent are at the discretion of the attending anesthesiologist.
   - During maintenance phase, if recovery after 1 Post-Tetanic-count (PTC) responses, a continuous infusion can be initiated to maintain deep NMB (TOF =0, PTC 1-2). The initial pump rate will be set at 0.5 mg/kg per hour. The pump rate could be increased or decreased to keep the target TOF and PTC.
   - During maintenance phase, Fentanyl 0.5 ug/kg may be administered when SBP or HR increase by 10%., as well as, Target propofol concentrations of 3

to 6 µg/mL usually maintain satisfactory anaesthesia.

- Electroencephalographic monitoring using either bispectral index (BIS) module system or Spectral Entropy is mandatory. BIS value is within the range of 40–60. The recommended range of reaction entropy (RE) and and state entropy (SE) is 40–60 in appropriate anesthesia depth, which is identical to that of BIS.
- **Deep** NMB should be maintained throughout the operation.
- At the end of surgery, continuous infusion Rocuronium and Propofol are discontinued and paralysis will be simultaneously reversed by Sugammadex 4mg/kg from PTC 1-2.
- TOF will be monitored every 15 seconds. The PTC will be recorded one minute after disappearance of single twitch[10]. PTC will be monitored every 6 minutes[10],[11] during surgery. When it is required TOF during emergence phase until patients discharge from PACU., it will be monitored every 15 seconds during emergence phase, at1,3,5,10 ,15 and subsequently every 5 minutes after extubation until arrive PACU, and every 15 minutes at PACU arrival time until patients discharge from PACU.

2. Moderate Neuromuscular blockade group:

- After the enrollment, following induction with Targeting propofol concentrations (TCI) of 4 to 4.5 µg/mL, single bolus injection Fentanyl of 1-2 µg/kg ,and single bolus injection rocuronium of 0.4mg/kg[5,6] will be administered. When following maximal depression of T1 or TOF count 1[6,9], endotracheal tube will be initiated in anesthetic procedures with endotracheal tube. Choices of other anesthetic agents except NMB agent are at the discretion of the attending anesthesiologist.
- During maintenance phase, if recovery at the presence of <10% of control T1 of TOF from initial doses of 0.4 mg rocuronium, a continuous infusion can be initiated to maintain TOF = 1 – 2. The initial pump rate will be set at 0.5 mg/kg per hour.
- During maintenance phase, Fentanyl 0.5 ug/kg may be administered when SBP or HR increase by 10%, as well as, Target propofol concentrations of 3 to 6 µg/mL usually maintain satisfactory anaesthesia. Electroencephalographic monitoring using either bispectral index (BIS) module system or Spectral Entropy is mandatory. BIS value is within the range of 40–60. The recommended range of reaction entropy (RE) and and state entropy (SE) is 40–60 in appropriate anesthesia depth, which is identical to that of BIS.
- **Moderate** paralysis should be maintained throughout an operation.
- Continuous infusion Rocuronium and Propofol are discontinued at the end of surgery. Reversed the paralysis by Sugammadex 2 mg/kg.will be administered.at reappearance of T2.
- TOF will be monitored every 15 seconds during intraoperative[10] and during emergence phase. It will be at 1,3,5,10,15 and subsequently every 5 minutes after extubation until arrival PACU and every 15 minutes at PACU arrival time until patients discharge from PACU.

Dosages of anesthetic agents:

At induction phase: Premedication with midazolam 1-2 mg single intravenously bolus could be administered at physician discretion.

1. **Rocuronium**[4] will be given at an initial dose of 0.6 mg/kg in Deep NMB group and 0.4 mg/kg at induction phase; with these doses, patients could obtain adequate intubation conditions. Following maximal depression of T1 or TOF count 1[6,9], endotracheal tube will be initiated in anesthetic procedures with endotracheal tube.

2. **Propofol** will be given administered with the assistance of a Target Controlled Infusion (TCI) system. In adult patients under 55 years of age anaesthesia or ASA I-II can usually be induced with target propofol concentrations of 3.5 to 4.5 µg/mL. Induction time with these targets is generally within the range of 60 to 120 seconds.

   A lower initial target concentration should be used in patients over the age of about 55 years or in patients of ASA grades III.

3. **Fentanyl** will be at the discretion of the attending anesthesiologist and is administered in single bolus injection of 1 to 2µg/kg.

At Maintenance phase:

1. **Rocuronium:** The initial pump rate will be set at 0.5 mg/kg per hour.
   - ***Deep NMB**:* After initial doses of 0.6 mg Rocuronium, a continuous infusion can be initiated to maintain 0 responses to train-of-four (TOF) stimulation or 1-2 responses to Post-Tetanic Count (PTC) (Deep NMB). The pump rate will vary and depends on the PTC value. The initial pump rate will be set at 0.5 mg/kg per h. In case of a deviation from the required PTC value the pump rate can be increased or decreased. This was left to the discretion of the attending anaesthetist.
   - ***Moderate NMB**:* After evidence of early spontaneous recovery (< 10% of control T1) from initial doses of 0.4 mg rocuronium, a continuous infusion can be initiated to maintain 1 to 2 responses to train-of-four stimulation (Moderate NMB). The initial pump rate will be set at 0.5 mg/kg per h. In case of a deviation from the required TOF value the pump rate can be increased or decreased. This was left to the discretion of the attending anaesthesiologist.

2. **Opioid** :Fentanyl 0.5 µg/kg will be administered when SBP or HR increase by 10%. If there was persistent increase SBP or HR after administration of Fentanyl 0.5 µg/kg, the subsequent dose of Fentanyl may be administered at the discretion of the attending anesthesiologist.

3. **Propofol:** Target Propofol concentrations of 3 to 6 µg/mL usually maintain satisfactory anesthesia.

At emergence phase:

1. **Sugammadex**[13] will be given 4 mg/kg at the end of surgery,which is from deep NMB (PTC = 1-2) or 2 mg/kg if spontaneous recovery has occurred up to at least the reappearance of T2

2. **Intravenousagents** will be stopped at the discretion of attending anesthesiologist.

3. **Extubation** when TOF is ≥ 0.9.

Withdrawal or Termination from Study:

Subjects may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur, such as hypersensitivity.

2.6 Study Duration	The total study duration is 16 months (4 months of institutional review board submission/approval, 8 months of recruitment, 3 months of study analysis and reporting)
2.7 Statistical Analysis and Sample Size Justification	The principle investigator will be responsible for analyzing the study data. Since the research team is not blinded to the muscle relaxant used and the level of NMB, either the attending anesthesiologist or the research assistant is responsible for both the administration of the muscle relaxant and the degree of NMB. The attending anesthesiologist is also not blinded. He or she will not discuss the NMB with the surgeon or the research team. After the surgery has finished, subjects who receive rocuronium will be reversed with sugammadex 4 mg/kg or 2 mg/kg. Again, this will be known by the attending anesthesiologist only and will be blinded to surgeon and Anesthesiologist and Otolaryngologist Experts who will rate the surgical conditions.. **Variables/Time Points of Interest:** 1. **Primary outcome:** 1) Proportion of patients who have a surgical conditions score of excellent, • Surgical conditions will be rated using a four-point surgical rating scale (SRS) by the Surgeon right after operation. • The SRS has been modified from Intubating score[10]. • There are three variables, which are ease of laryngoscopy, condition of the vocal cords and the Reaction to insertion of the endoscopic tube and cuff inflation. These are scored on a four-point scale (0-3) and **the total score** is a sum of each component to give an overall Surgical Conditions score for each patient. • The assessment is based on the time point right after operation. • A total score of 8-9 was considered excellent, 6-7 good, 3-5 poor and 0-2 bad; good and excellent were taken as clinically acceptable. 2. **Secondary outcomes:** 1) Proportion of patients who are ready to be discharged from post-operative care, defined as Modified Aldrete's score ≥ 9, at 0,15, 30, 60,90 minutes after reach of TOF > 0.9. • Modified Aldrete's score: A score ≥ 9 is required for discharge. . 2) Proportion of patients who are ready to be discharged from operating room, defined as TOF > 0.9 at time of tracheal Extubation, 1,3,5, 10 minutes after finish of a procedure. 3) Frequency of clinical signs of early recovery during Endolargyngeal Procedures.

Clinical signs of early recovery:

1) Airway pressure alarm
2) Movement of Vocal cords on Laryngeal Video monitor
3) Movement of the abdomen
4) Change of End Tidal CO_2

3. Other outcomes:

1) Proportion of patient at risk of of Post-Operative Residual Curarization (PORC) (TOF ration < 0.9) at 1,3,5,10 minutes after finish of a procedure and at 0, 15,30, 60, 90 minutes during Post-Operative Care Unit stay.
2) Time to readiness to discharge from Post-operative Care Unit which is time from Post-operative Care Unit (PACU) admission to reach "acceptable" score of Post-operative discharge score.
3) Time readiness to discharge from operating room, which is time from finish of procedures to train of Four ratio > 0.9
4) Proportion of patients who have a surgical conditions score in each category (Excellent, good, fair and poor).
    - Surgical conditions will be rated using a four-point surgical rating scale (SRS) by an anesthesiologist. (not attending physicians) every 15 minutes and every change seen or surgeon's complaint.
    - The SRS will be also rated by an expert anesthesiologist and expert ENT surgeon from VDO recorder every change seen at a vocal cord.

5) Intubating condition in patients who has endotracheal insertion. This will be assessed by anesthesiologist right after finishing intubation by using the same score of endolaryngeal surgical condition

Study Variables during anesthesia

Endolaryngeal surgical condition[10]:

During the endolaryngeal Procedures, a surgeon scores the surgical working conditions right after the end of procedures. We adapted the Intubation Condition criteria[11,12] included three variables:

1) jaw relaxation and resistance to laryngoscopy blade (laryngoscopy component)
2) the position and movement of vocal cords (vocal cord component)
3) coughing (reaction to endolaryngeal and endobroncheal Procedures component)

Evaluation of Endolaryngeal/Endobroncheal surgical conditions[12]

Variable assessed	Clinically acceptable		Not clinically acceptable	
	Excellent = 3	Good = 2	Poor = 1	Impossible = 0

Laryngoscopy‡ • **Jaw relaxation** • **Resistance to blade**	Easy • Relaxed • None	Fair • Not fully relaxed • Slight	Difficult • Poor relaxation • Active	Impossible • No relaxation
Vocal cord • **Position** • **Movement**	• Abducted • None	• Intermediated • moving	• Closing	• Closed
Reaction to insertion of the endoscopic tube and cuff inflation • **Diaphragmatic movement** • **coughing**	• None • None	• Slight[β] movement • None	• Vigorous movement[Ö] • Sustained coughing[Ö]	• Bucking • Severe coughing

‡Laryngoscopy
Easy: jaw relaxed, no resistance to blade insertion
Fair: jaw not fully relaxed, slight resistance to blade insertion
Difficult: poor jaw relaxation, active resistance of the patient to laryngoscopy.

β One to two weak contractions or movement for less than 5 s.
Ö More than two contractions and/or movement for longer than 5 s.

Endolaryngeal surgical site conditions[9]:

Excellent ;Score = 8-9
Good ;Score = 6 -7
Fair ;Score = 3-5
Poor ;Score =0-2

Surgical rating
During the laryngoscopic Procedures, the surgical condition is scored by the surgeon using a four-point SRS right after the Procedures. To reduce variability in the surgical rating, all surgeries are performed by a single surgeon at each institute.

The surgical rating scores (SRS) condition at 15-minute intervals will be recorded and rated by an anesthesiologist during the Procedures. In case of a sudden change in surgical conditions, additional scores are obtained. If conditions are poor (score 0 or 2), muscle relaxation is increased according to protocol.

Before commencing the study, both the surgeon and the anesthesiologists will receive training in how to use and implement the specific study Procedures and how to rate the surgical condition score.

Moreover, the first five Procedures performed in conformance with this protocol will not be used for data analysis; thus, the Procedures will be practiced five times before data collection starts.

Intubation score
At the end of intubation, the intubation condition is scored by anesthesiologist by using the same score of endolaryngeal surgical condition

Video images
The video images will be collected from the camera connected to endoscope placed

above vocal cord or field of the surgery**.** The images collected will be the images of Video monitor used by the surgeon to observe the surgical field throughout the Procedures. Variables that could not be captured by VDO recoder i.e. patients' reaction intra-operative, coughing, bucking, diaphragm movement and either physician's complaint of tightness/non-relaxation or request more relaxation agents will be recorded by anesthesiologist in the theater.

Thus, the collected video images are identical to the image of the surgeon during the Procedures as well as should be included surgical condition related-events occurs interoperations.

The videos will be rated by a surgical expert (one Ear-Nose-Throat surgeons with expertise in laryngoscopic Procedures) and an anesthesiologist (with expertise in giving anesthesia for laryngoscopic Procedures). These experts are blinded to the level of NMB and have no knowledge of the study endpoints. The rating score will be identical to the surgical rating score. All changes will be recorded.

Monitoring[10]:

Neuromuscular function using an acceleromyograph measured at the wrist (TOF-watch SX®). The TOF-watch generates an electrical stimulus to the ulnar nerve and measures contractions of the adductor pollicis muscle (causing adduction of the thumb) through a sensor attached to the tip of the thumb. The thumb is placed in a flexible adaptor that applied a constant preload to the thumb. Before administration of the NMB agent, the device is calibrated according the specifications of the manufacturer. To that end, before administration of the neuromuscular blocking agent after induction of general anesthesia, the following Procedures are conducted to standardize the neuromuscular monitoring: (i) application of a tetanic ulnar nerve stimulation (50 Hz for 5 s); (ii) calibration of the TOF watch; and (iii) performing a series of TOF measurements ensuring that the TOF ratio differs by <5% between measurements. If the TOF ratio differed by >5% the TOF watch is recalibrated. The TOF ratio is normalized to the values obtained during the calibration Procedures. After these steps, the neuromuscular blocking agent is administered according to protocol.
The number of thumb twitches upon electrical stimulation of the ulnar nerve is measured and recorded.

- At 15 seconds intervals, the TOF was measured and in the case of TOF¼ 0, this was followed by the PTC (30 Hz for 5 seconds, 3 seconds later Single twitch at 1 Hz) every 6 minutes. In our study, a TOF of 1–2 reflects a moderate NMB and a PTC of 1–2 reflects a deep NMB. Finally, when four twitches are present in the TOF, the ratio of the fourth to the first twitch was determined (the TOF ratio).
- The stimulation of TOF (2 Hz four stimuli) was changed to every 15 seconds after end of surgery and then measure at 1, 3, 5 ,10 minutes after finish the procedures, and at 0,15,30,60,90 during in PACU.

Neuromuscular data were collected via an interface to a computer by means of the TOF-Watch® SX Monitoring Program. TOF Watch® SX can also be used in GCP clinical studies. The easy-to-read display presents all relevant data. This data can be simultaneously uploaded, via a fiber-optic connection, to a computer running the TOF-Watch SX Monitor program.

Additional variables:

Additional variables will include duration of surgery, drug dosages (Propofol, fentanyl, muscle relaxant, reversal agent, other agents used during anesthesia), duration from reversal to extubation, ventilatory variables (Tidal volume, respiratory rate, breathing pressure), transfer to ward, to ICU or home.

Hemodynamic variables including heart rate (HR), and mean arterial pressure (MAP) are recorded pre-induction, 60 seconds after fentanyl injection, after applied of Propofol TCI, every minute after tracheal intubation. A HR of <55–60 beat/min is determined as bradycardia which is to be treated with atropine 10 μ/kg. The limit for hypotension is MAP <60 mmHg which is to be treated with the titration of ephedrine intravenously. The incidence of bradycardia or hypotension will be recorded.

Post Operative Residual Curarization Evaluation/Follow – Up:

Residual blockade will be evaluated after extubation in the OR and in the PACU, as well as at post day 1 (TOF Ratio < 0.9 [only in OR and PACU] , pulmonary complication i.e. desaturation <90%, desaturation < 80%, reintubation, aspirate pneumonia, hospital death).

Study measurements in the post-anesthesia care unit In the PACU, the following variables will be measured at 15 min, 30 min, 60 min and 90 min: respiratory rate, arterial oxygen saturation, numerical pain rating (on a scale from 0, no pain, to 10, most severe pain imaginable), bleeding, hoarseness and occurrence of nausea or vomiting.

Before discharging from Post-Operative Care Unit, patients will be assessed “time readiness to discharge from PACU” by evaluating Modified Aldrete recovery score. The score will be measured at least 15 minutes interval.

MODIFIED Aldrete recovery score[14]

Parameter	Description of patient	Score
Activity level	Moves all extremities voluntarily/on command	2
	Moves 2 extremities	1
	Cannot move extremities	0
Respirations	Breathes deeply and coughs freely	2
	Is dyspneic, with shallow, limited breathing	1
	Is apneic	0
Circulation (blood pressure)	Is 20 mm Hg > preanesthetic level	2
	Is 20 to 50 mm Hg > preanesthetic level	1
	Is 50 mm Hg > preanesthetic level	0
Consciousness	Is fully awake	2
	Is arousable on calling	1
	Is not responding	0
Oxygen saturation as determined by pulse oximetry	Has level >90% when breathing room air	2
	Requires supplemental oxygen to maintain level >90%	1
	Has level <90% with oxygen supplementation	0

Maximum total score is 10; a score of ≥9 is required for discharge.

- Main goals are controlling postoperative pain, controlling nausea and vomiting, and reestablishing normothermia prior to discharge
- Majority of patients can meet discharge criteria within 60 minutes in the PACU, no demonstrable benefit from a mandatory minimum duration of PACU care
- Outpatients who meet the above discharge criteria may be “fast-tracked” to phase 2 recovery, similarly inpatients who meet the same criteria may be transferred directly from the OR to their ward. This is required less extensively monitoring.

Statistical Methods:
All statistical analysis will be performed by STATA or SPSS, depends on availability.

Baseline Patients Characteristics:
We will describe the data distribution of each collected variable. We will characterize subjects in both groups by demographics, comorbidities, clinical characteristics i.e. neuromuscular weakness grading, and distribution of ASA Classification pattern. Categorical variables will be summarized by frequency and percent while continuous variables will be summarized by the mean, median, standard deviation, and range.

Clinical Outcomes:

The data analysis will be based on the intent-to-treat approach. All comparisons will be made using an alpha level of 0.05

1. **Primary Efficacy endpoints**:

   The Proportion of patients who have a surgical conditions score of excellent will be compared between the Moderate NMB and Deep NMB groups using Fisher’s Exact test

2. **Secondary outcome**

1) The proportion of patients who are ready to be discharged from post- operative care, defined as Modified Aldrete's score ≥ 9, at arrival, 15,30,60, 90 minutes after reach of TOF > 0.9 will be summarized.

2) The proportion of patients who are ready to be discharged from the operating room, defined as TOF > 0.9 at time of tracheal extubation, at 1,3,5, 10 minutes after finish of Procedures will be summarized.

3) The frequency of patients with clinical signs of early recovery during Endolargyngeal Procedures will be compared between the deep NMB and Moderate NMB arms using Fisher's Exact test.

   Clinical signs of early recovery:
   1) Airway pressure alarm
   2) Movement of Vocal cords on Laryngeal Video monitor
   3) Movement of the abdomen
   4) Change of End Tidal CO_2

Other outcomes:

-

1) Proportion of patient at risk of Post-Operative Residual Curarization (PORC) (PORC) (TOF ratio < 0.9) at 1,3,5,10, minutes after finish of Procedures and at arrival ,15,30, 60,90minutes during Post-Operative Care Unit stay.
2) Time to ready-to-discharge from Post-operative Care Unit which is time from Post-operative Care Unit (PACU) admission to reach "acceptable" score of Post-operative discharge score.
3) Time to ready-to-discharge from operating room, which is time from finish of Procedures to train of Four ratio > 0.9
4) Intubating condition in patients who has endotracheal insertion. This will be assessed by anesthesiologist right after finishing intubation by using the same score of endolaryngeal surgical condition

Categorical variables will be compared using the Fisher's exact test while continuous variables will be compared using the student's t-test or Mann-Whitney U test, depending on the sample distribution.

Descriptive will be utilized to describe surgical conditions rating by Anesthesiologists during the Procedures, and VDO Surgical condition scoring by an ENT surgeon and Anesthesiologist. Categorical variables will be summarized by frequency and percent while continuous variables will be summarized by the mean, median, standard deviation, and range.

Descriptive and univariate statistics may be utilized to describe demographics and baseline characteristics of subjects. Multivariate logistic regression analysis may be employed to examine the predictive value of various baseline factors on efficacy endpoints.

Sample size calculation:
The primary outcome's sample size calculation:

Based on data from the BLISS study[15], the proportion of patients a with a score of Excellent on the Surgical Rating Score (SRS) among subjects who receive deep NMB with Rocuronium is approximately 99%, while this proportion for patients who received moderate NMB with atacurium followed by mivacurium was lower (82%)..

By using 80% power and 1-sided α=0.05, we performed sample size calculation by using the following formula.

For the proportion outcomes

$$n = \frac{2(\overline{p})(1-\overline{p})(Z_{\beta} + Z_{\alpha})^2}{(p_1 - p_2)^2}$$

All expected primary outcome, secondary outcomes and calculated sample sizes are shown in the following table

	Deep NMB	Moderate NMB	Sample size
Primary outcome			80% Power
- Proportion of Excellent	99%	82%	36/arm

Since we expect 13% of withdrawal from the study[16], we need to inflate the total sample size to **80 subjects (40 subjects per arm).**

As mentioned in the earlier session, the first five Procedures performed in conformance with this protocol will not be used for data analysis; thus, the Procedures will be practiced five times each center before data collection starts.

Therefore, the total enrolled patients are 110 patients.

2.8 Specific Drug Supply Requirements

It is required 300 vials of open label-Esmeron® (Rocuconium), ,150 vials of open label-Sugammadex. . Rocuronium and Sugammadex supplies should be sent from Zeulig to the study site in a bulk container, on a quarterly basis. Study drugs will be sourced locally and in original packaging according to the sponsor suggestion. Our research nurse will be responsible for storing, distributing the supplies as well as dispositions the unused supplies.

Calculations:

Base on surgical duration of 1- 2 hours, 1 vial of 0.6 mg/kg rocuronium (10mg/ml in 5 ml) will be required at induction and starting continuous infusion of 0.5 mg/kg/hour rocuronium will be used for maintainence.

Patient's distribution according to weight from 50-85 kg were estimated and used for calculation for all studied medications.

- 50 kg = 50% of sample population
- 65 kg = 20% of sample population
- 75 kg = 20% of sample population
- 85 kg = 10% of sample population

Moderate NMB: 1Vials/case for maintenance with continuous infusion of 0.5 mg/kg/h rocuronium during the case.

Deep NMB: 1 vial/case for maintenance with continuous infusion of 0.5 mg/kg/h Rocuronium during the case

	(Total number of rocuronium for Deep and Moderate is required = 300 vials)) Sugammadex 4mg/kg or 2 mg/kg (200 mg /vials) will be given in Deep or Moderate rocuronium block arm, respectively. 2 vials are required for patients whose weight above 50 kgs in each arm. [Total number of Sugammadex required = 150 vials] The actual cost of some anesthetic agents/equipment i.e. Propofol, TCI pump, infusion pump, End Tidal CO2 and BIS monitoing are able to be reimbursed as these may not be used as the routine practice. The maximum reimbursement of these is 319,000 THB for entire study.
2.9 Adverse Experience Reporting	All serious adverse experiences, regardless of relatedness to study medications will be collected throughout the course of study therapy and at least 7 days after the end of study therapy. **1. Recording Adverse Experiences** An adverse experience is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study's products, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the product, is also an adverse experience. Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse experiences. Examples of this may include, but are not limited to, teething, typical crying in infants and children, and onset of menses or menopause occurring at a physiologically appropriate time. Adverse experiences may occur in the course of the use of a product in clinical studies or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse, and from withdrawal. Such events will be recorded at each examination on the Adverse Experience Case Report Forms/Worksheets. **2. Immediate Reporting of Adverse Experiences to the SPONSOR** **Serious Adverse Experiences** Any serious adverse experience, including death due to any cause, which occurs to any subject/subject entered into this study or within 14 days following cessation of treatment or within the established off therapy follow-up period for safety described in the protocol, whether or not related to the study product, must be reported within 24 hours to one of the individual(s) listed on the contact information page. Additionally, any serious adverse experience considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to one of the individuals listed on the sponsor contact information page found in the administrative binder. All subjects/subjects with serious adverse experiences must be followed up for outcome. **3. Responsibility for Reporting Adverse Experiences** All adverse experiences will be reported to regulatory agencies, IRB/IECs, in accordance with all applicable global laws and regulations.

2.10 Itemized Study Budget	**See attached excel in separate sheet**
2.11 References	1. Li et al. The Effects of Neuromuscular Blockade on Operating Conditions During General Anesthesia for Spinal Surgery. J Neurosurg Anesthesiol 2014;26:45–49. 2. Moerman AT, Herregods LL, De Vos MM, et al. Manual versus target-controlled infusion remifentanil administration in spontaneously breathing patients. Anesth Analg. 2009;108:828–834. 3. Nieuwenhuijs DJ, Olofsen E, Romberg RR, et al. Response surface modeling of remifentanil–propofol interaction on cardiorespiratory control and bispectral index. Anesthesiology. 2003;98:312–322. 4. Rocuronium, Local Package Insert: RA 8730 TH S1 (Ref 2.1) Latest updated July 2002 5. Lapisatepun W et al. Rapid sequence induction with rocuronium at 0.45 mg/kg: comparison of intubating conditions between ketamine and propofol induction. Chiang Mai Med J 2010; 49(1): 11-17 6. Siddik-Sayyid SM et al. Excellent intubating conditions with remifentanil-propofol and either low-dose rocuronium or succinylcholine. Can J Anaesth. 2009 Jul;56(7):483-8. 7. Rocuronium, Zemuron® Product Monograph Last Revised: August 7, 2012 Merck Canada Inc 8. Fuchs-Buder T et al. Rocuronium for anesthesia induction in elective procedures. Time course of muscular blockade and intubation after administration of 2-compartment ED95 (0.6 mg/kg) and dose reduction (0.4 mg/kg). Anaesthesist. 1999 Mar;48(3):164-8. 9. McGrath DC, Hunter MJ. Monitoring of neuromuscular block. Contin Educ Anaesth Crit Care Pain (February 2006) 6 (1): 7-12. 10. Fuchs-Buder T. et al. Good clinical research practice in pharmacodynamics studies of neuromuscular blocking agents II: the Stockholm revision. Acta Anaesthesiol Scand 2007; 51: 789–808 11. Howardy-Hansen P. et al. Tactile evaluation of posttetanic count (PTC). Anesthesiology 1984;60:372-374. 12. Cooper R. et al. Comparison of intubating conditions after administration of Org 9246 (Rocuronium) and Suxamethonium. British Journal of Anaesthesia 1992; 69: 269-273. 13. Sugammadex, Local Package Insert: RA 8700001 OS S2 (ref 1.0) Latest Updated 22 Jan 2017. 14. Vasanawala M, Macario A, Canales M. Some common problems in the postanesthetic care unit. Contemp Surg. 2000;56:691-700. 15. Martini CH et al. Evaluation of surgical conditions during laparoscopic surgery in patients with moderate vs. deep neuromuscular block. British Journal of Anaesthesia August 2013: doi:10.1093/bja/aet377. 16. Flockton E.A. et al. Reversal of rocuronium-induced neuromuscular block with sugammadex is faster than reversal of cisatracurium-induced block with neostigmine. Br. J. Anaesth. (2008) 100 (5): 622-630. doi: 10.1093/bja/aen037. 17. Jian-dong G et al. Evaluation of entropy for monitoring the depth of anesthesia compared with bispectral index: a multicenter clinical trial. Chinese Medical Journal 2012;125(8):1389-1392.
2.12 Publication Plan	Within 3 months after the study completion, we plan to submit an abstract of study to an international scientific meeting. Within 6 months after the study completion, we plan to submit one manuscript to the International Journal related to Anesthesiology field.

Study Flow Chart

Study Procedures	Day 0	Day 1				Day2
Inclusion/Exclusion Evaluation	x					
Informed Consent	x					
Medical History Review	x					
OR* Surgeon Assessment		Q15 min				
OR Anesthesiologist Assessment		Q15 min				
OR TOF Watch® monitoring		Q15 sec				
OR PTC monitoring		Q 6 min				
OR Anesthetic routine monitoring		Q15 min				
OR residual blockade		At Extubation, 1,3,5,10minutes				
Study Procedures		**Minutes**				
		15	**30**	**60**	**90**	
PACU** routine monitoring		x	x	x	x	
PACU TOF Watch® monitoring		x	x	x	x	
PACU residual blockade assessment		x	x	x	x	
PACU readniness time to discharge		x	x	x	x	
Study Procedures		**At arrival**				**(24 hours post PACU)**
Ward residual blockade assessment		x				x

*OR =Operating Room, ** PACU = Post Anesthetic Recovery Room

Patient characteristics	Gr M (N =48)	Gr D (N=49)
Gender		
Female	**20 (41.7%)**	**23 (46.9%)**
Male	**28 (58.3%)**	**26 (53.1%)**
ASA physical status		
1	**18 (37.5%)**	**19 (38.8%)**
2	**30 (62.5%)**	**30 (61.2%)**
Airway type		
Tracheal tube	**27 (56.3%)**	**25 (51.0%)**
Tubeless	**17 (35.4%)**	**21 (42.9%)**
Combination	**4 (8.3%)**	**3 (6.1%)**
AGE (years)	**43.5 (11.78)**	**42.31(13.28)**
BMI (kg/m^2)	**23.75(3.66)**	**22.07(5.15)**
Operation time (minutes)	**53.73(73.99)**	**78.84 (186.97)**
Anesthetics		
Fentanyl (μg)	**75.96 (54.0)**	**82.4(52.13)**
Propofol (mg)	**465.6 (257.26)**	**481.88 (206.56)**
Rocuronium (mg)	**38.36 (16.51)**	**53.65 (16.38)**
Sugammadex (mg)	**132.99 (35.7)**	**237.53 (37.66)**

Data were presented in number (%) or mean(SD)

Intraoperative outcomes	**Gr M**	**Gr D**	***p*-value**
Surgical Grading			
Clinically acceptable	43 (89.6%)	49(100%)	
Not acceptable	5(10.4%)	0	0.027*
Surgeon's compliant	9(18.7%)	5 (10.2%)	0.231
Cough	34(70.8%)	16(32.7%)	<0.001*
Total additional doses of Rocuronium	23 (47.9%)	10 (20.4%)	0.005*

Recovery parameters	Gr M	Gr D	*p*-value
Time to T4 (seconds)†	60(60-120)	60(60-120)	0.497
Time to TOF0.9 (seconds)‡	180(120-240)	120(109-180)	0.034*
PORC at PACU (number of patients)§	0	0	-
Time to ALD≥9 (minutes)¶	33(18-48)	27[14-42]	0.253
Nausea/Vomiting (number of patients)	0(0%)	4(8.2%)	0.117