Effect of Deep versus Moderate Neuromuscular Blockade on Peak Airway Pressures During Elective Laparoscopic Surgery

NCT02812186

Background

The frequency of surgical procedures that can be performed laparoscopically is rapidly increasing. Surgical conditions in laparoscopic surgery are largely determined by the depth of neuromuscular relaxation during surgery. Neuromuscular blockade (NMB) is frequently utilized in laparoscopic procedures to improve surgical conditions[1] by relaxing the abdominal muscles and thus facilitating insufflation with CO_2 to optimize surgical view. While studies have investigated the effects of neuromuscular blockade on surgical conditions and abdominal insufflation pressures, to our knowledge, little is known about the benefit, if any, a deep NMB blockade will have over a moderate NMB on airway pressures. Increased airway pressures can lead to an increase in alveolar and perivascular edema, a decline in dynamic lung compliance and hypoxemia. [16] A deep neuromuscular blockade could decrease the resistance to ventilation by increasing the compliance of the chest and abdominal wall, thereby allowing maximization of lung expansion at lower airway pressures.

Several studies have investigated surgical view under deep vs. moderate neuromuscular blockade. Across a single intraabdominal insufflation pressure, a deep neuromuscular blockade may provide better surgical conditions than a moderate block[6, 8-11]. Raising the intraabdominal insufflation pressure can result in several adverse outcomes such as increased airway pressures, postoperative pain, risk of CO_2 embolism, and hemodynamic disturbances[15]. Low insufflation pressures of < 12 mm Hg have been associated with fewer adverse effects than higher pressures (>15 mm Hg)[7]. Though studies have shown that surgical view under deep block is statistically superior to the view under a moderate NMB block across a single insufflation pressure [6,8-11], the primary outcome in these studies was a subjective, 5 point scale requiring the surgeon to grade his surgical view. Hence, there is a lack of objective outcomes assessed in these studies. Measuring the peak airway pressures in the deep vs. moderate block group will provide us with an objective indice to use in making the determination if one type of block is 'superior' to the other.

Additionally, the degree of neuromuscular block for optimal surgical procedures has been the focus of debate and research for several years. Firstly, different muscle groups have different sensitivity to neuromuscular blocking agents (NMBA). For example, though neuromuscular blockade is often measured at the adductor pollicis muscle in the thumb, the abdominal muscles and diaphragm are less sensitive to NMBA.[2,3] Consequently, surgeons may complain of insufficient NMB though the anesthesiologist observes no twitches at the thumb. Thus, some authors have argued that paralysis of the diaphragm and the abdominal wall muscles can only be

ensured by an intense NMB, quantified by post-tetanic count (PTC) of 1.[4] However, these results must be counterbalanced by the need for optimal extubating conditions which cannot occur unless there is full reversal of muscle paralysis, a condition which requires the presence of at least 1-2 twitches (if one uses the traditional drug, neostigmine, to antagonize paralysis which would not needed if we use the newly FDA approved drug, sugammadex). Thus, a deep block throughout the procedure carries the inherent risk of delaying extubation if sugammadex is not available.

The Table below shows known and theoretical risks/benefits related to deep vs medium NMB.

Deep NMB	**Medium NMB**
Literature supports better operating conditions/view by surgeon	Literature supports worse operating conditions/view by surgeon
Possibly lower airway pressures	Possibly worse airway pressures
Possibly longer duration to extubation	Possibly shorter duration to extubation
Possibly worse respiratory mechanics at the end of anesthesia	Possibly better respiratory mechanics at the end of anesthesia

Thus, there is clearly equipoise with regard to the comparative effectiveness of deep vs medium NMB. Therefore, we wish to ascertain if a deep neuromuscular block will decrease the airway pressures in patients undergoing laparoscopic procedures compared to those under a moderate block. A reduction in airway pressures may lead to a decrease in the complications associated with elevated airway pressures including hypoxemia, total static lung compliance, alveolar edema, and long term morbidity[16]. Additionally, we wish to understand if time from administration of sugammadex to reversal is different between patients that have a moderate NMB as compared to a deep NMB.

To test our hypotheses, we will conduct a two period cross-over study by randomizing patients undergoing laparoscopic surgery into 2 different groups: group 1 in which patients will receive "deep neuromuscular blockade" in the beginning portion of the surgery followed by a period of "moderate blockade", and group 2 in which patients will receive "moderate neuromuscular blockade" in the beginning portion of the surgery followed by a period of "deep blockade". The deep neuromuscular block will be defined as post tetanic count of 0 to 2 and the moderate neuromuscular block will be defined as 1-2 twitches. In all patients, sugammadex will be used to reverse the block at the end of surgery in order to obtain optimal extubating conditions. Time from administration of sugammadex to extubation will be calculated and compared.

Hypothesis

A deep neuromuscular blockade results in lower peak airway pressures and lower abdominal insufflation pressures in patients undergoing elective laparoscopic procedures.

Objectives

Primary Outcome: Peak Airway Pressures

Secondary outcomes:

- Hemodynamics (blood pressure (BP), Heart rate (HR)) measured q15 min at the time of airway pressure measurement
- Duration from administration of sugammadex (to be given at skin closure) to Train of Four (TOF) ratio = 0.7, 0.8 and 0.9 and extubation using the following guidelines (SpO2 >98% on 100% FiO2, Respiratory rate (RR) <35, tidal volume (TV) > 5 ml/kg, RR/Tidal Volume <100)
- Recovery variables in the post-anesthesia care unit (respiratory rate, arterial oxygen saturation, numerical pain rating, nausea or vomiting, and level of sedation or alertness).
- Adverse events (AE).

Methods

This will be a single-center, prospective, randomized, two-period crossover controlled trial. Approval from the local IRB will sought and patients will provide written informed consent.

Inclusion and exclusion criteria

Inclusion criteria:

The participant must fulfill ALL the criteria listed below for entry.

- Each participant must be willing and able to provide written informed consent for the study.
- Each participant must be greater than or equal to 18 years of age.
- Each participant must be ASA class I, II or III.
- Each participant must be scheduled for elective laparoscopic surgery (this includes robotic laparoscopic s).
- Expected surgical duration of 60 min or longer

Exclusion criteria:

- Inability to give informed oral or written consent
- Known or suspected neuromuscular disorders impairing neuromuscular function;
- True allergies as defined as hypotension, bronchospasm, or anaphylaxis to muscle relaxants, anesthetics or opioids
- A history (patient or family) of malignant hyperthermia
- A contraindication for neostigmine administration
- Renal insufficiency, as defined by serum creatinine levels at 2.5 fold the normal level
- Body mass index >45 kg/m
- Significant respiratory disease.
- Planned postoperative mechanical ventilation

Investigational plan and treatments (see Figure 1)

Subjects will be randomly assigned to one of two study groups using a random number generator and sealed envelope technique:

Group 1 D→M: After induction and intubation, the patient will be maintained in a "deep" (post-tetanic count of zero to two) neuromuscular block (NMB). Deep NMB will be obtained with an intubating dose of rocuronium of 0.5 mg/kg or as per clinical team's discretion. After surgical incision is made, the abdomen is insufflated, trocars are inserted, and prior to the beginning of the actual laparoscopic procedure, collection of data for "deep" NMB period will begin. Neuromuscular blockade level will be maintained and adjusted throughout the course of surgery using intravenous bolus doses of rocuronium. Dosing of rocuronium will be determined by the clinical team. Only the clinical team will administer any medications or fluids to patients enrolled in the study (no research team members will be administering drug or fluid). The surgeon will inform the study team member of the first Surgical Rating Scale (SRS) score for his/her view, and simultaneously, the first peak airway pressure and related variables will be collected (T_0). For the next 20 minutes of surgery during which a "deep" NMB is being maintained, peak airway pressure, heart rate, and blood pressure will be collected every minute by the study team member (as per the anesthesia machine's readings), and the surgeon will provide the SRS score every 5 minutes.
To minimize any type of carry-over effects, after the completion of the deep NMB 20 minute period, a "transition period" will begin (T_1).

Upon successful acclimation to a "moderate" NMB, data collection may begin again (T_2): the surgeon will again provide the SRS score simultaneously with the commencement of collection for peak airway pressure and related values. For the next 20 minutes of surgery during which a "moderate" NMB is maintained, peak airway pressure measurements (as well as other relevant secondary outcome measurements) will be collected every minute by the study team member by looking at the anesthesia machine's readings and the surgeon will provide the SRS score every 5 minutes. After 20 minutes (T_3), the patient will remain at the "moderate" NMB for the duration of the surgery unless a change in the depth of blockade is requested by the surgeon. Should such a request be made, this will be documented in the data collection (obtained from anesthesia record) along with the depth of blockade that the patient was switched to. By skin closure, the patient's NMB will be returned to "moderate."

Group 2 M→D: After induction and intubation, the patient will be maintained in a "moderate" (one or two twitches) neuromuscular block (NMB). Moderate NMB will be obtained with intubating dose of rocuronium of 0.5 mg/kg or as per clinical team's discretion. After surgical incision is made, the abdomen is insufflated, trocars are inserted and prior to the beginning of the actual laparoscopic procedure, collection of data for "moderate" NMB period will begin. Neuromuscular blockade level will be maintained and adjusted throughout the course of surgery

using intravenous bolus doses of rocuronium. Dosing of rocuronium will be determined by the clinical team. Only the clinical team will administer any medications or fluids to patients enrolled in the study (no research team members will be administering drug or fluid). The surgeon will inform the study team member of the first SRS score for his/her view, and simultaneously, the initial peak airway pressure and related values are collected (T_0). For the next 20 minutes of surgery (during which a "moderate" NMB is being maintained), peak airway pressure measurements, heart rate, and blood pressure will be collected every minute by the study team member by looking at the anesthesia machine's readings, and the surgeon will provide the SRS score every 5 minutes.

To minimize any type of carry-over effects, after completion of the moderate NMB 20 minute period, a "transition period" will begin (T_1). During this "transition period" additional IV bolus doses of rocuronium will be administered to the patient to achieve "deep" neuromuscular blockade. Upon successful acclimation to a "deep" NMB, data collection may begin again (T_2): the surgeon will again provide the SRS score simultaneously with the commencement of collection for peak airway pressure and related values. For the next 20 minutes of surgery (during which a "deep" NMB is maintained), peak airway pressure measurements (as well as other relevant secondary outcome measurements) will be collected every minute by the study team member by looking at the anesthesia machine's readings, and the surgeon will provide the SRS score every 5 minutes. After 20 minutes (T_3), the patient's "deep" NMB will be maintained for the duration of the surgery unless a change in the depth of blockade is requested by the surgeon. Should such a request be made, this will be documented in the data collection (obtained from the anesthesia record) along with the depth of blockade that the patient was switched to. By skin closure, the patient's depth will be returned to "deep."

(Both Group 1 and Group 2): At skin closure, subjects in both groups will be reversed with sugammadex 4 mg/kg or at the discretion of the clinical team (T_4). Patients will be extubated when the TOF ratio becomes 0.9 or higher (T_5). Time from administration of sugammadex to extubation will be recorded.

In the recovery room (T_6), the following variables will be measured by the study coordinator at 15 min intervals for the first 1 hour: respiratory rate, arterial oxygen saturation, numerical pain rating (on a scale from 0, no pain, to 10, most severe pain imaginable), occurrence of nausea or vomiting, and level of sedation or alertness. Additionally, the patient's maximum inspired volume will be assessed 30 minutes after arrival in the PACU via the use of an incentive spirometer. After one hour, all measurements will be complete (T_7).
Intraoperative and postoperative data will be collected by a research coordinator who is not blinded to the patient's randomization. The research coordinator will not be directly involved with the patient's care. Rather, his/her sole purpose will be to record the relevant data (airway pressures, abdominal insufflation pressures, PACU indices etc.) every 1 minute. The coordinator will have

access to the electronically recorded patient data and will make their recordings directly from the anesthesia machine and/or the electronic anesthesia record. The research coordinator will also review data from the patient's chart (anesthesia record, PACU record) after surgery to collect any additional information that may be necessary.

Anesthetic Technique

Before administering any medications a baseline inspired volume via an incentive spirometer in the holding area will be obtained. The type of anesthesia (general endotracheal) will be consistent with standard practice at Stony Brook and many other centers. Induction of general anesthesia will be achieved by an induction agent such as propofol [1 to 2.5 mg/kg (lean body mass)] combined with bolus doses of fentanyl. Should a rapid sequence induction be desired based on the patient's co-morbid conditions (reflux disease, etc.), succinylcholine or rocuronium may be used to obtain paralysis for intubation. In the event that succinylcholine is used, the patient will be allowed to obtain a full return of muscle strength (TOF 4/4), prior to administration of rocuronium for further paralysis during the surgery. Induction drugs and dosing may be modified at the discretion of the clinical anesthesia team. Maintenance of anesthesia will be achieved either through the use of volatile inhaled agents or intravenous anesthetic. The choice of agents for maintenance will be based upon the discretion of the anesthesiologist.

Neuromuscular monitoring

Neuromuscular monitoring is standard of care for general endotracheal anesthesia. In this study neuromuscular function will be monitored using the TOF-watch SX acceleromyograph (MSD BV, Haarlem, The Netherlands) at the adductor pollicis muscle. The thumb is attached to a flexible adaptor that applies a constant preload to the thumb. Neuromuscular stimulation will be applied to the ulnar nerve via two pediatric electrodes applied on the skin left and right of the ulnar nerve at the distal forearm. Before administration of any neuromuscular blocking agent, but after induction of general anesthesia, the following procedures will be conducted to standardize the neuromuscular monitoring: (1) application of a tetanic ulnar nerve stimulation (50 Hz for 5 seconds); (2) calibration of the TOF-watch (CAL 2); (3) performance of a series of TOF measurements, to ensure that the TOF ratio differs by less than 5% between measurements (if the TOF ratio differs by more than 5%, the TOF-watch will be recalibrated). After these steps, the neuromuscular blocking agent according to protocol is administered. In patients requiring rapid sequence induction, succinylcholine will be used for intubation and after return of 4/4 twitches, the aforementioned steps (steps 1-3) will be conducted. When, during the study, the number of measured twitches is zero, the PTC will be measured. A 50 Hz tetanic stimulation for 5 s is followed (after a 3 s rest) by 15 single stimulations at 1 Hz. The number of twitches generated (that is, the PTC) corresponds with the degree of NMB, with a PTC of 1 to 2 reflecting a deep level of NMB.

Ventilation

The mode of ventilation for these cases will be standardized consistent with routine practice. All of the patients will receive volume-controlled ventilation at a tidal volume of 6-8 ml/kg (5 cm PEEP). The respiratory rate will be adjusted at the discretion of the anesthesiologist to maintain an end-tidal CO_2 of 30-40 mmHg during the surgical procedure.

Study measurements during anesthesia

Primary Outcomes
Peak Airway Pressures: Airway pressures will be measured every 1 minute.

Secondary Outcomes
Mean Airway Pressure: In addition to the Peak airway pressure, the mean airway pressure will also be recorded every 5 minutes during the procedure.

Hemodynamic monitoring

Blood pressure and heart rate will be measured using the noninvasive blood pressure cuff and standard three lead EKG, respectively every 1 minute during the interval in which the peak airway pressures are being measured ("deep" vs. "moderate").

Additional variables

Additional variables will include duration of surgery, drug dosages (propofol, opioids, muscle relaxant, reversal agent, glycopyrrolate, other agents used during anesthesia), and duration from reversal to extubation. Standard extubation criteria will be (SpO2 >98% on 100% FiO2, RR <35, TV > 5 ml/kg).

Surgical rating

During the procedure, the surgical condition will be scored by the surgeon using a five-point SRS. To reduce variability in the surgical rating, all surgeries will be performed by a core group of surgeons who will receive training in how to report this information.
The rating scale will be a five-point ordinal scale ranging from 1 = poor condition to 5 = optimal surgical conditions (see appendix, Table 1). The surgeon scores the condition at 15-minute intervals. In case of a sudden change in surgical conditions, additional scores are obtained. If conditions are poor (score 1 or 2), muscle relaxation can be increased (in effect converting patient from moderate to deep according to methodology specified in this protocol using the rocuronium infusion).

Study measurements in the post-anesthesia care unit

In the recovery room, the following variables will be measured by a different study personnel, when possible, at 15 min intervals for the first 1 hour: respiratory rate, arterial oxygen saturation, numerical pain rating (on a scale from 0, no pain, to 10, most severe pain imaginable), occurrence of nausea or vomiting, and level of sedation or alertness. The level of sedation/alertness will be assessed in the recovery room using the validated Leiden Observer's Assessment of Alertness/Sedation (see appendix, table 2). Additionally, the patient's maximum inspired volume will be assessed 30 minutes after arrival in the PACU via the use of an incentive spirometer.

Post-operative day 1 follow up

QoR 9 on post op day 1 (via phone or in person)[17]

Other parameters

Time to optimal extubation conditions from the moment of reversal (with optimal conditions defined as TOF 4 with ratio >90%), time in the post-anesthesia care unit, and drug consumption will be recorded.

Safety evaluations

Serious adverse events (SAE) that occur during the study will be recorded in the case report form. The AE record in the case report form includes the nature of the event (with onset date and time, end date and time), severity, treatment, outcome, and the relationship to the treatment given. All AEs that meet reporting criteria will be reported to the medical ethics committee and authorities, as required by the GCP/GRP guidelines.

Statistical Analysis

Airway Pressure, Intra-abdominal pressure, Respiratory rate, arterial oxygen saturation, blood pressure, heart rate

In order to obtain the most accurate measurements possible, multiple readings for the primary outcome (peak airway pressure) and secondary outcomes (respiratory rate, arterial oxygen saturation, blood pressure, and heartrate) will be collected once per minute for a maximum of 20 minutes per treatment period. Summary measures (i.e. descriptive statistics including mean ± standard deviation, median, and interquartile range) for each data element will be generated for each patient, per each treatment period. Depending on the distribution of the peak airway pressure variable (as tested by Shapiro-Wilk tests), either a paired t-test or Wilcoxon Sign Rank test will be used to compare peak airway pressure between the two treatment conditions. Secondary outcomes

(respiratory rate, arterial oxygen saturation, blood pressure, and heartrate) will also be examined in a similar way for differences between the two treatment groups. P-values will be reported at the 95% confidence level.

Additionally, linear mixed effects models will be used for the peak airway pressure outcome, with treatment group and time as fixed effects, and subject as random effect. Group effect size and p-value will be reported at the 95% confidence level.

Duration from reversal to extubation

Summary statistics (mean ± standard deviation, median, IQR) will be summarized for each treatment condition. Two-sided t-test for independent groups will be used to compare the above variables between the two groups. P-values will be reported and 95% confidence interval of group difference will also be reported. Wilcoxon rank sum test will be used instead in the rare event of non-normality.

Surgical rating scores

Summary statistics (mean ± standard deviation, median, IQR) will be computed for surgical rating scores for each patient, per each treatment group. Wilcoxon sign rank tests will be used to compare surgical rating score between the two groups. P-values will be reported and 95% confidence interval of group difference will also be reported.

Numerical pain rating, occurrence of nausea or vomiting, and level of sedation or alertness
Numerical pain rating score and level of alertness will be presented as a graphical display of treatment group mean or median over each of the four time points in the recovery room. Contingency table (condition*group*time) for nausea/vomiting will be presented. GEE (Generalized estimating equation) will be used to compare the recovery room variables between the two treatment conditions with time and treatment group as covariates. Exchangeable correlation structure will be applied. The distribution of binary variable (occurrence of nausea or vomiting) is assumed to binomial, and the distribution of other ordinal variables are assumed to poison or negative-binomial based on the nature of data.

Power analysis

We will assume a normal distribution. Using the values found in the Casanova article,[18] we expect the difference in moderate versus deep block peak airway pressures to be approximately 2 cmH2O, with a standard deviation of 5. Converting these numbers to mmHg, we expect to see a difference of 1.48 mmHg, and a standard deviation of 3.68 mmHg. Using an α=0.05, we will need around 52 patients for a paired t-test to have approximately 81% power to detect a difference between moderate and deep peak airway pressures. We plan to enroll approximately 120 patients to account for drop outs.

Appendix

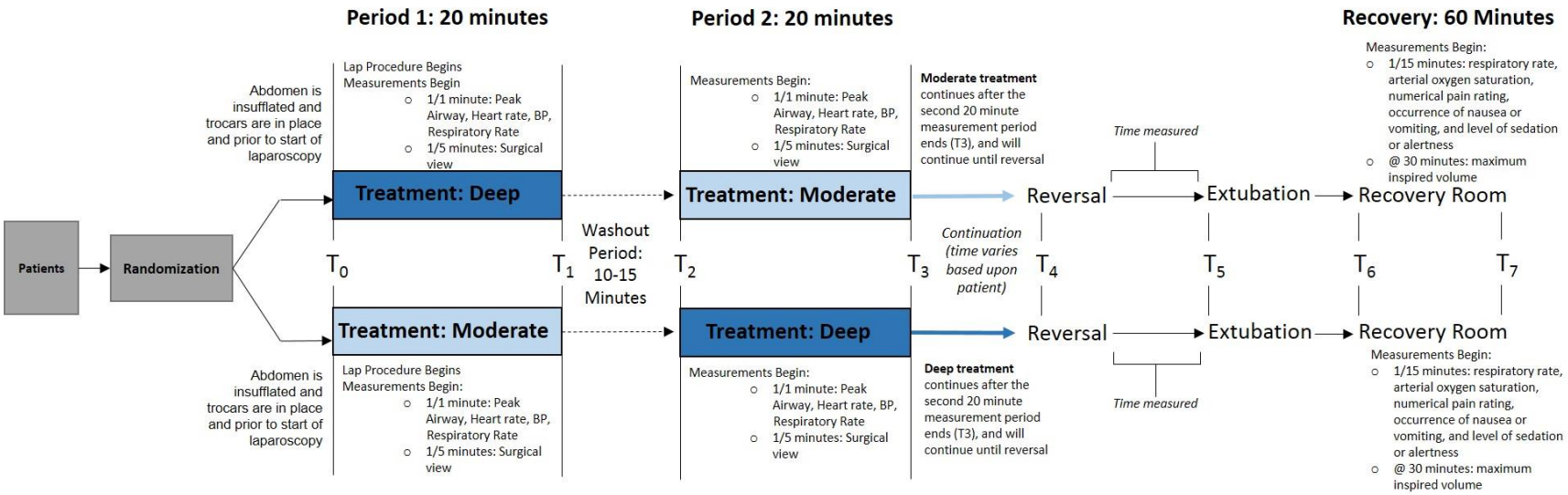
Table 1 Surgical rating score

1	Extremely poor conditions
2	Poor conditions
3	Acceptable conditions
4	Good conditions
5	Optimal conditions

Table 2. Observer's Assessment of Alertness and Sedation scale

Responsiveness score	Level*
Responds readily to name spoken in normal tone	0 (Alert)
Lethargic response to name spoken in normal tone	1
Responds only after name is called loudly and/or repeatedly	2
Responds only after mild prodding or shaking	3
Does not respond to mild prodding or shaking	4
Does not respond to noxious stimulus	5

Figure 1: Trial Timeline



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