

**A Prospective Randomized Clinical Trial Evaluating Surgical Conditions during
Laparoscopic Bariatric Surgery with Deep *versus* Moderate Neuromuscular
Blockade**

PI: Terri G. Monk, MD, MS¹
Professor

Co-PI: Purav Patel, MD¹
Resident

Co-I Michael Brown, MD
Associate Professor

Julie Marshall, MD
Associate Professor

Co-I: Roger de la Torre, MD²
Associate Professor
Director, Missouri Bariatric Services

Statistician: Greg Petroski, Ph.D.
Research Assistant Professor³

¹Department of Anesthesiology and Perioperative Medicine

²Department of General Surgery, Division of Bariatric Surgery

³Department of Health Management and Informatics, Office of Medical Research
University of Missouri
Columbia, Missouri 65212

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Contact Information: Terri G. Monk, MD, MS
Department of Anesthesiology and Perioperative Medicine
University of Missouri-Columbia

One Hospital Drive, 3w-27F; DC005.00

Columbia, MO 65212

Telephone: (573)-882-2568

Fax: (573)-882-2226

Email: monkt@health.missouri.edu

2.1 Objectives:

This prospective, randomized, single-blind trial will randomize patients undergoing laparoscopic bariatric surgery to either deep (0 twitches, 1-2 PTC) or moderate (reappearance of T2) neuromuscular blockade (NMB). Within each NMB group, patients the initial insufflation pressure will be either 10 or 15 mm Hg:

Primary Endpoint:

1. Surgeon initial satisfaction with operating conditions

Secondary Endpoints:

1. Percentage of procedures that can be performed at low (10 mm Hg) versus high (15 mm Hg) insufflation pressures at each level of NMB
2. Percentage of procedures requiring additional NMB and/or insufflation pressures to achieve satisfactory intraoperative surgical conditions
3. Quantification of postoperative pain medication requirements with deep versus moderate NMB

2.1.1 Clinical Hypotheses:

Primary Hypothesis:

We hypothesize that deep neuromuscular block (NMB)

1. provides better intra-operative surgical conditions than moderate NMB during laparoscopic bariatric surgery

Exploratory Hypotheses:

We hypothesize that deep neuromuscular block (NMB):

1. allows the use of lower insufflation pressures during laparoscopic bariatric surgery
2. decreases postoperative pain and the need for postoperative pain medication

2.2 Background & Rationale:

Obesity affects more than 78 million adults in the United States and it is estimated that 35% of the US population is obese (body mass index ≥ 30) with the highest incidence (40%) in women aged 40 to 59 years.¹ Obese individuals have increased comorbidity including an increased risk for coronary heart disease, hypertension, dyslipidemia, type 2 diabetes, and sleep apnea. The treatment of obesity and its related comorbidities costs nearly \$150 billion annually and this cost is expected to increase if obesity is not stemmed.² Dieting has proven to be only marginally effective in the treatment of obesity, but surgery results in substantial long-term weight loss.³ As a result, more than 179,000 bariatric procedures are performed in the US each year with the majority of these surgeries using laparoscopic techniques.⁴

Neuromuscular blockade (NMB) is routinely used during laparoscopic surgery to optimize both intubating and operating conditions for the anesthesiologist and the surgeon, respectively. Recent research has shown that in laparoscopic abdominal procedures, deep NMB is associated with superior operating conditions.⁵⁻⁸ However, maintaining deep NMB can be a challenge to anesthesiologists concerned about rapid emergence and the risk of postoperative residual paralysis. It is, therefore, obvious that surgeons and anesthesia providers have conflicting goals for the level of muscle relaxation that should be maintained during many surgical procedures.

The introduction of sugammadex (Bridion[®], Merck Sharp & Dohme Corp., Oss, The Netherlands), a new neuromuscular reversal agent with the ability to rapidly reverse deep rocuronium-induced NMB, will finally provide the anesthesia provider the opportunity to maintain deep neuromuscular relaxation throughout the entire surgery without compromising time to emergence and increasing post-operative complications.⁹ However, sugammadex will undoubtedly cost much more than neostigmine, the anticholinesterase inhibitor presently used to reverse NMB, and hospital pharmacies will

have to be convinced that the benefit of improved operating conditions is worth the additional cost associated with the use of sugammadex.

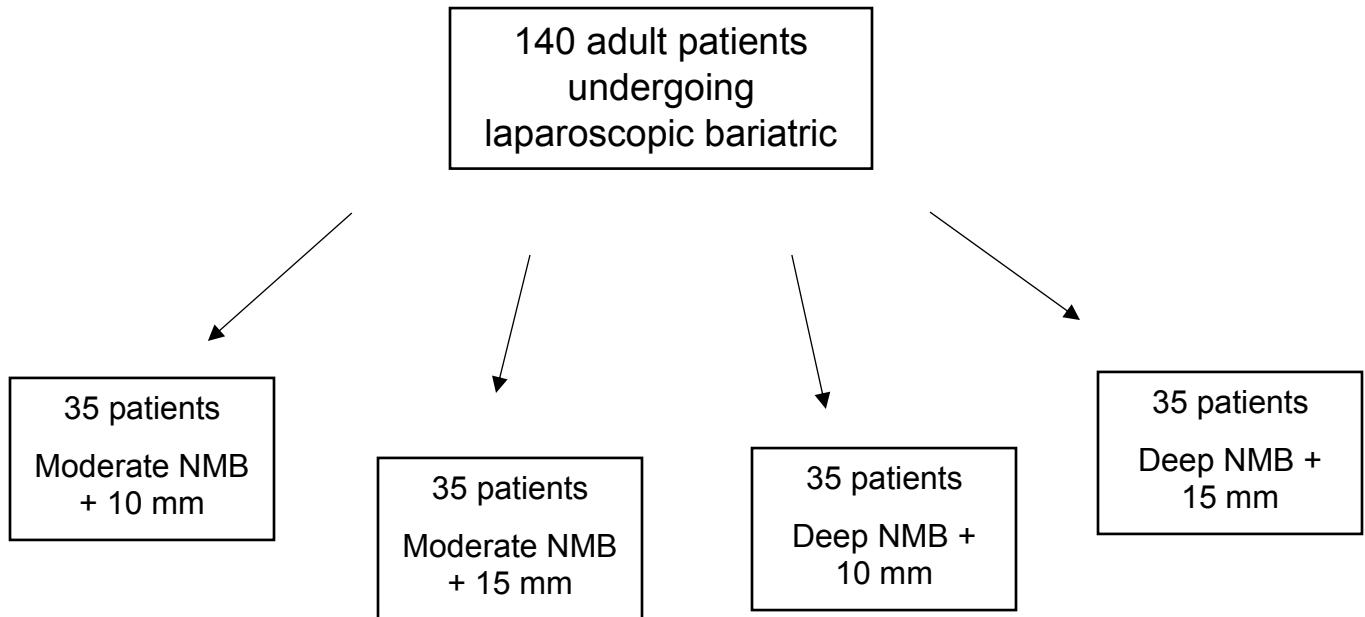
Recently, there has also been interest in maintaining low insufflation pressure during laparoscopic surgery because lower pressures may decrease postoperative pain.¹⁰ It is hypothesized that deep NMB will provide good surgical conditions and minimize postoperative pain at low insufflation pressures of 7 to 10 mmHg, but this theory has not been adequately evaluated, especially in obese patients.

At the present time, there is no conclusive evidence that surgeons need deep NMB for laparoscopic bariatric surgery and even that surgeons can discriminate between moderate and deep NMB.¹¹ The goal of this prospective, randomized, assessor-blinded controlled trial is to test the hypothesis that deep NMB provides optimal surgical conditions during laparoscopic bariatric surgery in the morbidly obese patient. In addition, we will determine if deep NMB allows the surgeon to utilize lower insufflation pressure and decreases postoperative pain requirements after laparoscopic bariatric surgery.

2.3 Study Design:

Study design: prospective, randomized, assessor-blinded controlled trial that will be performed at a single academic hospital. The surgeons, subjects, and individuals performing the postoperative assessments will be blinded to the study group assignment. The anesthesia providers responsible for the clinical care of the patients will be aware of the rocuronium NMB treatment group and NMB and insufflation status throughout the surgical procedure.

2.4 Study Design:



2.5 Study Procedures:

- I. Patient population: this study will enroll 145 adults undergoing elective laparoscopic bariatric surgery. Our aim is to randomize 140 patients and this will allow 5 subjects to drop out of the study after enrollment.
- II. Inclusion criteria:
 - a. Age \geq 18 years
 - b. ASA I-III
 - c. BMI \geq 35
- III. Exclusion criteria:
 - a. Inability to obtain written informed consent
 - b. Pregnancy or breastfeeding
 - c. Allergy to rocuronium, sugammadex, or any anesthetic agents used in the protocol
 - d. Known or suspected neuromuscular disorders
 - e. Significant renal disease with a serum creatinine \geq 2 mg/dl
 - f. Significant liver disease
 - g. A family history of malignant hyperthermia
- IV. Randomization: On the day of surgery, patients will be randomized to one of four groups: 1. moderate NMB + 10 mm insufflation pressure (IP); 2. moderate NMB + 15 mm IP; 3. deep NMB + 10 mm IP; or 4. deep NMB + 15 mm IP. Randomization will be stratified for the four groups so that obese patients with BMI of 35 to 45 and those with a BMI $>$ 45 are equally distributed between the groups.
- V. Blinding: The surgeon, operating room staff, patients, personnel in the postanesthesia care unit (PACU) as well as the investigators collecting the postoperative data will be blinded to the group allocation. The surgeon will also

be blinded to the initial insufflation pressure. The rocuronium infusions will be prepared in a room away from any of the blinded personnel. The anesthesia providers administering the anesthesia will be aware of the randomization and the dose of rocuronium that the patient is receiving. The TOF watch will be draped so that the surgeons and operating room personnel are unable to observe it during the procedure. The insufflation pressures will also be covered. .

VI. Anesthetic management

a. Monitoring

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

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

1. Premedication – midazolam, 1-2 mg iv in the holding area
2. Preoxygenation with 100% oxygen for a minimum of 3 minutes
3. Induction – propofol, 2 – 2.5 mg/kg, iv and fentanyl, 2-3 micrograms/kg, iv. Additional propofol or fentanyl may be administered at the discretion of the anesthesia provider
4. Intubation – succinylcholine, 1.5 mg/kg, iv after loss of consciousness to facilitate tracheal intubation

5. Maintenance – ventilation with air/oxygen to achieve a $\text{FiO}_2 = 0.6$ and inhaled desflurane adjusted to maintain a BIS® level of 40-60, and fentanyl, 25-50 micrograms iv as needed determined by the anesthesia provider. The FiO_2 of oxygen can also be increased if determined necessary by the anesthesia provider.
6. Maintenance of muscle relaxation – after return of neuromuscular function (return of twitches) after intubation with succinylcholine, patients will be dosed in accordance with their randomization assignment to achieve either moderate or deep NMB during surgery.

c. The rocuronium dosing protocol during the maintenance phase of anesthesia will be:

1. Moderate NMB group [1-3 twitches in the train of four (TOF)] – rocuronium, 0.2 mg/kg iv, followed by a rocuronium infusion which will be started at the appearance of 1 twitch and adjusted to maintain 1-3 twitches throughout the procedure
2. Deep NMB group [0-1 posttetanic count (PTC)] – rocuronium, 0.6 mg/kg iv, followed by a rocuronium infusion at 10 mcg/kg/min. The infusion will be adjusted to maintain 0-1 PTC throughout the procedure.

d. Reversal of NMJ blockade - The rocuronium infusions will be continued until the fascia is closed. At that point, the rocuronium infusions will be discontinued. The level of NMJ block will be assessed with the TOF watch and the patients will be reversed with sugammadex (using actual body weight) after assessment of the TOF ratio. Reversal will be dosed as follows:

1. Deep block (defined as a TOF count of 0 with recovery of 1-2 post-tetanic counts) will be reversed with sugammadex, 4 mg/kg, iv
2. Moderate block (defined as the reappearance of T_2 in the TOF) will be reversed with sugammadex, 2 mg/kg iv

- e. Extubation: Prior to extubation, patients will be following verbal commands (opening eyes, head lift) and will also manifest a sustained tetanic response to ulnar nerve stimulation using a standard neuromuscular stimulator. The information in combination with the clinical judgement of the anesthesia provider will be used to determine the time of extubation. The TOF ratio will not be used to determine when to extubate the patient but the TOF ratio at the time of extubation will be recorded.

VII. Postoperative Pain Management

- a. Acetaminophen, 1000 mg iv, will be given during the maintenance phase and repeated every 6 hours for the first 24 hours after surgery.
- b. Fentanyl PCA will be started in the postanesthesia recovery room and continued for the first 24 – 48 hours after surgery.

VIII. Perioperative assessments

- a. Surgeon satisfaction – the primary endpoint is the surgeon's satisfaction with the level of NMB during surgery at the start of the case (the initial score). The satisfaction level will be rated with a five-point ordinal scale ranging from 1 (extremely poor) to 5 (optimal conditions). This scale is outlined in detail in table 1 (page 15) and is adopted from a previously published studies.⁶ For each patient, the first surgeon satisfaction rating during the procedure (prior to any rescue measure) will be the primary outcome measure.
- b. During the laparoscopic procedure, the surgeon will score the surgical working conditions. The first rating will occur when the NMB level is stable at either deep or moderate block (per randomization) and the intra-abdominal pressure is either 10 or 15 mm Hg per a second randomization list. The surgeon will be blinded to the insufflation pressure at this point. If the conditions are rated as extremely poor or poor (surgical rating of 1-2, Table 1), the following steps will be taken in an incremental manner. The surgeon may also request rescue

treatment if the surgical rating scale is 3 (acceptable), but he anticipates deterioration in the surgical condition during the procedure :

1. Increase the insufflation pressure to a maximum of 15 mm Hg –the surgeon will reassess the surgical field after the intra-abdominal pressure is stable at 15 mm Hg for 2-3 minutes. At this point the insufflation pressure will remain at 15 mm Hg for the remainder of the procedure.
2. Additional muscle relaxation – if the surgeon rates the working conditions as 1 (extremely poor) or 2 (poor) after increasing the insufflation pressure to 15 mm Hg, the surgeon may then request additional muscle relaxant. At this point the anesthesia provider will check the level of NMB. If the patient is in the moderate group and has 1 or more twitches, the anesthesia provider will administer a bolus dose of rocuronium, 0.3 mg/kg iv. If the patient has only 0-1 PTC, the anesthesia provider will administer an equal volume of iv saline. The surgeon will rate the surgical working conditions at 2-3 minutes after the additional dose of medication.

- c. Intra-abdominal insufflation pressures and TOF ratio measurements will be recorded every 15 minutes during the procedure.
- d. Surgeons will be asked to rate their satisfaction with the surgical field every 30 minutes during the procedure.
- e. Perioperative variables will also be recorded including the duration of surgery, time from administration of NMJ reversal (sugammadex) to extubation, time from end of surgery to exit from the OR, time in the PACU, and length of hospital stay.
- f. Postoperative verbal pain levels (0 = no pain to 10 = worst imaginable pain) and opioid requirements will be assessed daily. Patients will also be asked about the presence or absence of shoulder pain.

- g. Postoperative variables including the need for postoperative mechanical ventilation, re-intubation, residual paralysis, pneumonia, infections, and other adverse events during the hospital stay. The need for ICU admission and length of hospital stay will also be collected.

2.6 Study Duration:

The Missouri Bariatric Service at the University of Missouri-Columbia performs over 600 bariatric procedures per year. The Director for this service, Dr. Roger de la Torre, is a co-investigator on the study. He has 3 full day operating blocks per week and we estimate that we can easily enroll 15 patients per month.

We estimate that patient enrollment can be completed in 9 months. We will need an additional 3 months after enrollment is complete for data analysis and abstract/manuscript preparation.

Statistical Analysis and Sample Size Justification:

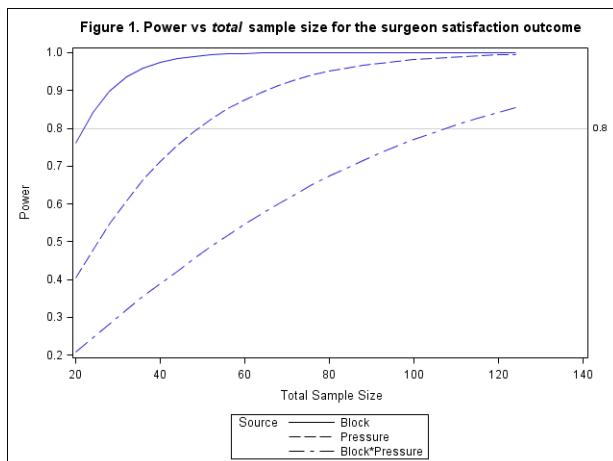
Data analysis will be based on an intent-to-treat approach. The primary endpoint will be the first surgeon satisfaction rating measured on a five-point ordinal scale (Table 1). The experimental layout is a randomized two-factor design so the primary analysis will be the two-way Analysis of Variance (ANOVA) with interaction. A statistically significant interaction will be followed by pairwise comparisons to identify and estimate treatment combination differences. The standard ANOVA assumes a normally distributed outcomes with homogeneous variances and so the robustness of the results will be checked against an aligned-rank test for the two-way layout.¹²

Secondary outcomes will be time to extubation or discharge, and total pain medication requirements. The same two-way analysis as described for surgeon satisfaction will be used for each of these endpoints. Residuals will be examined and need for a modest transformation or rank-based methods considered. Moderate and deep NMB will also be compared with respect to the proportion of cases randomized to low insufflation pressure that were completed at low pressure. The chi-square test of proportions will be used for that analysis.

Sample size – Sample size estimates are based surgeon satisfaction rating as this is the primary outcome. Figure 3 of Martini et al.⁶ gives the frequency distribution of the surgeon satisfaction score under moderate and deep block. Scores for the moderate block have the greatest variability and so for sample size purpose the proportions from Fig. 3 were used to estimate the standard deviation of the surgeon satisfaction score ($\sigma = 1.1$). Based on literature and clinical judgement we powered the study to have at least 80% power to detect statistically significant ($p < 0.05$) effects for the main effects and interaction term in a two-way analysis of variance assuming the following configuration of mean satisfaction scores and a common standard deviation of 1.1.

		Pressure	
		10mmHG	15mmHG
Block	Moderate	2.5	4.0
	Deep	4.3	4.8

Power curves for each of the ANOVA effects are displayed in Figure 1. The required minimum sample size is 108 subjects, allocated 27 per treatment combination. To guard against potential optimism in these calculations (actual variances could be larger or effects smaller) we intend to recruit 35 subject per treatment combination for a total sample size of 140.



Power calculations were carried out using GLMPOWER procedure in SAS v 9.3.

Specific Drug Supply Requirements:

The anesthetic agents utilized in this study (including rocuronium) are routinely used for this type of surgery and are acceptable patient costs. However, sugammadex just received FDA approval in December 2015 and is not currently used for NMB reversal at our institution. We will receive adequate supplies of sugammadex from Merck &Co. so that there will be no charge to the patients for this medication.

2.11 References:

1. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines and the obesity society. *Circulation* 2014; 129:S102-38.
2. Finkelstein EA, Trodron JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer and service-specific estimates. *Health Aff (Millwood)* 2009; 28: w822-w831.
3. Livingston EH, Zylke JW. Progress in obesity research: reasons for optimism. *JAMA* 2012; 308:1162-5.
4. American Society of Metabolic and Bariatric Surgery website. <http://connect.asmbs.org/may-2014-bariatric-surgery-growth.html>, accessed 4/3/2015.
5. Blobner, M. Frick CG, Stäuble RB et al. Neuromuscular blockade improves surgical conditions (NISCO). *Surg Endosc* 2015; 29: 627-36.
6. Martini CH, Boon M, Bevers RF, Aarts LP, Dahan A. Evaluation of surgical conditions during laparoscopic surgery in patients with moderate vs. deep neuromuscular block. *Br J Anaesth* 2013; 112:498-505.
7. Dubois PE, Putz L, Jamart J, Marotta ML, Gourdin M, Donnez O. Deep neuromuscular block improves surgical conditions during laparoscopic hysterectomy. *Eur J Anaesthesiol*. 2014; 31:430-6.
8. Madsen MV, **Caron** M, Veronese S, Foletto M, Ori C.. Neuromuscular blockade for optimising surgical conditions during abdominal and gynaecological surgery: a systematic review. *Acta Anesthesiol Scand* 2015; 59:1-16.
9. Caron M, Veronese S, Foletto M, Ori C. Sugammadex allows fast-track bariatric surgery. *Obes Surg*. 2013; 23:1158-63.
10. Gurasamy KS, Vaughan J, Davidson BR. Low pressure versus standard pressure pneumoperitoneum in laparoscopic cholecystectomy. *Cochrane Database Syst Rev* 2014; 3:CD006930.
11. Kopman AF, Naguib M. Laparoscopic surgery and muscle relaxants: Is deep block helpful? *Anesth Analg* 2015; 120:51-8.
12. H. Mansouri R, Paige L, Surles JG.. Aligned rank transform techniques for analysis of variance and multiple comparisons. *Communications in Statistics - Theory and Methods* 2004; 33:2217-32.

Table 1: The surgical rating scale[£]

- 1. Extremely poor conditions**; the surgeon is unable to work because of coughing or because of the inability to obtain a visible laparoscopic field because of inadequate muscle relaxation. Insufflation pressure must be increased and/or additional neuromuscular blocking agents must be given.
- 2. Poor conditions**; there is a visible laparoscopic field, but the surgeon is severely hampered by inadequate muscle relaxation (continuous muscle contractions, movements or both with the hazard of tissue damage) or inadequate insufflation pressure (inadequate space in the operative field) or both. Insufflation pressure must be increased and/or additional neuromuscular blocking agents must be given.
- 3. Acceptable conditions**; there is an acceptable visible laparoscopic field but muscle contractions, movements or both occur regularly causing some interference with the surgeon's work. The surgeon may request an increase in the insufflation pressure and/or additional neuromuscular blocking agents to prevent deterioration.
- 4. Good conditions**; there is a wide laparoscopic working field with sporadic muscle contractions, movements, or both. There is no immediate need for additional neuromuscular blocking agents or an increase in the insufflation pressure unless there is the fear of deterioration.
- 5. Optimal conditions**; there is a wide visible laparoscopic working field without any movements or contractions. There is no need for additional neuromuscular blocking agents or increased insufflation pressure.

[£]Adapted from reference 6.

2.12 Publication Plan

We plan to present this data at both anesthesia and bariatric surgery meetings. We will target the American Society for Metabolic and Bariatric Surgery and the American Society of Anesthesiologists Annual meetings for abstract presentations and the journal *Anesthesiology* for publication of the final data.