Title: Impact of Sugammadex vs. Neostigmine Reversal on Post-Operative Recovery And Postoperative Complications In Patients With Obstructive Sleep Apnea Undergoing Bariatric Surgery: A Double-Blind, Randomized Controlled Trial

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Objectives

Primary Objective:

To compare the impact of reversal of neuromuscular blockade with sugammadex vs. neostigmine on discharge time from the operating room in obese patients with OSA undergoing bariatric surgery.

Secondary Objectives:

To compare the effect of reversal of neuromuscular blockade with sugammadex vs. neostigmine on time: the patient open eyes to command, extubation, moves independently from the OR table to the bed, TOF at extubation, and the readiness for discharge from PACU of obese patients with OSA undergoing bariatric surgery.

Exploratory Objectives:

To compare the impact effect of reversal of neuromuscular blockade with sugammadex vs. neostigmine on perioperative complications in obese patients with OSA undergoing bariatric surgery.

2.1.1 Hypotheses

1. Reversal of NMBD with sugammadex is associated with faster recovery than neostigmine resulting in faster discharge from the operating room (OR) in obese patients with OSA undergoing bariatric surgery.
2. Reversal of NMBD with sugammadex is associated with faster time for the patient to: open eyes to command, extubation, move independently from the OR table to the bed, higher TOF at extubation, and the readiness for discharge from PACU than neostigmine in obese patients with OSA undergoing bariatric surgery.

Neuromuscular blocking drugs (NMBD) are administered intra-operatively to facilitate intubation and to achieve muscle relaxation for surgical procedures such as laparoscopic bariatric surgery. Traditionally, at the end of surgery, neostigmine - an anticholinesterase is given to reverse NMBD; however reversal of NMBD with neostigmine may be associated with residual neuromuscular blockade in up to 64% patients in the post-anesthesia care unit (PACU).[1,2] Even mild degrees of residual neuromuscular blockade can have serious clinical consequences in the postoperative period.[3,4]

Obstructive sleep apnea (OSA) is a common form of sleep disordered breathing. The prevalence of OSA is estimated to be 71-86% in patients undergoing bariatric surgery.[5,6] The severity of OSA often worsens after surgery[7] and patients with OSA are at increased risk for early respiratory complications after extubation and in the PACU.[8] Morbid obesity is associated with critical respiratory complications in patients with OSA.[7] The increase in early respiratory complications including hypoxemia,[10] emergent re-intubation, and mechanical or non-invasive ventilation[11,12] in patients with OSA may be due to residual neuromuscular blockade. Morbidly obese patients with OSA have anatomical risk factors that increase vulnerability to airway collapse and obstruction of the upper airway placing them at greater risk for postoperative complications from residual neuromuscular blockade, opioids, and anesthetics.

Our systematic review showed that patients with OSA who received NMBD were at higher risk for residual neuromuscular blockade, respiratory failure, and hypoxemia than patients without OSA[13-15] (manuscript under review). The previous studies did not control the amount of opioids administered during the surgery, making it difficult to assess the differential effect of opioids vs. residual neuromuscular blockade on early postoperative respiratory complications. Minimizing the amount of opioids, using short-acting anesthetics, and complete reversal of NMBD in these vulnerable patients may reduce risks for early respiratory complications. Providing a moderate level of muscle relaxation as defined by a TOF count of 1-2 during laparoscopic bariatric surgery optimizes surgical conditions. However, in obese patients with OSA, anesthesiologists often give minimal NMBD in the latter half of the surgical procedure due to concerns about the inability of neostigmine to completely reverse NMBD leading to subsequent respiratory complications after extubation. This practice may reduce the risk for postoperative respiratory complications but can lead to sub-optimal surgical conditions. The usual standard of care is to administer neostigmine to reverse residual neuromuscular relaxant at the end of surgery. For bariatric surgery, in order to minimize risks for postoperative complications, short acting anesthetics and minimal opioids are administered.

Sugammadex is a newer NMBD reversal agent that rapidly and completely reverses rocuronium. It is a modified gamma cyclodextrin that forms a complex with the neuromuscular blocking agent rocuronium. It reduces the amount of neuromuscular blocking agent available to bind to nicotinic cholinergic receptors in the neuromuscular junction. It has been shown to more rapidly reverse residual neuromuscular blockade than neostigmine in obese patients without obstructive sleep apnea (OSA). Two systematic reviews showed that reversal of NMBD with sugammadex is associated with a lower incidence of residual neuromuscular blockade

compared to neostigmine,[16] and fewer composite adverse events.[17] However, the OSA status was not reported in these reviews, limiting the ability to evaluate a differential effect in this sub-population. We have conducted a systematic review (as part of the Society of Anesthesia and Sleep Medicine's guidelines on intraoperative management of OSA patients) showing there are only a few low-quality studies[18,19] that have compared sugammadex with neostigmine in patients with OSA (guidelines manuscript in press, systematic review under review). We identified a knowledge gap and unmet needs in the area of reversal of NMBD for surgical patients with OSA. It is unclear from previous studies whether sugammadex may improve discharge times of patients with OSA from the OR.

Rationale and Significance

The prevalence of OSA has increased over the last two decades, and is likely to continue to increase in association with the rise of the obesity epidemic. There is currently a lack of high-quality evidence (randomized double-blinded trials) to determine whether sugammadex has any advantages over neostigmine in obese patients with OSA. In this study, we will provide a moderate level of muscle relaxation during surgery to optimize surgical conditions, use short-acting anesthetics and minimize intraoperative opioids allowing us to assess the impact of sugammadex vs. neostigmine on postoperative recovery, patient care efficiency, and postoperative complications in patients with OSA. Our study is designed to simulate usual clinical practice, increasing generalizability of our results. Our study will provide evidence for whether sugammadex has any advantages over neostigmine in obese patients with OSA undergoing bariatric surgery. Ensuring that an obese patient with OSA has optimal muscle relaxation and surgical conditions, but is completely reversed after surgery may ensure patient safety, reduce the risks for postoperative respiratory complications in this vulnerable patient population, while at the same time, improving workflow in the operating room (OR), justifying the higher cost of sugammadex.

Study Design

This study is a prospective, double-blinded randomized controlled superiority trial with two parallel groups. Randomization will be performed with a 1:1 allocation into reversal of NMBD with sugammadex or neostigmine. This study will be conducted at Toronto Western Hospital, University Health Network – a Bariatric Centre of Excellence located in Toronto, Ontario, Canada. A total of 120 patients will be included in this study. This study will be registered with clinicaltrials.gov prior to enrolment of participants.

Participants:

Inclusion Criteria: Adult (≥18 yrs.) patients with OSA diagnosed by polysomnography for elective bariatric surgery under general anesthesia.

Exclusion Criteria: Allergy to rocuronium, sugammadex or neostigmine, malignant hyperthermia, hepatic or renal insufficiency, neuromuscular diseases, pregnancy, inability to give consent.

Study Procedures

Screening: Research Ethics Board approval will be obtained from the institution, and informed consent will be obtained from all subjects for participation in this study. A research coordinator will screen patients in the preoperative clinic or bariatric clinic for eligibility criteria and obtain informed consent from participants.

Randomization:

Treatment/Intervention: Patients will be randomized to receive: 1) sugammadex 2 mg/kg actual body weight or 2) neostigmine 2.5 mg and glycopyrrolate 0.4 mg at the end of surgery (defined as “at skin closure”), and the train of four (TOF) stimulation reveals at least 2 responses.

A research analyst who is not involved in the study will create a computer generated randomization list. The patient assignments will be placed in serially numbered, opaque-sealed envelopes corresponding with the randomization schedule. An anesthesiologist who is not involved in administering the anesthetic will open the envelope and prepare the study medication. The study medications will be identical in volume and appearance. The sugammadex will be mixed with saline to produce a volume equivalent to the neostigmine/glycopyrrolate dose. The dose of neostigmine - 2.5 mg will be used In order to simulate real clinical practice since this dose is the standard dose used to reverse NMBD when the TOF shows at least 2 responses at most institutions including ours.

All study investigators, research coordinators, patients, surgeons, anesthesiologists, health care personnel will be blinded to the treatment arm allocation.

Perioperative Management:

The perioperative management of patients in both groups will be identical except for the administration of NMBD reversal agent. There will be no change in the usual surgical or postoperative management of patients. The intraoperative abdominal pressures will be recorded at 10-minute intervals.

Anesthetic management will be standardized. Routine monitors including electrocardiography, pulse oximetry, noninvasive blood pressure, and capnography will be applied. The depth of anesthesia will be monitored using entropy – an electroencephalography based method for determining hypnotic levels. Neuromuscular function will be assessed using the GE Healthcare NeuroMuscular Transmission (NMT) module. The ElecroSensor will be used with the electrodes placed over the ulnar nerve. The TOF count will be assessed by delivering a train of four impulses 500 milliseconds apart (2 Hz) at 80 mA with a pulse width of 200 microseconds.

After 3-5 minutes of preoxygenation with 100% oxygen by face mask with the patient on a TROOP elevation pillow, general anesthesia will be induced using propofol (2.5-3 mg/kg) based on the lean scaled weight (LSW), , fentanyl (1-2 mcg/kg), rocuronium (0.6 mg/kg) – LSW, ± 30-50 mcg remifentanil. The LSW will be determined using the following formulas; for men: LSW = 11,432 x total body weight/(6,680 + 216 x body mass index); for women: LSW = 14, 148 x total body weight/(8,780 + 244 x body mass index).[20,21]

General anesthesia will be maintained with desflurane – an inhalational volatile anesthetic that has a low blood gas partition coefficient allowing rapid recovery and emergence from general anesthesia. Desflurane will be adjusted to maintain the age-adjusted minimum alveolar concentration (MAC) between 0.9 – 1.2. The inspired oxygen concentration will be 50-60% with an air mixture to maintain an oxygen saturation >96%. Additional doses of fentanyl 25-50 mcg may be administered intraoperatively at the discretion of the anesthesiologist Up to 1mg of hydromorphone may be administered intraoperatively. As per standard practice, local infiltration with bupivacaine – a long acting local anesthetic will be administered at the beginning of surgery to reduce postoperative pain and the amount of opioids required. Additional doses of 10 mg rocuronium will be given as needed to maintain a moderate level of muscle relaxation (TOF count of 1-2) or as requested by the surgeon. Prophylactic antiemetic medications will be given as per usual practice. The total doses of all medications administered intraoperatively will be recorded.

Five minutes before the end of surgery, desflurane will be titrated to an age-adjusted MAC of 0.7-0.8. As per usual clinical practice, at the end of surgery, defined as at skin closure, the NMBD reversal agent will be administered when the TOF reveals at least 2 responses. Desflurane will be discontinued, and the fresh gas flow will be increased to 15L/min. The TOF ratio will be recorded prior to administration of NMBD reversal agent, and at 15-second intervals until prior to extubation. The anesthesiologist will be aware of the TOF prior to administration of NMBD reversal agent.

In order to simulate typical clinical practice, the anesthesiologist will not be aware of the TOF ratio when considering extubation but the patient will be extubated based on the clinical judgment of the attending anesthesiologist based on whether the patient is awake, opens eyes to command, has good hand grip strength, sustained head lift for >5 seconds, is stable hemodynamically, is breathing spontaneously with an expired tidal volume between 5 and 8 ml/kg, respiratory rate between 12 and 25 breaths/min, and maintaining oxygen saturation ≥97%. The TOF ratio will be recorded prior to and at the time of extubation. As per usual clinical practice for bariatric patients at this institution, the patient will be asked to move independently from the OR table to the bed. The patient will be discharged from the OR to PACU when they are awake, responding to commands, has stable vital signs, is breathing spontaneously and maintaining oxygen saturation ≥97% with supplemental oxygen via a face mask. Episodes of upper airway obstruction, hypoxemia and need for interventions after extubation will be recorded. If incomplete NMBD reversal is suspected after extubation, the anesthesiologist will be informed of the TOF ratio.

The vital signs including heart rate, oxygen saturation, respiratory rate, blood pressure, pain scores, nausea/vomiting and level of sedation (Ramsey Scale)[22] will be recorded in the PACU. All complications including episodes of upper airway obstruction, hypoxemia, respiratory failure will be recorded.

The time from administration of NMBD reversal agent to the time the patient is extubated, moves from the OR table to the bed, is discharged from the OR, and is ready for discharge from PACU will be recorded. The time from first incision to extubation, time from first incision to OR discharge, total time in the operating room, time to readiness for discharge from PACU (achieving a modified Aldrete score ≥ 9),[23] actual length of stay in PACU, and duration of hospital stay will be recorded. Postoperative abdominal and shoulder tip pain scores and opioid consumption while in hospital will be recorded.

Postoperatively, patients will be monitored with continuous pulse oximetry on the ward as per usual care for bariatric patients. All in-hospital complications including length of stay will be recorded.

Outcomes:

The primary outcome will be the time from administration of NMBD reversal agent to discharge from the OR.

The secondary outcomes will include the time from administration of NMBD reversal agent to the time: the patient open eyes to command, extubation, moves independently from the OR table to the bed, TOF prior to and at the time of extubation, and the readiness for discharge from PACU. Other evaluated outcomes will include all in-hospital complications including cardiovascular complications (tachycardia, bradycardia, hypertension, hypotension, myocardial ischemia or infarction, etc.), and respiratory complications (hypoxemia, airway obstruction, aspiration, need for re-intubation, etc.), and length of stay.

Study Duration

The recruitment of the participants will occur over a period of 15 months beginning on January 14, 2019 and continue until April 15, 2020. The follow-up for all patients will be completed by May 15, 2020. The study data will be analyzed by a statistician who is blinded to the treatment allocation. Unless a serious adverse event occurs that is deemed by the PI to be possibly related to the study drug – necessitating unblinding, blinding will be maintained until the study statistician cleans the data. The data cleaning, analysis, and preparation of the manuscript will require 4 months.

Statistical Methods

The primary outcome – time from administration of NMBD reversal agent to discharge from the OR will be compared and the difference will be assessed with student t-test (parametric data) or Wilcoxon-Mann-Whitney test (non-parametric data) as appropriate. An intention-to-treat analysis will be conducted to compare the two groups. Statistical significance will be assessed using two-sided tests with P values < 0.05 considered significant for all comparisons.

The secondary outcomes for this study include the time from administration of NMBD reversal agent to the time: the patient opens his/her eyes to verbal command, extubation, the patient moves from the OR table to the bed, TOF prior to and at extubation, readiness for discharge from PACU will be assessed using student t-test (parametric data) or Wilcoxon-Mann-Whitney test (non-parametric data) as appropriate**.**

The study is not powered to detect a difference in complications since complications are rare, however, other outcomes including**:** signs of residual neuromuscular blockade, and all in-hospital complications will be summarized (numbers and rates of events) and the comparison of differences in frequency of each outcome in both groups will be assessed by using Chi-Square test.

Demographic data, vital signs, intra-abdominal pressures, pain, all medications administered to patients in both groups will be summarized using summary statistics for continuous variables.

The time from first incision to extubation, time from first incision to OR discharge, total time in the operating room, time to readiness for discharge from PACU, actual length of stay in PACU, and duration of hospital stay will be described using summary statistics. To compare the mean time for the above events between the two groups of reversal agents, a student t-test (parametric data) or Wilcoxon-Mann-Whitney test (non-parametric data) will be used as appropriate.

Sample Size

The estimation of sample size is based on the primary outcome of time from administration of the reversal agent until discharge from the OR. There are no previous studies comparing sugammadex to neostigmine for obese patients with OSA undergoing bariatric surgery. However, a previous study comparing sugammadex vs. neostigmine for discharge readiness from the OR to PACU reported discharge times for sugammadex vs. neostigmine of 9.15 ± 4.23 vs. 13.87 ± 11.47 minutes.[24] Using a minimal clinically acceptable difference of 5 minutes, assuming a power of 0.90, and a two-sided level of

significance of alpha =0.05, a total sample size of 120 patients (60 in each group) is required. Given the short duration of follow up, no adjustment is made for potential dropouts.

Drug Handling

Open-label supplies of sugammadex for 60 patients will be provided from Merck. Clinical supplies will be received by the PI at the study site, handled and stored safely and properly, and kept in a secured location to which only the study investigators and designated research coordinators have access. Clinical supplies will be dispensed in accordance with the protocol. The PI and co-investigators will be responsible for keeping accurate records of the clinical supplies, the amount dispensed to and returned by the patients, and the disposition at the end of the study. The study medication will be handled and stored safely and properly according to ICH/GCP Guidelines and the institutional policies. At the end of the study, the PI will be responsible for the destruction of the supplies at the study center pursuant to the ICH/GCP Guidelines, local regulations and the PI's institutional policies.

Potential Risks

There are no anticipated risks expected with this study as the administration of reversal agents is consistent with standard practice. Sugammadex is approved by Health Canada for reversal of NMBD, but is not used routinely due to the higher cost compared to neostigmine. Sugammadex may reduce the effectiveness of birth control pills or non-oral hormonal contraception for up to 7 days. Female patients with child-bearing potential using birth control pills or non-oral hormonal contraception should use an additional, non-hormonal contraceptive for the next 7 days after their surgery.

Adverse Experience Reporting

All adverse events will be recorded and serious adverse events will be reported to the institutional REB.

Direct Access to Source Data/Documents

Health information will only be shared with members of the research team. Original study forms and research charts will be kept on file at the participating study site.

Data Handling and Record Keeping

All paper based documents and data will be stored in a locked cabinet in a locked research office. Electronic data will be stored in a password-protected electronic database that will be stored on the departmental network drive and only be accessible via password-protected departmental computers. A study code ID will be used to identify all participants, instead of names. The participants' personal identifying information and names will be stored separately from the study data. Only the principal investigator, co-investigators, research assistants, and research statistician will have access to the final trial dataset.

Financing and Insurance

This study will be supported by a research grant from Merck Canada.

Publication Policy

Research study results will be presented for publication in peer reviewed journals and research study meetings. Participants will be asked whether they would like to receive a copy of the research publication.

References

1. Fortier L-P, McKeen D, Turner K, de Medicis E, Warriner B, Jones PM, Chaput A, Pouliot J-F, Galarneau A. The RECITE study: a Canadian prospective, multicenter study of the incidence and severity of residual neuromuscular blockade. Anesth Analg 2015; 121:366-72.

2. Murphy GS, Brull SJ. Residual neuromuscular block: lessons unlearned. Part I: definitions, incidence, and adverse physiologic effects of residual neuromuscular block. Anesth Analg 2010;111:120-8.
3. Fuchs-Buder T, Nemes R, Schmartz D. Residual neuromuscular blockade: management and impact on postoperative pulmonary outcome. Curr Opin Anesthesiol 2016; 29:662-7.
4. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS. Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit. Anesth Analg 2008;107:130-7.

5. Ravesloot MJ, van Maanen JP, Hilgevoord AA, van Wagensveld BA, de VN. Obstructive sleep apnea is underrecognized and underdiagnosed in patients undergoing bariatric surgery. Eur Arch Otorhinolaryngol 2012;269:1865-1871.
6. Sharkey KM, Machan JT, Tosi C, Roye GD, Harrington D, Millman RP. Predicting obstructive sleep apnea among women candidates for bariatric surgery. J. Womens Health (Larchmt.) 2010;19:1833-1841.
7. Chung F, Liao P, Elsaid H, Shapiro CM, Kang W. Factors associated with postoperative exacerbation of sleep-disordered breathing. Anesthesiology 2014; 120:299-311.
8. Opperer M, Cozowicz C, Bugada D, Mokhlesi B, Kaw R, Auckley D, Chung F, Memtsoudis SG. Does Obstructive Sleep Apnea Influence Perioperative Outcome? A Qualitative Systematic Review for the Society of Anesthesia and Sleep Medicine Task Force on Preoperative Preparation of Patients with Sleep-Disordered Breathing. Anesth Analg 2016;122:1321-34.
9. Subramani Y, Nagappa M, Wong J, Patra J, Chung F. Death or near-death in patients with obstructive sleep apnoea: a compendium of case reports of critical complications. Br J Anaesth 2017; 1-15.
10. Kaw R, Chung F, Pasupuleti V, Mehta J, Gay PC, Hernandez AV. Meta-analysis of the association between obstructive sleep apnoea and postoperative outcome. Br J Anaesth 2012;109:897-906.
11. Mokhlesi B, Hovda MD, Vekhter B, Arora VM, Chung F, Meltzer DO. Sleep-disordered breathing and postoperative outcomes after bariatric surgery: Analysis of the nationwide inpatient sample. Obes Surg 2013; 23:1842-51.
12. Memtsoudis SG, Stundner O, Rasul R et al. The impact of sleep apnea on postoperative utilization of resources and adverse outcomes. Anesth Analg 2014; 118:407-18.
13. Ahmed S, Nagle A, McCarthy R, Fitzgerald PC, Sullivan JT, Prystowsky J. Postoperative hypoxemia in morbidly obese patients with and without obstructive sleep apnea undergoing laparoscopic bariatric surgery. Anesth Analg 2008; 107:138-43.
14. Pereira H, Xara D, Mendonca J, Santos A, Abelha FJ. Patients with a high risk for obstructive sleep apnea syndrome: Postoperative respiratory complications. Rev Port Pneumol 2013; 19:144-151.
15. Sudré ECM, De Batista PR, Castiglia YMM. Longer immediate recovery time after anesthesia increases risk of respiratory complications after laparotomy for bariatric surgery: A Randomized Clinical Trial and a Cohort Study. Obes Surg 2015; 25:2205-12.
16. Abad-Gurumeta A, Ripolles-Melchor J, Casans-Frances R, Espinosa A, Martinez-Hurtado E, Fernandez-Perez C, Ramirez JM, Lopez-Timoneda F, Calvo-Vecino JM. A systematic review of sugammadex vs neostigmine for reversal of neuromuscular blockade. Anaesthesia 2015;70:1441-52.

17. Hristovska AM, Duch P, Allingstrup M, Afshari A. Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults. Cochrane Database Syst Rev 2017;8:Cd012763.
18. Unal DY, Baran I, Mutlu M, Ural G, Akkaya T, Ozlu O. Comparison of sugammadex versus neostigmine costs and respiratory complications in patients with obstructive sleep apnoea. Turk J Anaesth Reanim 2015; 43:387-95.
19. Llaurado S, Sabate A, Ferreres E, Camprubi I, Cabrera A. Postoperative respiratory outcomes in laparoscopic bariatric surgery: Comparison of a prospective group of patients whose neuromuscular blockade was reverted with sugammadex and a historical one reverted with neostigmine. Rev Esp Anestesiol Reanim 2014; 61:565-70.
20. Friesen JHP. Lean-scaled weight: a proposed weight scalar to calculate drug doses for obese patients. Can J Anaesth. 2013 Feb;60(2):214–5.
21. Friesen JHP. Lean Body Weight Is Not a Weight Scalar for Estimating Drug Doses in Morbid Obesity. Obes Surg. 2015;25(8):1496–7.
22. Ramsay MAE, Savege TM, Simpson BRJ & Goodwin R. Controlled sedation with alpaxalone-alphadolone. BMJ 1974; 2: 656-659.
23. Aldrete JA. The post-anesthesia recovery score revisited. J Clin Anesth 1995; 7:89-91.
24. Putz L, Dransart C, Jamart J, Marotta ML, Delnooz G, Dubois PE. Operating room discharge after deep neuromuscular block reversed with sugammadex compared with shallow block reversed with neostigmine: a randomized controlled trial. Journal of Clinical Anesthesia 2016;35: 107–113.

Study Flowchart