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REPORTS OF ORIGINAL INVESTIGATIONS

A randomized-controlled trial of sugammadex *versus* neostigmine: impact on early postoperative strength

Une étude randomisée contrôlée comparant le sugammadex à la néostigmine : impact sur la force postopératoire initiale

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Abstract

Background *Residual neuromuscular blockade after surgery is associated with airway obstruction, hypoxia, and respiratory complications. Compared with neostigmine, sugammadex reverses neuromuscular blockade to a train-of-four ratio > 0.9 more rapidly. It is unknown, however, whether the superior reversal profile of sugammadex improves clinically relevant measures of strength in the early postoperative period.*

Methods *Patients undergoing general, gynecological, or urologic surgery were randomized to receive either neostigmine (70 $\mu g \cdot kg^{-1}$, maximum 5 mg) or sugammadex (2 or 4 $mg \cdot kg^{-1}$) to reverse neuromuscular blockade. The primary outcome was the ability to breathe deeply measured by incentive spirometry at 30, 60, and 120 min after reversal.*

Results *We randomized 62 patients to either a neostigmine (n = 31) or sugammadex (n = 31) group. The incentive spirometry volume recovery trajectory was not different between the two groups (P = 0.35). Median spirometry volumes at baseline, 30, 60, and 120 min postoperatively were 2650 vs 2500 mL, 1775 vs 1750 mL, 1375 vs 2000 mL, and 1800 vs 1950 mL for the sugammadex and neostigmine groups, respectively. Postoperative incentive spirometry decrease from baseline was not different between the two groups. Hand grip strength, the ability to sit unaided, train-of-four ratio on postanesthesia care unit (PACU) admission, time to extubation, time to PACU discharge readiness, and Quality of Recovery-15 scores were also not different between the groups.*

Conclusions *Measures of postoperative strength, such as incentive spirometry, hand group strength, and the ability to sit up in the early postoperative period were not different in patients who received neostigmine or sugammadex for the reversal of neuromuscular blockade.*

Trial registration *www.clinicaltrials.gov (NCT02909439); registered: 21 September, 2016.*

Résumé

Contexte *Les blocs neuromusculaires résiduels après une chirurgie sont associés à l'obstruction des voies aériennes, à l'hypoxie et à des complications respiratoires. Par rapport à la néostigmine, le sugammadex neutralise le bloc neuromusculaire à un ratio de train-de-quatre (TOF) > 0,9 plus rapidement. Nous ne savons toutefois pas si le profil de neutralisation supérieur du sugammadex améliore les mesures pertinentes d'un point de vue clinique de la force en période postopératoire initiale.*

Méthode *Nous avons randomisé des patients subissant une chirurgie générale, gynécologique ou urologique à recevoir de la néostigmine (70 $\mu g \cdot kg^{-1}$, maximum 5 mg) ou du sugammadex (2 ou 4 $mg \cdot kg^{-1}$) pour neutraliser le bloc neuromusculaire. Le critère d'évaluation principal était la capacité des patients à respirer profondément telle que mesurée par spirométrie incitative à 30, 60 et 120 min après la neutralisation.*

Résultats *Au total, 62 patients ont été randomisés dans les groupes néostigmine (n = 31) ou sugammadex (n = 31). Aucune différence dans la trajectoire de récupération de volume de spirométrie incitative n'a été observée entre les deux groupes (P = 0,35). Les volumes médians de spirométrie préopératoire et à 30, 60 et 120 min postopératoires étaient de 2650 vs 2500 mL, 1775 vs*

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1750 mL, 1375 vs 2000 mL, et 1800 vs 1950 mL pour les groupes sugammadex et néostigmine, respectivement. La diminution postopératoire de la spirométrie incitative par rapport aux valeurs de base était similaire dans les deux groupes. La force de préhension, la capacité à s'asseoir sans assistance, le ratio de train-de-quatre à l'admission à la salle de réveil, le délai jusqu'à l'extubation, le délai jusqu'à l'obtention des critères de congé de la salle de réveil et les scores de QoR-15 (mesurant la qualité de récupération) ne différaient pas non plus entre les groupes.

Conclusion *Les mesures de la force postopératoire, telles que la spirométrie incitative, la force de préhension et la capacité de s'asseoir en période postopératoire initiale, ne différaient pas entre les patients ayant reçu de la néostigmine ou du sugammadex pour neutraliser le bloc neuromusculaire.*

Enregistrement de l'étude *www.clinicaltrials.gov (NCT02909439); enregistrée le 21 septembre 2016.*

Anesthesiologists routinely administer neuromuscular blocking drugs to facilitate endotracheal intubation and optimize surgical operating conditions. Residual neuromuscular blockade after surgery has been associated with adverse patient outcomes including airway obstruction, hypoxia, respiratory complications, and symptoms of muscle weakness and dyspnea.[1] The use of neuromuscular blockade, especially without reversal, has been associated with an increased risk of postoperative pneumonia.[2]

Administering anticholinesterase agents, such as neostigmine, has been the standard method for reversing neuromuscular blockade. Anticholinesterase agents have been associated with a high rate of residual neuromuscular blockade (train-of-four ratio [TOFR] < 0.9) at the time of extubation and at postanesthesia care unit (PACU) admission.[3] Within routine clinical practice, the Residual Curarization and its Incidence at Tracheal Extubation study found that 65% of patients had a TOFR < 0.9 and 31% had a much more concerning TOFR < 0.6 at the time of tracheal extubation.[4]

Sugammadex, a newer agent approved by the United States Food and Drug Administration in 2015, is a cyclodextrin molecule that encapsulates rocuronium bromide, facilitating reversal of paralysis via a mechanism different to that of traditional anticholinesterase agents.[5] Compared with neostigmine, sugammadex reverses neuromuscular blockade to a TOFR of > 0.9 faster and more reliably, especially from profound block.[6] Sugammadex also reverses paralysis more quickly (2 min *vs* 12.9 min) from intermediate blockade (2 twitches on the train-of-four) than neostigmine does.[7] Sugammadex also reverses paralysis significantly faster (2 min *vs* 48.8 min) from deep blockade (post-tetanic count of 1 to 5).[7] Residual neuromuscular blockade, as defined by a TOFR $<$ 0.9 on admission to the PACU, was observed in 43% of patients reversed with neostigmine compared with 0% of patients reversed with sugammadex.[8] Some interpret this study to suggest that patients administered sugammadex were stronger in the PACU, however, this and other studies have largely focused on TOFR, and have not assessed clinically relevant endpoints, such as breathing capacity, ability to sit up unaided, aspiration, and postoperative pneumonia.

Therefore, we conducted a randomized-controlled trial to compare the impact of sugammadex and neostigmine on clinical outcomes of strength, such as the ability to breathe deeply using incentive spirometry, handgrip strength, and the ability to sit unaided. Our hypothesis was that patients who received sugammadex would have superior strength in clinical endpoints during the early postoperative period.

Methods

Study design and patient selection

This was an investigator-initiated, randomized-controlled, assessor-blinded trial conducted at Stony Brook University Medical Center. This study was approved by Stony Brook University Institutional Review Board (IRB 917402-12), and a research coordinator obtained written consent from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT 02909439, Principal investigator: Ramon Abola, Date of registration: September 21, 2016). The first patient was enrolled on December 20, 2016. The manufacturer of sugammadex (Merck Sharp & Dohme Corp) provided this medication and partially funded this trial through their Investigator-Initiated Studies Program, but they had no role in the conduct of the study, including data collection, statistical analyses, and preparation of the manuscript.

Inclusion criteria included age $\geq$ 18 yr, American Society of Anesthesiologists (ASA) class I, II, or III, planned use of neuromuscular blocking drugs, planned use of endotracheal intubation, and planned extubation in the operating room. Exclusion criteria included known or suspected neuromuscular disorder impairing neuromuscular function, allergy to muscle relaxants, a personal or family history of malignant hyperthermia, a contraindication for neostigmine or sugammadex administration, a serum creatinine of > 2.0 mg·dL^{-1} (177 μmol·L^{-1}), surgery where the patient's arm would not

available for neuromuscular monitoring, and a plan to extubate under deep anesthesia.

Anesthesia

Induction and maintenance of general anesthesia were at the discretion of the providing anesthesiologist. Recommendations were made to standardize doses of midazolam (2 mg prior to induction of general anesthesia) and fentanyl (1–3 $\mu g \cdot kg^{-1}$ at induction and 1–2 $\mu g \cdot kg \cdot hr^{-1}$ during surgery). Additional fentanyl or other opioids could be administered when the anesthesiologist deemed it appropriate. Rocuronium was the only nondepolarizing neuromuscular agent utilized in all study patients. In all patients, the depth of neuromuscular blockade was measured with a peripheral nerve stimulator at the ulnar nerve on one arm and with a TOF-Watch SX acceleromyograph at the ulnar nerve of the other arm. For all patients, the TOF-Watch SX was calibrated during induction of anesthesia to measure the TOF ratio at the time of PACU admission. Anesthesiologists were asked to maintain a neuromuscular blockade depth of 1–2 twitches on the TOF monitor during maintenance of anesthesia.

Patients were given their assigned reversal agent (neostigmine or sugammadex) at the end of wound closure (i.e., last suture or last staple). Patients were extubated based on the following criteria: awake and following simple commands, hemodynamically stable, adequate muscle strength (five-second head lift or sustained tetanus without fade), spontaneous breathing with acceptable oxygenation and ventilation ($\geq$ 8 $breaths \cdot min^{-1}$, and tidal volume $> 5\ mL \cdot kg^{-1}$). Train-of-four ratio values were available for the clinical teams during emergence from anesthesia, but they were not used as extubation criteria. Our extubation criteria were designed to reflect routine anesthesia care, as acceleromyography is not widely available for clinical use.

Randomization, allocation concealment, and blinding

Patients were randomized (1:1) to receive either sugammadex ($2\ mg \cdot kg^{-1}$ for 2-4 twitches on TOF or 4 $mg \cdot kg^{-1}$ for $<$ 2 twitches on TOF) or neostigmine (70 $\mu g \cdot kg^{-1}$, max 5 mg) with glycopyrrolate (10 $\mu g \cdot kg^{-1}$). Patients were randomized using a sealed envelope technique. Randomization was stratified by the case duration (cases scheduled for $<$ three hours and cases scheduled for $\geq$ three hours).

The patients were blinded to their reversal assignment. A research coordinator opened the sealed opaque envelope to determine study arm assignment. The reversal drug was brought to the anesthesia team in an opaque plastic bag within a plastic box provided by our research pharmacist. To prevent study group assignment from affecting the anesthesia care, the anesthesia team was blinded to reversal assignment until 15 min prior to the expected end of surgery. Reversal of neuromuscular blocking drugs was given at the end of wound closure.

Outcomes and data collection

Preoperative information was collected for each patient including age, body mass index, medical comorbidities, sex, ASA class, and race/ethnicity. In the preoperative holding area, baseline measurements of the ability to sit up, hand grip using a Jamar dynamometer (JLW Instruments, Chicago, IL, USA), and incentive spirometry volumes using a Voldyne 5000 (Teleflex, Morrisville, NC, USA) were taken. Intraoperative data were collected by an unblinded member of the study team. The patient was assessed in the PACU by a research coordinator/assistant blinded to the patient's randomization. The research coordinator/assistant was not directly involved in the patient's care.

Our primary outcome was the recovery trajectory of incentive spirometry volumes at 30, 60, and 120 min from the reversal of neuromuscular blockade. Patients were sitting at a 45° angle in a stretcher for all incentive spirometry measurements. For each measurement, the patient performed three incentive spirometry measurements and the highest value was recorded.

Train-of-four count was measured immediately prior to sugammadex or neostigmine administration and TOFR was measured at the time of PACU admission using the TOF-Watch SX (Organon, Dublin, Ireland). Hand grip strength was measured with the Jamar dynamometer at 30, 60, and 120 min after reversal of neuromuscular blockade. Patients performed three handgrip assessments at each time point with a 30-sec rest in between each attempt. The highest value was recorded. The ability to sit independently was measured at 30, 60, and 120 min after reversal. Patients were assessed if they were able to sit from a supine position with their head elevated 30° with allowance to use the bed rails. The level of sedation using the Richmond Agitation Sedation Scale (RASS)[9] was measured at 30, 60, and 120 min after reversal of neuromuscular blockade. Time to PACU discharge readiness was assessed by the PACU nursing staff using the Aldrete score.[10] Twenty-four hours after surgery, patients completed a Quality of Recovery-15 survey (QoR-15)[11] either in person (if still hospitalized) or via telephone from a research coordinator/assistant blinded to the patient's study arm assignment. Data were prospectively collected and entered into a study database (Microsoft Access, Microsoft, Redmond WA, USA).

Statistical methods

All statistical analyses were performed by the trial's statistician (J.R.) using Statistical Analysis Software (Cary, NC, USA). Our hypothesis was that patients reversed with sugammadex would be able to breathe more deeply compared with patients reversed with neostigmine. Our secondary hypotheses was that patients would have stronger handgrip and would be able to sit independently earlier if reversed with sugammadex.

Recovery at each time point was defined by the difference from baseline. The prespecified primary outcome was the difference in recovery trajectories for incentive spirometry between the two drugs. A linear mixed model with Kenward–Roger degrees of freedom and an autoregressive covariance structure (based on minimization of the Akaike information criterion) was used to assess differences in trajectories over time between the two groups. In addition, changes from the baseline spirometry score were calculated for each patient. Incentive spirometry and change in incentive spirometry from baseline were compared by study drug at each time point using Wilcoxon rank-sum tests. Each variable was tested for normality using the Shapiro–Wilk test.

The primary population for data analysis was an "intention to treat" grouping. Our secondary population for analysis was an "actual medication received." In the secondary population analysis, patients were grouped according to the reversal agent they received.

For statistical testing of secondary endpoints, a Bonferroni correction for multiplicity was used; each secondary outcome was tested at an alpha of 0.008 (0.05/6 = 0.008) for level of significance. Grip strength and change in grip strength from baseline were compared by drug at each time point using *t* tests. The ability to sit independently, time to extubation, time to PACU discharge readiness, QoR-15 survey, and TOFR on PACU admission were compared by drug using Chi square, Fisher's exact, or Wilcoxon rank-sum tests. Effect sizes for normally distributed variables were calculated as the difference between group means with a 95% confidence interval (CI). Effect sizes for non-normal variables were calculated by bootstrapping a difference in medians with a bootstrapped 95% CI.[12] Effect sizes for categorical variables were calculated as a relative risk with a 95% CI.

For our sample size calculation, we anticipated that patients would have a preoperative incentive spirometry volume of 2,200 mL and a postoperative incentive spirometry volume of 1,540 mL after reversal with neostigmine (control group). These volumes were based on previous measurements of inspiratory reserve capacity before and after surgery.[13,14] We deemed a 20% difference to be clinically significant; therefore, we hypothesized that use of sugammadex would translate to a 300 mL increase in inspiratory spirometry volume (1,840 mL *vs* 1,540 mL). Assuming a power of 80% and an alpha of 0.05, the number of patients needed per study group was 30.

Results

Demographics and perioperative characteristics

Eighty patients consented to participate between December 20 2016 and November 8 2017. As shown in Fig. 1, 18 patients were not randomized: ten patients did not continue to meet inclusion/exclusion criteria, three patients withdrew from the study prior to randomization, and five patients were not randomized because of scheduling and weather (i.e., blizzard) related issues. Sixty-two patients were randomized with 31 assigned to receive neostigmine and 31 assigned to receive sugammadex. Two cross-over patients received sugammadex instead of neostigmine per the attending anesthesiologist's wishes. In these cases, the primary anesthesiologist felt that because of patient factors or depth of neuromuscular blockade, reversal with neostigmine was inappropriate.

The groups were not different with respect to age, weight, body mass index, ethnicity, ASA classification, or surgical division (Table 1). Medical comorbidities including coronary artery disease and hypertension were not different between the groups; however, there were more diabetic patients in the neostigmine group. Baseline incentive spirometry volumes and grip strength measurements were also not different. All patients were able to sit up unaided prior to surgery.

Intraoperative management was not different between the two groups with respect to duration of surgery and propofol, opioid, rocuronium, and fluid administration (Table 2). For maintenance of anesthesia, a volatile agent (sevoflurane or desflurane) was used more often in the sugammadex group and a combination of volatile plus propofol was used more often in the neostigmine group. The depth of neuromuscular blockade was sufficient for surgery. There were only two surgeries where a deeper block was requested. TOF was measured when the neuromuscular blockade was reversed. A slightly higher portion of neostigmine patients had a TOF in the 2–4 twitch range: sugammadex: 0–1 twitch, $n = 14$ (45%); 2–4 twitches, $n = 17$ (54%); neostigmine: 0–1 twitch, $n = 8$ (26%); 2–4 twitches, $n = 22$ (71%). Because of a logistical issue, TOF information was not collected on one patient from the neostigmine group.

The time from reversal to PACU admission was not different between the groups. We assessed levels of alertness in the PACU using the RASS score to

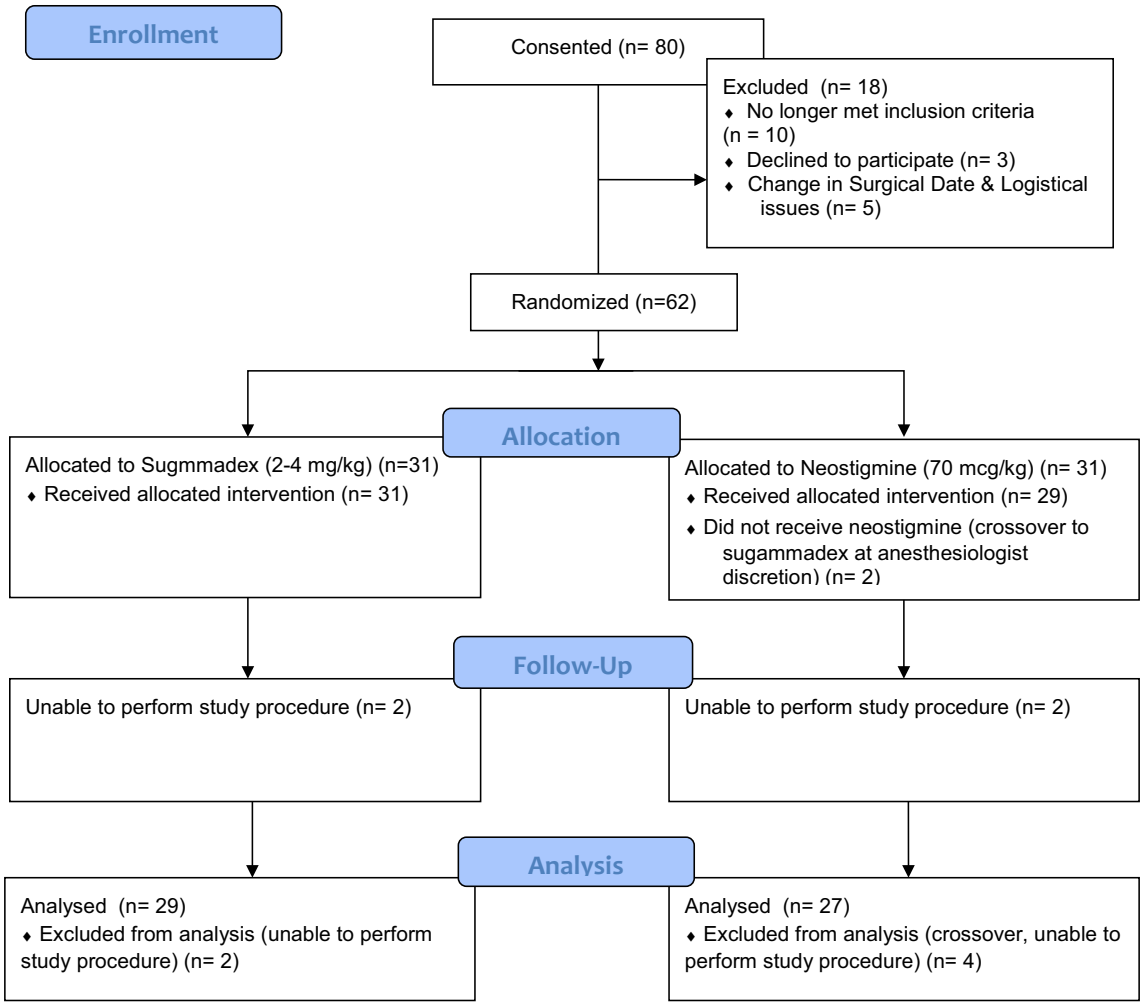

Fig. 1 CONSORT flow diagram

determine if the two study arms were balanced. The RASS scores were not different between the two groups at the PACU assessment times of 30, 60, and 120 min after reversal of neuromuscular blockade. There were no adverse events determined to be related to the reversal of neuromuscular blockade.

Primary outcome

As expected, spirometry volumes were lower after anesthesia and surgery compared with baseline (Fig. 2). Some patients could not do incentive spirometry in the first 120 min after reversal of neuromuscular blockade because of significant sedation or pain. This was observed to a similar degree in both study arms: the 30, 60, and 120 min time periods had 39 patients (sugammadex group = 18, neostigmine group = 21), 54 patients (sugammadex = 29, neostigmine = 25), and 54 patients (sugammadex =27, neostigmine = 27), respectively, who were able to perform these assessments.

With respect to the primary endpoint, using a mixed models approach, there was no statistical difference (P = 0.35) in the recovery trajectory between the two groups (Fig. 2). To confirm this result, further analyses found no difference between the two groups at each individual time point (30, 60, and 120 min after reversal) with respect to decrease in incentive spirometry from baseline or absolute incentive spirometry volumes. The sugammadex arm was not superior to neostigmine with respect to reduced incentive spirometry volumes between the two groups for any of the three postoperative time points (Fig. 2, Table 3). Secondary population analysis using "actual medication received" grouping, in which the two cross-over patients were included in the sugammadex arm, was not different from our prespecified intent to treat analysis.

Table 1 Demographics and intraoperative data

	Sugammadex $n = 31$	Neostigmine $n = 31$
Age, yr	54.4 (13.5)	53.1 (13)
Weight, kg	96.6 (21.0)	97.6 (23.1)
BMI, $kg \cdot m^{-2}$	33.6 (7.7)	33.9 (7.6)
Sex, male/female	15 (48)/16 (52)	14 (45)/17 (55)
Ethnicity		
Black, African American	3 (9.7)	2 (6.5)
White, Caucasian	28 (90)	28 (90)
Other	0 (0)	1 (3)
Medical comorbidities		
Coronary artery disease	2 (6.5)	0 (0)
Hypertension	9 (29)	13 (42)
Diabetes	3 (9.7)	8 (26)
ASA classification		
II	10 (32)	15 (48)
III	21 (67)	16 (52)
Surgery		
General	20 (64)	19 (61)
Gynecology	8 (26)	9 (29)
Urology	3 (10)	3 (10)
Baseline incentive spirometry, mL	2650 [2250–3500]	2500 [2100–3500]
Baseline grip strength, pounds	74 (28)	77 (28)
Preoperative ability to sit up	31 (100)	31 (100)

ASA = American Society of Anesthesiologists; BMI = body mass index. Data are shown as mean (standard deviation), # (%), or median [interquartile range].

Table 2 Intraoperative management and characteristics

	Sugammadex $n = 31$	Neostigmine $n = 31$
Surgery time, min	106 (74)	119 (83)
Anesthesia maintenance		
Volatile	16 (52)	11 (35)
Volatile + propofol	13 (42)	20 (65)
Total intravenous anesthesia	2 (6)	0 (0)
Propofol		
Total amount, mg	542 (516)	632 (518)
Amount/hour, $mg \cdot hr^{-1}$	331 (258)	346 (203)
Opioids, fentanyl equivalents		
Total amount, μg	318 (168)	362 (184)
Amount/hour, $\mu g \cdot hr^{-1}$	215 (102)	234 (123)
Rocuronium		
Total amount, mg	89 (41)	98 (37)
Amount/hour, $mg \cdot hr^{-1}$	60 (25)	69 (45)
Total fluids, mL	1283 (783)	1574 (1747)
TOF @ reversal		
0–1 twitch	14 (45)	8 (26)
2–4 twitches	17 (54)	22 (71)
Dose of reversal, mg	256 (85)	4.4 (1.2)
Time from reversal to PACU entry, min	19.7 (9.8)	18.5 (7.5)
PACU RASS score		
30 min	−0.57 (0.8)	−0.65 (0.8)
60 min	−0.29 (0.6)	−0.26 (0.5)
120 min	−0.14 (0.4)	0.10 (0.4)

Number (%) or mean (standard deviation).

PACU = postanesthesia care unit; RASS = Richman Agitation Sedation Scale; TOF = train-of-four.

Secondary outcomes

Results from our key secondary endpoints mirrored those of the primary outcome (Fig. 3). Grip strength and ability to sit up were worse early after anesthesia and surgery, but there was no trend toward benefit in the sugammadex-treated patients.

There were also no significant differences observed between the groups for other secondary outcomes (Table 3). The median [interquartile range (IQR)] time between reversal administration and extubation was not different between the groups (sugammadex: 7 [4–11] min; neostigmine: 8 [5–16], $P = 0.12$). The TOFR measurements on admission to the PACU were not different between the two groups. We observed a TOFR of > 0.9 at PACU admission in 89% and 85% of sugammadex and neostigmine treated patients, respectively. The median [IQR] time to PACU discharge readiness was not different between the two groups (sugammadex: 112 [77–158] min, neostigmine: 109 [99–128] min; $P = 0.94$). Postoperative day 1 QoR-15 survey scores were collected for approximately 50% of the patients and were not different between the two groups.

Secondary analyses of secondary endpoints were performed for the "actual drug received" population (sugammadex $n = 33$, neostigmine $n = 29$) and there were no significant differences in these postoperative outcomes between the two groups.

Discussion

Rocuronium is a neuromuscular blocking drug that induces paralysis by competitively inhibiting the post-synaptic receptors at the neuromuscular junction. Neostigmine facilitates neuromuscular blockade reversal by inhibiting acetylcholinesterase. The breakdown of acetylcholine is slowed; there is an increase in acetylcholine in the neuromuscular junction, resulting in a reversal of paralysis.[15] In contrast, sugammadex is a cyclodextrin

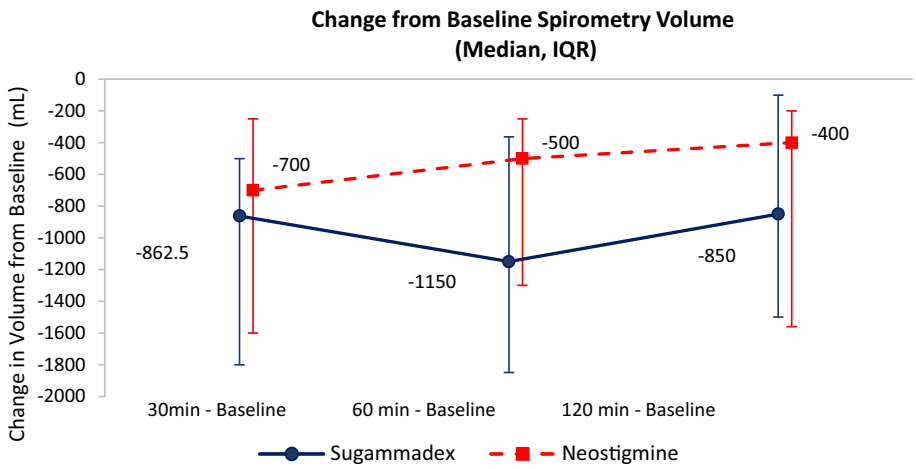

Fig. 2 Change of incentive spirometry volumes from baseline

Table 3 Outcome measures

	Sugammadex $n = 31$	Neostigmine $n = 31$	Effect size (difference in medians/means, relative risk) (95% CI)	*P* value
Incentive spirometer volume, mL				
Baseline	2650 [2250–3500]	2500 [2100–3500]	150 (−150 to 800)	0.24
@ 30 min	1775 [1000–2500]	1750 [1500–2500]	25 (−850 to 750)	0.76
@ 60 min	1375 [1100–2250]	2000 [1400–2500]	−625 (−1225 to 325)	0.06
@ 120 min	1800 [1200 2250]	1950 [1250–2250]	−150 (−700 to 500)	0.99
Grip strength, pounds				
Baseline	74 (28)	77 (28)	−3 (−18 to 12)	0.72
@ 30 min	55 (33)	53 (34)	3 (−16 to 22)	0.76
@60 min	59 (27)	64 (34)	−5 (−21 to 11)	0.53
@ 120 min	61 (29)	66 (33)	−5 (−22 to 12)	0.54
Ability to sit up				
Baseline	31 (100%)	31 (100%)		
@ 30 min	14 (47%)	15 (52%)	0.9 (0.5 to 1.5)	0.7
@ 60 min	22 (71%)	24 (77%)	0.8 (0.5 to 1.6)	0.56
@ 120 min	23 (82%)	27 (90%)	0.7 (0.3 to 1.8)	0.46
Time to extubation, min	7 [4–11]	8 [5–16]		0.12
TOF ratio on PACU admission				
> 70%	26 (93%)	26 (96%)	0.7 (0.1 to 3.4)	1
> 90%	25 (89%)	25 (85%)	1.2 (0.6 to 2.4)	0.7
Time to PACU Discharge readiness, min	112 [77–158]	109 [75–156]	3 (−30 to 33)	0.94
QoR-15 score on postoperative day #1	105 [94–124]	117 [99–128]	−12 (−24 to 13)	0.48

Normally distributed continuous variables are presented as mean (SD), and effect size is presented as the difference in means (95% CI). Non-normally distributed continuous variables are presented as medians [IQR], and effect size is presented as a bootstrapped difference in medians (bootstrapped 95% CI). Categorical variables are presented as n (%), and effect size is presented as relative risk (95% CI).

CI = confidence interval; IQR = interquartile range; PACU = postanesthesia care unit; QoR-15 = Quality of Recovery 15 survey; SD = standard deviation; TOF = train-of-four.

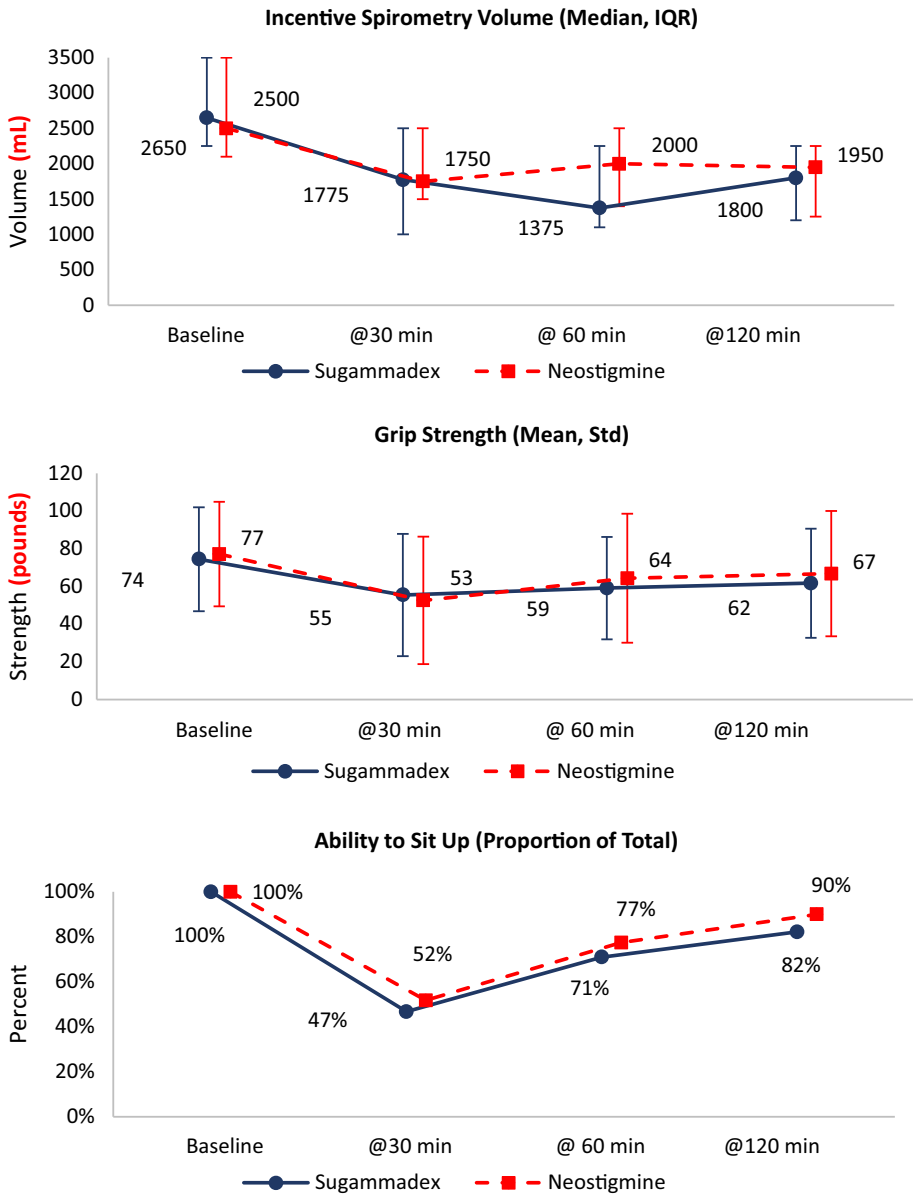

Fig. 3 Incentive spirometry (absolute values), grip strength, and ability to sit unaided

molecule that binds to rocuronium with high affinity to form an inactive complex. Encapsulated rocuronium circulates in the plasma and is unable to bind to muscle acetylcholine receptors. Rocuronium rapidly diffuses away from the neuromuscular junction as the effective plasma concentration of rocuronium decreases.[15]

Within the context of this clinical trial, we showed no difference in patients' strength in the PACU after paralysis was reversed with sugammadex or neostigmine. We observed no difference between study groups in our primary outcome—the ability to breathe deeply in the PACU. We also observed no differences in hand grip strength, ability to sit unaided, time to extubation, TOFR on PACU admission, PACU discharge readiness time, or postoperative day 1 QoR-15 scores.

There was an expected decline in incentive spirometry volumes from baseline to immediately after surgery, which has been shown in previous studies.[16] Over the next 90 min, patients in both study arms showed similar recovery toward baseline incentive spirometry volumes, handgrip, and the ability to sit independently. It is not clear why we did not observe a difference between the two reversal agents. The most likely reason is that sugammadex is not superior to neostigmine with regards to patient strength in the early postoperative time period. In the PACU, patients reversed with neostigmine may have already recovered to full strength. This is supported by previous studies showing that reversal of moderate rocuronium blockade (recovery of T2 in the TOF response) with neostigmine will return patients to a TOFR of > 0.9 within 18.6 min.[17] So while,

sugammadex may be superior over the first few minutes after reversal, by the time patients are in the recovery room it appears that reversal with neostigmine has had sufficient time to yield similar measures of strength compared with sugammadex. This finding better defines which clinical outcomes are improved (or in this case not) in patients reversed with sugammadex.

The decrease in spirometry volume from preoperative to postoperative 30 min was larger (i.e., worse) in the sugammadex group. Although this was not significantly different from neostigmine, this was the opposite of what we had anticipated. The *mean* (standard deviation) change of spirometry volume from baseline to 30 min was −952 (777) mL for neostigmine, and −1,132 mL (908) mL for sugammadex. The difference between these two values is 180 mL, which was a much smaller difference than we anticipated, but again, the neostigmine group was closer to recovering to the baseline spirometry volume at each time point. Even though the differences between the two groups were small, these differences persisted in the same direction at each time point. While our sample size was reduced at the 30-min time point, we would need a sample size of over 650 patients (using these numbers as estimates) to have sufficient power to detect a significant difference for the superiority of neostigmine.

The median time between reversal and extubation was not different between the two groups (sugammadex, 7 min; neostigmine, 8 min). Previous studies have consistently shown a faster reversal of neuromuscular blockade with sugammadex. The decision to extubate was based on the clinical judgement of the anesthesiologist, and stricter extubation criteria may have yielded different results. Train-of-four ratio data at the time of extubation was not collected and may have shown a difference between the two groups. Reversal of neuromuscular blockade is only one component of emergence from anesthesia. Our results suggest that reversal with sugammadex does not result in a faster time to extubation, but our study was not designed to address this question.

A Cochrane review concluded that, for reversal of rocuronium-induced moderate neuromuscular blockade, sugammadex (2 $mg{\cdot}kg^{-1}$) was 10.2 min (6.6 times) faster than neostigmine 0.05 $mg{\cdot}kg^{-1}$ (2.0 *vs* 12.9 min) in reversing from the second twitch to a TOFR of 0.9. For reversal of rocuronium-induced deep neuromuscular blockade, sugammadex 4 $mg{\cdot}kg^{-1}$ was 45.8 min (16.8 times) faster than neostigmine 0.07 $mg{\cdot}kg^{-1}$ (2.0 *vs* 48.8 min) in reversing neuromuscular blockade from a post-tetanic count of 1–5 to TOFR > 0.9.[7] Patients receiving sugammadex had 40% fewer adverse events compared with neostigmine, specifically bradycardia, postoperative nausea and vomiting, and postoperative residual paralysis. This meta-analysis suggested a superior recovery profile with sugammadex, but it did not report the functional measures of strength described here.

Breuckmann observed that 43% of patients reversed with neostigmine had a TOFR of < 0.9 on PACU admission compared with 0% of patients who received sugammadex.[8] Within our study, 15% and 11% of patients had a TOFR of < 0.9 on PACU admission in the neostigmine and sugammadex groups, respectively. Neostigmine dosing by weight in our study was 45 $\mu g{\cdot}kg^{-1}$, as we limited maximum dosing to 5 mg, similar to the study by Breuckmann (51 $\mu g{\cdot}kg^{-1}$). It is possible that our observed difference in TOFR readings may be related to a monitor artifact as our patients were awake on PACU admission. This may have limited the accuracy of the TOF-Watch.[18]

There are several limitations to our study. Despite our protocol, a higher percentage of patients in the neostigmine group were reversed from 2–4 twitches to 0–1 twitches compared with the sugammadex group. Twenty-six percent of patients received neostigmine with a TOF of 0 or 1. Previous studies have shown that neostigmine reversal at this depth of neuromuscular blockade can be slow and incomplete.[19,20] Nevertheless, the anesthesia team was monitoring for evidence of residual neuromuscular blockade, such as inadequate five-second head lift or weak handgrip, and they determined if the patient was appropriate for extubation. No patients required reintubation in our study. This difference in patient depth of neuromuscular blockade at the time of reversal may have influenced PACU assessment results. A few patients were unable to cooperate for PACU assessments because of pain or sedation, and these missing values may have influenced our results. Nevertheless, this is unlikely given a lack of apparent benefit for sugammadex in all our measures of strength.

Our study did not use TOFR as a criterion for extubation. The routine use of quantitative neuromuscular monitoring, such as acceleromyography, has been advocated as a way to ensure a TOFR > 0.9 prior to extubation and improve patient safety.[15] Clinical signs and symptoms of neuromuscular blockade recovery, such as five-second head lift, have low sensitivities around 20%. The five-second head lift could be performed with a TOFR < 0.6.[21] Nevertheless, the use of quantitative neuromuscular monitoring has not been widely adopted by anesthesiologists. Only 23% of American clinicians reported the availability of quantitative neuromuscular monitoring in their departments.[22] Peripheral nerve stimulation, or qualitative monitoring, is a more widely available neuromuscular monitoring tool, however 19% of European and 9% of American clinicians reported never using them.[22] We designed our clinical trial to reflect

routine clinical practice and thus used our (and most) institution's standard criteria for extubation.

There are several strengths of our clinical trial. We compared clinical measures of strength and breathing in the PACU instead of TOFR results. Previous trials have assessed patients for general muscle weakness or five-second head lift, but none have measured breathing capacity between reversal agents.[19,23] Incentive spirometry is quantitative, and the ability to breathe deeply is clinically significant after general anesthesia. We do not dispute the relevance of TOFR as an endpoint in some studies, but it is clearly a surrogate not a direct measure of more clinically relevant measures, such as ability to breathe deeply and ability to sit up unaided.

Another strength of our study was the blinding of the anesthesia team to reversal assignment until 15 min before the end of surgery to minimize an effect of bias on the anesthesiologist's intraoperative management. A blinded member of the research team who was unaware of which reversal agent the study patient had received performed PACU assessments. The RASS scores were measured in the PACU so that sedation did not explain any differences between our treatment arms.

Additionally, multiple measures of strength (incentive spirometry, hand grip, and the ability to sit up) were used to assess patients' postoperative condition. Multiple time points were used (30, 60, 120 min) so as not to limit our findings to one arbitrary time point. Multiple analyses of strength measures, including the recovery trajectory as a continuum, change from baseline at individual time points, and absolute values for each individual time point were performed to assess if there were any differences in the study arms, and all analyses consistently showed no differences between study arms.

Conclusion

The improved recovery profile of neuromuscular reversal with sugammadex compared with neostigmine does not appear to extend to measures of patient strength such as incentive spirometry, hand grip strength, and the ability to sit up at 30, 60, and 120 min after reversal.

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Conflict of interest None.

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