BJA

British Journal of Anaesthesia, xxx (xxx): xxx (xxxx)

doi: 10.1016/j.bja.2020.01.016
Advance Access Publication Date: xxx
Clinical Investigation

CLINICAL INVESTIGATION

Randomised controlled trial of sugammadex or neostigmine for reversal of neuromuscular block on the incidence of pulmonary complications in older adults undergoing prolonged surgery

Brandon M. Togioka[1,*], David Yanez[2], Michael F. Aziz[1], Janna R. Higgins[1], Praveen Tekkali[1] and Miriam M. Treggiari[1,2]

[1]Department of Anesthesiology and Perioperative Medicine, Oregon Health & Science University, Portland, OR, USA and [2]Department of Anesthesiology, Yale University, New Haven, CT, USA

*Corresponding author. E-mail: togioka@ohsu.edu

This work was presented in part at the annual meetings for the Association of University Anesthesiologists and the International Anesthesia Research Society in May 2019.

Abstract

Background: Residual neuromuscular block has been associated with postoperative pulmonary complications. We hypothesised that sugammadex reduces postoperative pulmonary complications in patients aged ≥70 yr having surgery ≥3 h, compared with neostigmine.

Methods: Patients were enrolled in an open-label, assessor-blinded, randomised, controlled trial. At surgical closure, subjects were equally randomised to receive sugammadex 2 mg kg^{-1} or neostigmine 0.07 mg kg^{-1} (maximum 5 mg) for rocuronium reversal. The primary endpoint was incidence of postoperative pulmonary complications. Secondary endpoints included residual paralysis (train-of-four ratio <0.9 in the PACU) and Phase 1 recovery (time to attain pain control and stable respiratory, haemodynamic, and neurological status). The analysis was by intention-to-treat.

Results: Of the 200 subjects randomised, 98 received sugammadex and 99 received neostigmine. There was no significant difference in the primary endpoint of postoperative pulmonary complications despite a signal towards reduced incidence for sugammadex (33% *vs* 40%; odds ratio [OR]=0.74; 95% confidence interval [CI]=[0.40, 1.37]; *P*=0.30) compared with neostigmine. Sugammadex decreased residual neuromuscular block (10% *vs* 49%; OR=0.11, 95% CI=[0.04, 0.25]; *P*<0.001). Phase 1 recovery time was comparable between sugammadex (97.3 min [standard deviation, SD=54.3]) and neostigmine (110.0 min [SD=62.0]), difference −12.7 min (95% CI, [−29.2, 3.9], *P*=0.13). In an exploratory analysis, there were fewer 30 day hospital readmissions in the sugammadex group compared with the neostigmine group (5% *vs* 15%; OR=0.30, 95% CI=[0.08, 0.91]; *P*=0.03).

Conclusions: In older adults undergoing prolonged surgery, sugammadex was associated with a 40% reduction in residual neuromuscular block, a 10% reduction in 30 day hospital readmission rate, but no difference in the occurrence of postoperative pulmonary complications. Based on this exploratory study, larger studies should determine whether sugammadex may reduce postoperative pulmonary complications and 30 day hospital readmissions.

Clinical trial registration: NCT02861131.

Keywords: acetylcholinesterase inhibitor; cyclodextrin; neostigmine; neuromuscular block; pulmonary complications; rocuronium; sugammadex

Accepted: 28 January 2020

Editor's key points

- Sugammadex is associated with reduced residual neuromuscular block, but whether this reduces postoperative pulmonary complications is unknown.
- A single-centre RCT compared the effects of sugammadex or neostigmine on the incidence of postoperative pulmonary complications.
- There was no significant difference in the primary endpoint of postoperative pulmonary complications despite a signal towards reduced incidence for sugammadex.
- Sugammadex was associated with less residual paralysis but no difference in early recovery metrics.
- Larger studies powered to detect a difference in postoperative pulmonary complications in at-risk patients are warranted.

Each year, more than 230 million major surgical procedures are performed worldwide and most include administration of neuromuscular blocking drugs.[1] Neuromuscular blocking drugs are considered essential because they can facilitate airway instrumentation and improve surgical conditions. However, multiple studies have linked use of neuromuscular blocking drugs with postoperative pulmonary complications,[2–4] which can occur in 5% of surgeries[5] and impact on hospital length of stay and costs.[6]

Residual neuromuscular block is associated with upper airway obstruction,[7] hypoxaemia,[7,8] atelectasis,[9,10] and pneumonia.[3,9] Furthermore, even low levels of neuromuscular block (train-of-four [TOF] ratio <0.9 or <0.95[11]) in healthy volunteers not exposed to anaesthesia or surgery was associated with pharyngeal[12,13] and laryngeal dysfunction,[14,15] and depressed hypoxic ventilatory drive.[16] It has been suggested that reducing residual neuromuscular block may decrease postoperative pulmonary complications.[9,10]

Acetylcholinesterase inhibitors are commonly administered to reduce the incidence of these complications. Regular monitoring of neuromuscular transmission and accurate dosing of acetylcholinesterase inhibitors can reduce the incidence of residual neuromuscular block[17]; however, this is not eliminated by these strategies.[17,18] It is conceivable that these interventions failed because of underutilisation of quantitative assessment of neuromuscular transmission or because overdosing of acetylcholinesterase inhibitors can impact respiratory and upper airway dilator muscle activity.[19,20] Acetylcholinesterase inhibitors are ineffective at reversing deep neuromuscular block,[21,22] and are less effective when administered with inhalational anaesthetics.[23] Sugammadex, a gamma-cyclodextrin that selectively binds rocuronium, lacks intrinsic negative effects on upper airway dilator activity,[24] provides faster, more complete reversal than neostigmine,[25–27] effectively reverses deep neuromuscular block,[21,22,28] and is equally effective when administered with inhalational or intravenous anaesthetics.[29] Although sugammadex provides higher quality reversal, the efficacy of sugammadex in preventing postoperative pulmonary complications in older adults undergoing prolonged surgery is not firmly established.

We therefore designed an RCT in patients ≥70 yr of age with planned surgery ≥3 h to receive rocuronium reversal by sugammadex or neostigmine. We hypothesised that sugammadex would reduce the incidence of postoperative pulmonary complications, incidence of residual neuromuscular block in the PACU, and PACU Phase 1 recovery time.

Methods

Study population

Institutional Review Board approval from Oregon Health & Science University (Portland, OR, USA) was obtained in November 2016 and the trial was registered on clinicaltrials.gov (NCT02861131) in August 2016. This manuscript includes all components of the Consolidated Standards of Reporting Trials (CONSORT) checklist.

Between January 2017 and March 2018, patients having elective surgery at Oregon Health and Science University in Portland, OR, USA, were evaluated for eligibility. Eligible patients were aged ≥70 yr, scheduled for surgery of expected duration of ≥3 h under general tracheal anaesthesia, and without a surgical or medical contraindication to neuromuscular block. Exclusion criteria included significant kidney disease (stage 4 kidney disease or higher), significant liver disease (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] greater than twice the upper limit of institutional normal), allergies to study drugs, and refusal of consent. Written informed consent was obtained from all enrolled subjects.

Primary and secondary endpoints

The primary endpoint, incidence of postoperative pulmonary complications, was a composite of in-hospital lung or airway dysfunction (Table 1).[5] Secondary endpoints were the proportion of patients with residual neuromuscular block in the

Table 1 Definition of postoperative pulmonary complications. Table modified from Canet and colleagues.[5] CPAP, continuous positive airway pressure; Pa_{O_2}, partial pressure of oxygen in arterial blood; Sa_{O_2}, peripheral blood oxygen saturation; WBC, white blood cell count.

Complication	Definition
Postoperative pneumonia	Antibiotic administration for a respiratory indication with at least one of the following: WBC >12 000 cells μl^{-1}, temperature >38°C, increased or changed sputum, new lung opacity on thoracic imaging
Aspiration pneumonitis	Radiological evidence of acute lung injury with a clinical history consistent with inhalation of gastric contents
Atelectasis	Diagnosis of more than minimal atelectasis on thoracic imaging interpreted by a radiologist
Pneumothorax	Diagnosis of a pneumothorax on thoracic imaging interpreted by a radiologist
Desaturation/ hypoxaemia	Re-initiation of supplemental oxygen to treat a Pa_{O_2} <8 kPa or a Sa_{O_2} <90% in the absence of hypoventilation after weaning from adult oxygen mask
Upper airway obstruction	Upper airway obstruction requiring a nasal airway, oral airway, or initiation of CPAP
Acute respiratory insufficiency	Postoperative initiation of either noninvasive or invasive mechanical ventilation

PACU (defined by a TOF ratio <0.9), and PACU Phase 1 recovery time (duration of time required to attain pain control and stable respiratory, haemodynamic, and neurological status). Additional endpoints were hospital length of stay, the proportion of patients with hospital readmission within 30 days, and the proportion of patients diagnosed with a respiratory complication as defined by the National Surgical Quality Improvement Program (postoperative pneumonia, unplanned intubation, ventilator dependency >48 h).[30]

Randomisation, blinding, and recruitment

The study was an open-label, assessor-blinded, randomised controlled parallel-group trial. Participants were randomly allocated to rocuronium neuromuscular block reversal with sugammadex or neostigmine based upon a computer-generated random allocation sequence (1:1 assignment ratio). The allocation sequence was created before study commencement by a member of the clinical research department not involved in recruitment, coordination, or data collection. Allocation was concealed in sequentially numbered opaque envelopes. Anaesthesia providers were blinded until when they were ready to prepare and administer reversal, typically when surgical closure began.

To avoid influencing the intraoperative management of neuromuscular block by the anaesthesia or surgical teams and to avoid randomising patients who would not receive the allotted intervention (accounting for intraoperative changes in surgical needs related to neuromuscular block), subjects were not randomised until the anaesthesia team was ready to reverse neuromuscular block. This trial feature was designed to minimise provider bias in changing anaesthetic or ventilation management. Study personnel involved in recruitment, consent, and outcomes assessment were blinded to group allocation until study completion. Assessors were not involved in patient care and did not access anaesthesia records.

An automated electronic screening tool was created within the EPIC Electronic Health Record (Epic Systems Corporation, Verona, WI, USA) software to identify patients who met age and surgical duration inclusion criteria. Eligible patients were contacted by a research coordinator to introduce the study. Patients interested in trial participation provided written consent in person either at a preoperative office visit or on the day of surgery.

Intraoperative management

Anaesthesia providers received study instructions and a flowchart describing the study procedures before induction. Subjects received either rocuronium or succinylcholine to facilitate tracheal tube placement. The recommended location of conventional peripheral nerve stimulation (qualitative device) was the adductor pollicis. If the upper extremities were not accessible during surgery, the nerve stimulator was placed on the orbicularis oculi and moved to the adductor pollicis at the end of surgery. Final dosing of neostigmine or sugammadex was always based on qualitative monitoring at the adductor pollicis. The TOF count was monitored every 15 min. Anaesthesia providers were instructed to make their best effort to maintain a TOF count of 2 during the procedure, and to reverse neuromuscular block at a TOF count of at least 2. At the time of surgical closure, when the anaesthesia team was preparing for reversal, they paged the study team to deliver the envelope containing the randomisation assignment. The recommended dose of sugammadex was 2 mg kg^{-1} of actual body weight, rounded to the nearest 10 mg. The recommended dose of neostigmine was 0.07 mg kg^{-1} of actual body weight (maximum 5 mg) rounded to the nearest 0.1 mg. Glycopyrrolate was administered at a dose of 0.1–0.2 mg per 1 mg of neostigmine administered. To maintain blinding, the study team was not present in the room when the anaesthesia providers accessed the randomisation assignment, and did not access the anaesthesia record. Intraoperative temperature, heart rate, blood pressure, ventilation, and pain management were left to the discretion of the anaesthesia team.

Postoperative study procedures

A TOF ratio was obtained on all patients within 5 min of PACU arrival with a TOF-Watch SX acceleromyograph (Organon, Dublin, Ireland). To prevent phalange movement during TOF ratio testing, the forearm was taped, proximal to the surface electrodes, and phalanges 2–5 were taped to a bedside stand. After cleaning the skin with isopropanol, the negative lead was attached to a paediatric surface electrode on the volar side of the forearm over the ulnar nerve just proximal to the wrist crease. The positive electrode was placed over the ulnar nerve 2–4 cm proximal to the negative electrode. The acceleration transducer was appended to the volar side of phalange 1 via a hand adaptor that supplied a constant preload of 75–150 g (TOF-Watch Handadaptor; Organon). The TOF ratio was determined while applying a current intensity of 50 mA through four pulses of 0.2 ms duration over 2 s. Two TOF measurements were obtained 15 s apart. If ratios were within 10%, the average was recorded. If ratios differed by more than 10%, additional measurements were obtained until two ratios were within 10%, and these were averaged.

A research coordinator monitored for adverse events (hypoxaemia, desaturation, upper airway obstruction, bronchospasm, hypersensitivity reaction, cough, headache, nausea or vomiting, itching, dysgeusia) at the subject's bedside during PACU Phase 1 recovery. Thereafter, the study team conducted in-person daily assessment of mental status, new or changed sputum, increased secretions or suctioning requirements, new cough, dyspnoea, and malaise, evidence of aspiration, signs or symptoms of heart failure, and chest radiography reports until hospital discharge. A phone call and screen of electronic medical records was completed 30 days after hospital discharge to check for readmission. A standard pro forma was used for the daily in-person hospital assessment and the 30 day post-discharge phone call (Supplement 1). There were no changes to the methods or general clinical practice during trial implementation.

Statistical analysis

We collected the following baseline characteristics: age, sex, race, weight, BMI, ASA physical status classification, creatinine clearance, liver enzymes, smoking status, history of diabetes mellitus, cancer history, and history of pathology related to the airway, heart, or lungs.

Descriptive summaries are presented using mean and standard deviation (SD) for quantitative characteristics and frequencies (%) for categorical characteristics. We tested for treatment differences using Welch's t-test for mean comparisons of quantitative characteristics and χ^2 or Fisher's exact test of associations for binary or categorical characteristics. Mood's test was used to assess the equality of medians. The χ^2 test was used to test for a treatment effect for the primary

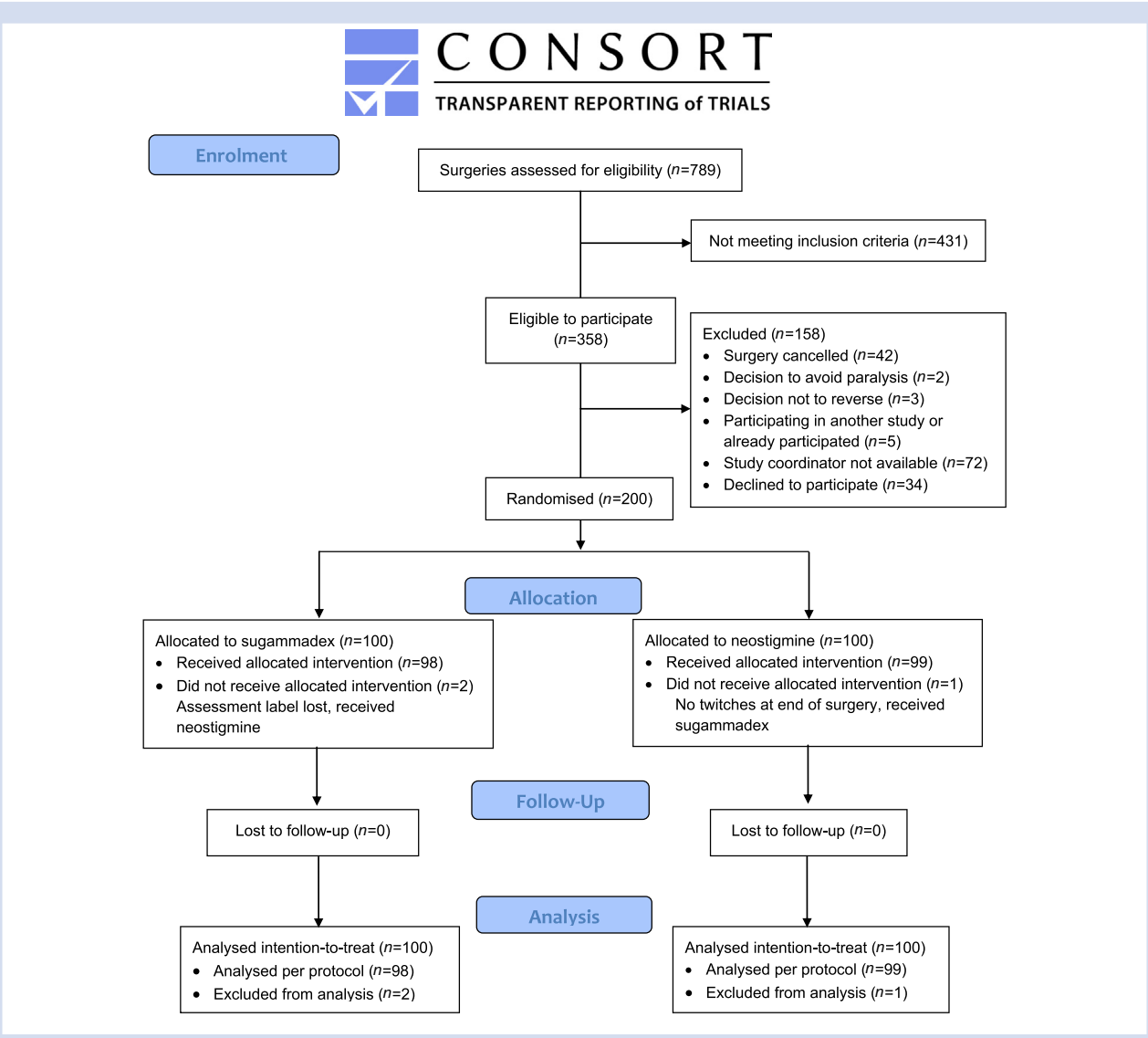

Fig 1. CONSORT flowchart. CONSORT, Consolidated Standards of Reporting Trials.

endpoint, incidence of any postoperative pulmonary complication, and for the secondary endpoint, residual neuromuscular block in the PACU. We used Welch's *t*-test for the secondary endpoint, PACU Phase 1 recovery time. All hypothesis tests evaluated were two-sided, and all analyses were conducted using the Stata (version 15.1; Stata Statistics Software, College Station, TX, USA). The same statistical package was used to create the random sequence for the fair-coin randomisation assignment.

The study was designed to detect a 45% relative reduction in postoperative pulmonary complications with 80% power, assuming a 42.1% complication rate in the neostigmine group.[5]

Results

Participant flow

During the study period, 789 surgeries met the inclusion criteria. After chart review, 358 patients were eligible for enrollment. Between January 24, 2017 and March 30, 2018, 200 subjects were randomised (Fig. 1). Of the 100 subjects allocated to receive sugammadex, two did not receive sugammadex: one randomisation envelope was lost and one anaesthesia provider failed to notify the study team at time of reversal. Both anaesthesia providers defaulted to neostigmine for these subjects. Of the 100 subjects allocated to receive neostigmine, one had no twitches at the end of surgery and the anaesthesia team gave sugammadex to avoid a prolonged operating room time. There were no withdrawals and no subjects were lost to follow-up. Follow-up was completed by April 30, 2018. Complete data were available for the primary and secondary endpoints.

Study population baseline characteristics

Table 2 shows baseline population characteristics by treatment assignment. Baseline characteristics were comparable between the two study groups for age, sex, Caucasian race, weight, BMI, smoking status and prevalent diseases. The sugammadex group appeared to have slightly higher

Table 2 Subject baseline characteristics stratified by randomisation assignment. ALT, alanine aminotransferase; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; max, maximum; min, minimum; SD, standard deviation.

Characteristic	Sugammadex (n=100)	Neostigmine (n=100)
Age (yr), mean (SD)	74.8 (4.3)	75.1 (4.0)
Median (range: min, max)	74 (70, 89)	74 (70, 86)
Sex, n (%)		
Female	52 (52)	56 (56)
Male	48 (48)	44 (44)
Caucasian race, n (%)	97 (97)	93 (93)
Weight (kg), mean (SD)	83.4 (18.8)	79.6 (18.8)
Height (cm), mean (SD)	169.4 (10.5)	167.5 (11.1)
BMI (kg m^{-2}), mean (SD)	28.8 (5.0)	28.4 (6.7)
ASA physical status, n (%)		
1	0 (0)	2 (2.0)
2	41 (41)	29 (29.3)
3	52 (52)	67 (67.7)
4	7 (7)	1 (1.0)
Smoking status, n (%)		
Current	3 (3)	4 (5)
Former	55 (63)	47 (57)
Never	29 (33)	31 (38)
Respiratory infection in the preceding month, n (%)	9 (9)	10 (10)
COPD or chronic lung disease, n (%)	1 (1)	1 (1)
Asthma, n (%)	0 (0)	2 (2)
Obstructive sleep apnoea, n (%)	2 (2)	5 (5)
CPAP use, n (%)	1 (1)	0 (0)
History of myocardial infarction, n (%)	0 (0)	1 (1)
History of congestive heart failure, n (%)	0 (0)	0 (0)
Diabetes mellitus, n (%)	6 (6)	11 (11)
Cancer, n (%)	19 (19)	16 (16)
Creatinine, mg dl^{-1}; mean (SD)	0.93 (0.32), n=87	0,95 (0.29), n=81
AST, U L^{-1}; mean (SD)	265.3 (300.6), n=11	78.8 (122.2), n=14
ALT, U L^{-1}; mean (SD)	309.1 (322.1), n=11	134.5 (240.3), n=14

representation of patients with ASA physical status 2 and lower representation in ASA physical status 3 relative to the neostigmine group.

Intra- and postoperative characteristics

Table 3 shows intra- and postoperative characteristics stratified by treatment assignment. Randomisation performed well in generating groups with similar surgical and anaesthetic characteristics. The mean heart rate 5 min after reversal was lower in the sugammadex group compared with the neostigmine group (75.8 [SD=13.4] *vs* 82.9 [SD=13.9]; P<0.001).

Primary and secondary endpoints

The primary endpoint, incidence of any postoperative pulmonary complication, is summarised in Table 4. The incidence of any postoperative pulmonary complication was lower for the sugammadex group (33%) than the neostigmine group (40%). The relative odds of postoperative pulmonary complication was lower for subjects receiving sugammadex (odds ratio [OR]=0.74, 95% CI=[0.40, 1.37]), but this difference did not reach statistical significance (P=0.30).

For the secondary endpoints, the incidence of residual neuromuscular block (TOF <0.9) was estimated to be 10% for the sugammadex group and 49% for the neostigmine group. The relative odds of residual neuromuscular block was 89% lower comparing subjects receiving sugammadex to neostigmine (OR=0.11, 95% CI=[0.04, 0.25]; P<0.001). Similarly, the estimated mean TOF ratio for subjects randomised to sugammadex was 0.96 (SD=0.11) *vs* 0.81 (SD=0.24) for patients randomised to neostigmine. The estimated mean difference of 0.16 (95% CI=[0.10, 0.21]) was statistically significant (P<0.001).

The estimated mean PACU Phase 1 recovery time was 97.3 min (SD=54.3) for the sugammadex group and 110.0 min (SD=62.0) for the neostigmine group. The estimated mean difference of 12.7 min (95% CI=[−29.2, 3.9]) was not statistically different between groups (P=0.13).

The 30 day hospital readmission rate was 70% lower for subjects randomised to sugammadex than to neostigmine (OR=0.30, 95% CI=[0.08, 0.91]; P=0.03), whereas hospital length of stay and NSQIP Respiratory Complication were not different between groups.

There were no differences in the incidence of adverse events between treatment groups.

Discussion

In this rigorously conducted single-centre randomised trial comparing sugammadex and neostigmine in older adults undergoing prolonged surgery, we failed to detect a significant reduction in the primary endpoint of the occurrence of in-hospital pulmonary complications. The estimated effect size of 19%, although clinically relevant, was an overestimation; our observed 7% lower rate of pulmonary complications with sugammadex is consistent with previous studies.[9,31] Of our secondary endpoints, reversal of moderate block (TOF count ≥2) with sugammadex decreased the occurrence of residual neuromuscular block by 40% and was associated with a 10% lower 30 day hospital readmission rate.

Prior reports have produced conflicting results on the effect of sugammadex on in-hospital pulmonary complications. Several studies failed to detect a reduction in pulmonary complications such as re-intubation,[32] laryngospasm,[33,34] pneumonia,[31] and increased airway secretions,[34] or in composite pulmonary outcomes[2,33] with the use of sugammadex. Other reports suggest that sugammadex may reduce the incidence of postoperative respiratory complications in the PACU. In a prospective observational study in which neuromuscular blocking and reversal decisions were at the discretion of the anaesthesiologist, a decrease in upper airway obstruction requiring intervention and desaturation to Spo_2 <94% was seen in patients administered rocuronium–sugammadex (2.3%) compared with cisatracurium–neostigmine (17.4%).[9] This lower incidence of PACU desaturation has been found in other observational[35] and randomised trials.[32,34,36]

The most common respiratory complication observed in our study was atelectasis, which was diagnosed in 25% of subjects given neostigmine and 19% of subjects given sugammadex. Atelectasis was likely underdiagnosed because chest radiographs were ordered only when clinically

Table 3 Intra- and postoperative data stratified by randomisation assignment. TOF, train-of-four; SD, standard deviation.

Characteristic	Sugammadex (n=100)	Neostigmine (n=100)	P-value
Surgical specialty, n (%)			0.25
General surgery	41 (41.0)	53 (53.0)	
Orthopaedic surgery	18 (18.0)	13 (13.0)	
Otolaryngology	1 (1.0)	0 (0.0)	
Plastic surgery	1 (1.0)	0 (0.0)	
Surgical oncology	23 (23.0)	16 (16.0)	
Urology	16 (16.0)	16 (16.0)	
Vascular surgery	0 (0.0)	2 (2.0)	
Categorised surgical procedures, n (%)			0.46
Open abdominal surgery	23 (23)	20 (20)	
Laparoscopic abdominal surgery	23 (23)	34 (34)	
Urological procedures	16 (16)	14 (14)	
Joint arthroplasty	12 (12)	6 (6)	
Spine surgery	8 (8)	6 (6)	
Video-assisted thoracoscopic surgery	11 (11)	15 (15)	
Other	7 (7)	5 (5)	
Surgical position, n (%)			0.18
Supine	54 (56)	50 (56)	
Prone	11 (11)	4 (4)	
Lateral decubitus	19 (20)	16 (18)	
Lithotomy	10 (10)	18 (20)	
Beach chair	2 (2)	1 (1)	
Primary anaesthetic, n (%)			0.47
Sevoflurane	28 (28)	25 (25)	
Isoflurane	72 (72)	73 (73)	
Desflurane	0 (0)	2 (2)	
Cumulative rocuronium dose, mg			
Mean (SD)	106.3 (39.4)	104.2 (39.5)	0.71
Median (range: min, max)	100 (20, 210)	100 (30, 250)	0.77
Succinylcholine, n (%)	12 (12)	12 (12)	1.00
Dose, mg; mean (SD)	114.2 (10.0)	110.0 (9.4)	0.76
Neuromuscular monitoring site, n (%)			0.20
Ulnar nerve	68 (68)	62 (62)	
Facial nerve	30 (30)	38 (38)	
Posterior tibial nerve	2 (2)	0 (0)	
TOF count at time of reversal, n (%)			0.19
1	4 (4)	12 (12.1)	
2	58 (58)	49 (49.5)	
3	16 (16)	15 (15.2)	
4	22 (22)	23 (23.2)	
Heart rate 5 min after reversal, mean (SD)	75.8 (13.4)	82.9 (13.9)	< 0.001
Blood transfusion, n (%)	4 (4.0)	5 (5.0)	1.000
Epidural for postoperative analgesia, n (%)	20 (20)	25 (25)	0.40
Peripheral nerve block, n (%)	8 (8)	5 (5)	0.57
Duration of anaesthesia, min; mean (SD)	299.6 (121.0)	302.8 (123.7)	0.85
Duration of surgery, min; mean (SD)	215.8 (105.7)	212.9 (110.7)	0.85
Reversal time to PACU, min; mean (SD)	22.8 (10.9)	23.9 (10.6)	0.46
Initial PACU temperature, °C; mean (SD)	36.4 (0.38)	36.3 (0.37)	0.61

indicated. Furthermore, detection of atelectasis by chest radiography is limited by variability in the phase of the respiratory cycle and subjective interpretation. Nevertheless, our study confirms previous results that found no difference in the incidence or area of atelectasis, measured by lung ultrasound, at 1 or 24 h after surgery.[31] On a theoretical basis, compared with neostigmine,[37] sugammadex protects from development of atelectasis by improving electromyographic activity of the diaphragm and intercostal muscles leading to higher tidal volumes and improved ability to clear secretions.

In our study, the incidence of residual neuromuscular block (TOF ratio <0.9) was 10% in the sugammadex group and 49% in the neostigmine group. The incidence of residual block has been reported as 0–3% with sugammadex[9,22,25] and 10–71% with neostigmine.[7,8,17,18,25,31] Our study confirms that sugammadex is superior to neostigmine in reducing the incidence of residual neuromuscular paralysis. Not using quantitative monitoring in the operating room and underdosing some subjects may explain the high rate of residual paralysis in the sugammadex group.

A noteworthy finding of this trial is the threefold increased 30 day hospital readmission rate in subjects given neostigmine (15%), compared with sugammadex (5%). This finding is consistent with reports of a lower incidence of unplanned 30 day readmission when sugammadex is administered during abdominal surgery *vs* neostigmine,[38] and a dose-dependent association between intraoperative neuromuscular blocking drug dose and 30 day readmission.[39] It has been hypothesised that the improved efficacy of sugammadex combined with avoidance of negative cardiovascular and upper airway effects

Table 4 Trial endpoints, stratified by randomisation assignment. *Odds ratios are reported for binary variables and estimated mean differences for continuous variables. †NSQIP respiratory complications include the following: postoperative pneumonia, unplanned intubation, and ventilator dependency for longer than 48 h. ‡Without adjustment, odds ratios for TOF ratio levels were obtained via logistic regression with TOF ratio level 0.9–1.0 as the reference category. CI, confidence interval; NSQIP, National Surgical Quality Improvement Program; SD, standard deviation; TOF, train-of-four.

Characteristic	Sugammadex (n=100)	Neostigmine (n=100)	Effect size* (95% CI)	P-value
Primary endpoint				
Any postoperative pulmonary complication, n (%)	33 (33.0)	40 (40.0)	0.74 (0.40, 1.37)	0.30
Secondary endpoints				
Specific pulmonary complications, n (%)				
Pneumonia	3 (3.0)	2 (2.0)	1.52 (0.17, 18.48)	1.00
Aspiration pneumonitis	1 (1.0)	0 (0.0)	–	1.00
Atelectasis	19 (19.0)	25 (25.0)	0.70 (0.34, 1.45)	0.31
Pneumothorax	7 (7.0)	8 (8.0)	0.87 (0.26, 2.86)	0.79
Desaturation/hypoxaemia	6 (6.0)	7 (7.0)	0.85 (0.23, 3.07)	0.77
Upper airway obstruction	7 (7.0)	14 (14.0)	0.46 (0.15, 1.30)	0.11
Acute respiratory insufficiency	4 (4.0)	5 (5.0)	0.79 (0.15, 3.81)	1.00
NSQIP defined respiratory complications†	4 (4.0)	2 (2.0)	2.04 (0.28, 22.98)	0.68
TOF ratio, mean (SD)	0.96 (0.11)	0.81 (0.24)	0.16 (0.10, 0.21)	< 0.001
TOF ratio distribution, n (%)‡				< 0.001
0.9–1.0	85 (90.4)	47 (50.5)	1.00 (ref)	–
0.8–0.89	5 (5.3)	16 (17.2)	0.17 (0.06, 0.50)	0.001
0.7–0.79	1 (1.1)	9 (9.7)	0.06 (0.01, 0.50)	0.01
< 0.7	3 (3.2)	21 (22.6)	0.08 (0.02, 0.28)	< 0.001
Residual neuromuscular block (TOF <0.9), n (%)	9 (10)	46 (49)	0.11 (0.04, 0.25)	< 0.001
PACU phase 1 recovery time, min; mean (SD)	97.3 (54.3)	110.0 (62.0)	−12.7 (−29.2, 3.9)	0.13
Hospital length of stay, day; mean (SD)	4.0 (3.4)	4.5 (5.0)	−0.50 (−1.7, 0.7)	0.42
30 day hospital readmission, n (%)	5 (5)	15 (15)	0.30 (0.08, 0.91)	0.03
Adverse events n (%)				
Bronchospasm	1 (1.0)	2 (2.0)	0.49 (0.01, 9.68)	1.00
Hypersensitivity reaction	0 (0)	0 (0)	–	1.00
Cough	4 (4.0)	5 (5.1)	0.78 (0.15, 3.73)	0.75
Headache	7 (7)	7 (7)	0.99 (0.28, 3,45)	1.00
Nausea or vomiting	14 (14)	17 (17)	0.78 (0.33, 1.82)	0.56
Itching	5 (5)	8 (8)	0.60 (0.15, 2.17)	0.41
Foul, salty, or metallic taste	19 (19)	13 (13)	1.55 (0.68, 3.66)	0.33

associated with neostigmine may be the cause of a reduced 30 day hospital readmission rate with sugammadex compared with neostigmine.[40] Given the high rate of hospital readmission after surgery and the significant associated cost, the ability of sugammadex to prevent hospital readmission deserves further attention.

Our study has several limitations. We evaluated a protocolised scenario with 100% qualitative monitoring and reversal at two twitches at the adductor pollicis. Such practices may improve the quality of neostigmine reversal. A protocolised approach to reversal has been shown to reduce the incidence of residual paralysis.[17] However, only 50% of subjects were reversed at two twitches and the dose of neostigmine was not adjusted according to TOF count. Some subjects were overdosed with neostigmine, which increases risk for airway failure.[19,20] Other limitations and potential sources of bias include not controlling intraoperative ventilation, administration of succinylcholine before rocuronium in some patients, not using quantitative neuromuscular monitoring in the operating room, not performing calibration and signal stabilisation with the TOF-Watch, and relying on primary providers to diagnose pulmonary complications or to order imaging.

We choose a high-risk population because increasing patient age and duration of surgery are two strong independent predictors of postoperative pulmonary complications.[5] The contribution of reversal to decrease postoperative pulmonary complications may be masked in the high-risk population through a greater impact of concomitant disease on the incidence of these complications. Accordingly, our findings may not be generalisable to younger and healthier populations having shorter surgery, or to patients reversed at deeper levels of neuromuscular block. Sugammadex can reliably and quickly reverse neuromuscular block regardless of the depth of blockade,[21,22,28] whereas neostigmine takes longer and becomes less effective as neuromuscular block deepens.[21,22] Our results may also not apply to surgical clinics with less access to specialists and medical technology such as remote pulse oximeter monitoring.

In summary, in older patients having surgery longer than 3 h, reversal of moderate blockade with sugammadex decreased the occurrence of residual neuromuscular block and reduced the 30 day hospital readmission rate. Our study was underpowered to test a 7% difference in rate of postoperative pulmonary complications between sugammadex and neostigmine. A larger trial is necessary to confirm this effect size.

Authors' contributions

Conception and design: BMT, NDY, MFA, MMT
Acquisition of data: BMT, JRH
Analysis and interpretation of data: BMT, NDY, PT, MMT

Drafting of the article: BMT, NDY, MMT
All authors participated in the revision of the manuscript, gave final approval of the version to be published and agreed to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Declarations of interest

The authors declare no conflicts of interest. MFA is a member of the associate editorial board of the *British Journal of Anaesthesia*.

Funding

Investigator-Initiated Studies Program of Merck Sharp & Dohme Corp.

Acknowledgements

The authors thank the anaesthesiology providers at OHSU for their support during the trial implementation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.01.016.

References

1. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008; **372**: 139–44
2. Kirmeier E, Eriksson LI, Lewald H, et al. Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): a multicentre, prospective observational study. *Lancet Resp Med* 2019; **7**: 129–40
3. Bulka CM, Terekhov MA, Martin BJ, Dmochowski RR, Hayes RM, Ehrenfeld JM. Nondepolarizing neuromuscular blocking agents, reversal, and risk of postoperative pneumonia. *Anesthesiology* 2016; **125**: 647–55
4. Grosse-Sundrup M, Henneman JP, Sandberg WS, et al. Intermediate acting non-depolarizing neuromuscular blocking agents and risk of postoperative respiratory complications: prospective propensity score matched cohort study. *BMJ* 2012; **345**, e6329
5. Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology* 2010; **113**: 1338–50
6. Dimick JB, Chen SL, Taheri PA, Henderson WG, Khuri SF, Campbell Jr DA. Hospital costs associated with surgical complications: a report from the private-sector national surgical quality improvement program. *J Am Coll Surg* 2004; **199**: 531–7
7. 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
8. Murphy GS, Szokol JW, Franklin M, Marymont JH, Avram MJ, Vender JS. Postanesthesia care unit recovery times and neuromuscular blocking drugs: a prospective study of orthopedic surgical patients randomized to receive pancuronium or rocuronium. *Anesth Analg* 2004; **98**: 193–200
9. Martinez-Ubieto J, Ortega-Lucea S, Pascual-Bellosta A, et al. Prospective study of residual neuromuscular block and postoperative respiratory complications in patients reversed with neostigmine versus sugammadex. *Minerva Anestesiol* 2016; **82**: 735–42
10. Berg H, Roed J, Viby-Mogensen J, et al. Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. *Acta Anaesth Scand* 1997; **41**: 1095–103
11. Blobner M, Hunter JM, Meistelman C, et al. Use of a train-of-four ratio of 0.95 versus 0.9 for tracheal extubation: an exploratory analysis of POPULAR data. *Br J Anaesth* 2020; **124**: 63–72
12. Sundman E, Witt H, Olsson R, Ekberg O, Kuylenstierna R, Eriksson LI. The incidence and mechanisms of pharyngeal and upper esophageal dysfunction in partially paralyzed humans: pharyngeal videoradiography and simultaneous manometry after atracurium. *Anesthesiology* 2000; **92**: 977–84
13. Eriksson LI, Sundman E, Olsson R, et al. Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans: simultaneous videomanometry and mechanomyography of awake human volunteers. *Anesthesiology* 1997; **87**: 1035–43
14. Herbstreit F, Peters J, Eikermann M. Impaired upper airway integrity by residual neuromuscular blockade: increased airway collapsibility and blunted genioglossus muscle activity in response to negative pharyngeal pressure. *Anesthesiology* 2009; **110**: 1253–60
15. Eikermann M, Vogt FM, Herbstreit F, et al. The predisposition to inspiratory upper airway collapse during partial neuromuscular blockade. *Am J Resp Crit Care* 2007; **175**: 9–15
16. Broens SJL, Boon M, Martini CH, et al. Reversal of partial neuromuscular block and the ventilatory response to hypoxia: a randomized controlled trial in healthy volunteers. *Anesthesiology* 2019; **131**: 467–76
17. Thilen SR, Ng IC, Cain KC, Treggiari MM, Bhananker SM. Management of rocuronium neuromuscular block using a protocol for qualitative monitoring and reversal with neostigmine. *Br J Anaesth* 2018; **121**: 367–77
18. Fortier LP, McKeen D, Turner K, et al. The RECITE study: a Canadian prospective, multicenter study of the incidence and severity of residual neuromuscular blockade. *Anesth Analg* 2015; **121**: 366–72
19. Kent NB, Liang SS, Phillips S, et al. Therapeutic doses of neostigmine, depolarising neuromuscular blockade and muscle weakness in awake volunteers: a double-blind, placebo-controlled, randomised volunteer study. *Anaesthesia* 2018; **73**: 1079–89
20. Herbstreit F, Zigrahn D, Ochterbeck C, Peters J, Eikermann M. Neostigmine/glycopyrrolate administered after recovery from neuromuscular block increases upper airway collapsibility by decreasing genioglossus muscle activity in response to negative pharyngeal pressure. *Anesthesiology* 2010; **113**: 1280–8
21. Geldner G, Niskanen M, Laurila P, et al. A randomised controlled trial comparing sugammadex and neostigmine at different depths of neuromuscular blockade in patients undergoing laparoscopic surgery. *Anaesthesia* 2012; **67**: 991–8
22. Jones RK, Caldwell JE, Brull SJ, Soto RG. Reversal of profound rocuronium-induced blockade with sugammadex: a

randomized comparison with neostigmine. *Anesthesiology* 2008; **109**: 816–24
23. Kim KS, Cheong MA, Lee HJ, Lee JM. Tactile assessment for the reversibility of rocuronium-induced neuromuscular blockade during propofol or sevoflurane anesthesia. *Anesth Analg* 2004; **99**: 1080–5
24. Eikermann M, Zaremba S, Malhotra A, Jordan AS, Rosow C, Chamberlin NL. Neostigmine but not sugammadex impairs upper airway dilator muscle activity and breathing. *Br J Anaesth* 2008; **101**: 344–9
25. Brueckmann B, Sasaki N, Grobara P, et al. Effects of sugammadex on incidence of postoperative residual neuromuscular blockade: a randomized, controlled study. *Br J Anaesth* 2015; **115**: 743–51
26. Flockton EA, Mastronardi P, Hunter JM, et al. Reversal of rocuronium-induced neuromuscular block with sugammadex is faster than reversal of cisatracurium-induced block with neostigmine. *Br J Anaesth* 2008; **100**: 622–30
27. Gaszynski T, Szewczyk T, Gaszynski W. Randomized comparison of sugammadex and neostigmine for reversal of rocuronium-induced muscle relaxation in morbidly obese undergoing general anaesthesia. *Br J Anaesth* 2012; **108**: 236–9
28. Puhringer FK, Rex C, Sielenkamper AW, et al. Reversal of profound, high-dose rocuronium-induced neuromuscular blockade by sugammadex at two different time points: an international, multicenter, randomized, dose-finding, safety assessor-blinded, phase II trial. *Anesthesiology* 2008; **109**: 188–97
29. Rex C, Wagner S, Spies C, et al. Reversal of neuromuscular blockade by sugammadex after continuous infusion of rocuronium in patients randomized to sevoflurane or propofol maintenance anesthesia. *Anesthesiology* 2009; **111**: 30–5
30. Program ACoSNSQI. *NSQIP user guide 2018.pdf. User guide for the 2018 ACS NSQIP participant use data file (PUF)*. https://www.facs.org/quality-programs/acs-nsqip/participant-use. [Accessed 13 February 2020]
31. Alday E, Munoz M, Planas A, Mata E, Alvarez C. Effects of neuromuscular block reversal with sugammadex versus neostigmine on postoperative respiratory outcomes after major abdominal surgery: a randomized-controlled trial. *Can J Anaesth* 2019; **66**: 1328–37
32. Abad-Gurumeta A, Ripolles-Melchor J, Casans-Frances R, et al. A systematic review of sugammadex vs neostigmine for reversal of neuromuscular blockade. *Anaesthesia* 2015; **70**: 1441–52
33. Hakimoglu S, Tuzcu K, Davarci I, et al. Comparison of sugammadex and neostigmine-atropine on intraocular pressure and postoperative effects. *Kaohsiung J Med Sci* 2016; **32**: 80–5
34. 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
35. Ledowski T, Hillyard S, O'Dea B, Archer R, Vilas-Boas F, Kyle B. Introduction of sugammadex as standard reversal agent: impact on the incidence of residual neuromuscular blockade and postoperative patient outcome. *Indian J Anaesth* 2013; **57**: 46–51
36. 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 Anaesthesiol Reanim* 2015; **43**: 387–95
37. Cammu G, Schepens T, De Neve N, Wildemeersch D, Foubert L, Jorens PG. Diaphragmatic and intercostal electromyographic activity during neostigmine, sugammadex and neostigmine-sugammadex-enhanced recovery after neuromuscular blockade: a randomised controlled volunteer study. *Eur J Anaesth* 2017; **34**: 8–15
38. Oh TK, Oh AY, Ryu JH, et al. Retrospective analysis of 30-day unplanned readmission after major abdominal surgery with reversal by sugammadex or neostigmine. *Br J Anaesth* 2019; **122**: 370–8
39. Thevathasan T, Shih SL, Safavi KC, et al. Association between intraoperative non-depolarising neuromuscular blocking agent dose and 30-day readmission after abdominal surgery. *Br J Anaesth* 2017; **119**: 595–605
40. Bose S, Xu X, Eikermann M. Does reversal of neuromuscular block with sugammadex reduce readmission rate after surgery? *Br J Anaesth* 2019; **122**: 294–8

Handling editor: Hugh C Hemmings Jr