BJA

British Journal of Anaesthesia, 115 (5): 743–51 (2015)

doi: 10.1093/bja/aev104
Advance Access Publication Date: 2 May 2015
Clinical Practice

Effects of sugammadex on incidence of postoperative residual neuromuscular blockade: a randomized, controlled study

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Abstract

Background: This study aimed to investigate whether reversal of rocuronium-induced neuromuscular blockade with sugammadex reduced the incidence of residual blockade and facilitated operating room discharge readiness.
Methods: Adult patients undergoing abdominal surgery received rocuronium, followed by randomized allocation to sugammadex (2 or 4 mg kg^{-1}) or usual care (neostigmine/glycopyrrolate, dosing per usual care practice) for reversal of neuromuscular blockade. Timing of reversal agent administration was based on the providers' clinical judgement. Primary endpoint was the presence of residual neuromuscular blockade at PACU admission, defined as a train-of-four (TOF) ratio <0.9, using TOF-Watch® SX. Key secondary endpoint was time between reversal agent administration and operating room discharge-readiness; analysed with analysis of covariance.
Results: Of 154 patients randomized, 150 had a TOF value measured at PACU entry. Zero out of 74 sugammadex patients and 33 out of 76 (43.4%) usual care patients had TOF-Watch® SX-assessed residual neuromuscular blockade at PACU admission (odds ratio 0.0, 95% CI [0–0.06], $P<0.0001$). Of these 33 usual care patients, 2 also had clinical evidence of partial paralysis. Time between reversal agent administration and operating room discharge-readiness was shorter for sugammadex *vs* usual care (14.7 *vs* 18.6 min respectively; $P=0.02$).
Conclusions: After abdominal surgery, sugammadex reversal eliminated residual neuromuscular blockade in the PACU, and shortened the time from start of study medication administration to the time the patient was ready for discharge from the operating room.
Clinical trial registration: Clinicaltrials.gov:NCT01479764.

Key words: neostigmine/glycopyrrolate; neuromuscular blockade; neuromuscular blocking agents; randomized-controlled trial; rocuronium; sugammadex

Accepted: February 11, 2015

Editor's key points

- Residual neuromuscular blockade after surgery is associated with increased morbidity and mortality.
- This study compared sugammadex with neostigmine for reversal of rocuronium after major abdominal surgery.
- 43% of patients receiving neostigmine had evidence of residual neuromuscular blockade on arrival in PACU.
- The incidence was zero in patients receiving sugammadex.

Respiratory complications such as pneumonia and post-extubation respiratory failure represent the second most common type of postoperative complication after wound infection.[1–3] Moreover, post-extubation respiratory failure has been shown to be one of the most significant factors associated with poor patient outcomes, leading to a longer hospital stay,[2–4] and increased financial cost.[1 2]

Neuromuscular blockers (NMBs) are commonly used during induction of anaesthesia to facilitate intubation, and optimize surgical conditions. However use of NMBs has been associated with negative side effects, and we recently demonstrated an increased incidence of postoperative respiratory failure, expressed as re-intubation and unplanned intensive care unit (ICU) admission post-surgery, after use of intermediate-acting NMBs.[5] These complications translated to a 90-fold increase in mortality,[5] and are likely to have resulted from lingering effects of NMBs, leading to residual neuromuscular blockade in the recovery room. Residual neuromuscular blockade occurs in approximately 20–60% of patients at arrival in the post-anaesthesia care unit (PACU) ,[6 7] and is associated with an increased incidence of postoperative hypoxemia, pneumonia, and atelectasis in the postoperative period[8–10] and an increased length of stay in the PACU.[6] To decrease the likelihood of residual neuromuscular blockade after surgery, intra-operative monitoring of neuromuscular transmission may be performed, to allow the NMB to be titrated to the desired effect during surgery and confirm recovery from neuromuscular blockade before extubation.[11] Acetylcholinesterase inhibitors such as neostigmine may also be administered at the end of surgery, to reverse the neuromuscular blockade. However, neostigmine is unable to effectively reverse deep concentrations of neuromuscular blockade,[12] and additionally may be associated with both nicotinic and muscarinic side effects.[13 14] Furthermore, neostigmine has been associated with an increased risk of postoperative de-oxygenation and atelectasis.[5 15 16] In contrast to neostigmine, sugammadex reverses any degree of rocuronium or vecuronium-induced blockade by encapsulating the NMB, thereby inactivating it.[17–20]

We therefore investigated whether sugammadex reduces the incidence of post-surgical residual neuromuscular blockade upon arrival in the PACU, compared with usual care.

Methods

Study design and patient selection

This was a randomized, parallel-group, assessor-blinded trial (protocol P07981), conducted at Massachusetts General Hospital from December 2011 until November 2012, in subjects undergoing elective laparoscopic or open abdominal surgery, under general anaesthesia with rocuronium-induced neuromuscular blockade. The study was conducted in accordance with principles of Good Clinical Practice and was approved by the Institutional Review Board of the Massachusetts General Hospital, Boston, MA, USA (unique identifier: NCT01479764). All patients provided written informed consent before enrolment.

Patients 18 yrs of age or older, and of ASA Class I to III were included. Exclusion criteria were: suspected difficult intubation, neuromuscular disorder(s), known or suspected severe renal insufficiency (defined as estimated creatinine clearance of <30 ml min^{-1}) or significant hepatic dysfunction, history or family history of malignant hyperthermia, allergies to sugammadex, opioids, NMBs or other medication(s) used during general anaesthesia, toremifene application 24 h before or within 24 h after study drug administration, planned ICU admission after surgery or overnight (>12 h) stay in the PACU, cardiac pacemaker, pregnancy and breast-feeding. Patients were excluded if they used any other investigational drugs within 30 days of randomization, or participated in another clinical trial within 30 days.

Patients were randomly assigned to receive either sugammadex or neostigmine/glycopyrrolate. Before study activation, a sample of 200 sealed envelopes were prepared by the sponsor: 100 for the sugammadex group and 100 for the neostigmine/glycopyrrolate group. Patients who fulfilled the criteria for inclusion were assigned to the next free subject number and corresponding treatment as defined in the randomisation envelope, in ascending sequence of subject numbers. Each subject number was only assigned once throughout the study. The entire randomisation process was accessible only for un-blinded team members at the trial site.

Blinding

The anaesthesiologist was un-blinded to the study drug, as he/she needed to be able to adjust the anaesthesia and neuromuscular blockade according to the treatment group, and assess the effects of sugammadex on the patient flow through the operating room. The safety and TOF-Watch® SX assessors were blinded to the treatment group, did not observe preparation of trial medications and were not involved in randomization, preparation of the study drug, or allowed in the operating room during surgery.

Anaesthesia

Anaesthesia was induced and maintained according to the clinical need of the patient, and per usual centre practice, with i.v. induction agents, i.v. opioids, inhaled anaesthetics, and other agent(s); most commonly a combination of fentanyl, propofol and sevoflurane was used. Rocuronium was used to facilitate intubation. During the surgical procedure, each patient received one or more maintenance dose(s) of rocuronium. The timing and dosing of rocuronium was according to the clinical judgement of the anaesthesiologist. To antagonize the effect of the NMB at the end of surgery, the anaesthesiologist administered either sugammadex or usual care (neostigmine/glycopyrrolate) per randomization within 10 s into a fast-running i.v. infusion.

Neuromuscular function monitoring and reversal agent administration

The level of neuromuscular blockade during surgery was determined via neuromuscular monitoring using acceleromyography (TOF-Watch® SX, Organon Ireland Ltd., a subsidiary of Merck & Co., Inc., Swords, Co. Dublin, Ireland) at the adductor pollicis muscle. Usage of TOF monitoring was not mandatory intra-operatively and left to the discretion of the Anaesthesiologist. The intra-operative TOF-count values were collected from the Anesthesia Information Management System (a data system used as

part of centre's usual care practice and not associated with sponsor). According to the response to train-of-four (TOF) and post-tetanic-count stimulation, two depths of neuromuscular blockade were defined: moderate (TOF count 1 to 3 in response to TOF stimulation), or deep [no response to TOF stimulation; but a response to post-tetanic-count (≥1)]. Sugammadex was to be administered at a dose of 2 mg kg^{-1} if spontaneous recovery had reached moderate neuromuscular blockade, or at a dose of 4 mg kg^{-1} if recovery had reached deep neuromuscular blockade. Administration and dosing of neostigmine/glycopyrrolate was consistent with the centre's usual care practice and according to the product label(s) for reversal, with a maximum dose of 5 mg (that is a neostigmine dose between 17.1–84.8 μg kg^{-1}). The appropriate timing of administration of either NMB or reversal agent or extubation was based on the decision of the anaesthesiologist. A TOF ratio was recorded for each patient within 5 min of arrival to the PACU by an assessor blinded to the study treatment. The TOF-watch was calibrated in each patient before performing the measurements. The stimulation current was set to 30 mA and the TOF-watch SX was calibrated in the calibration 1 mode.[21] This TOF ratio indicated the level of recovery from neuromuscular blockade at PACU entry.

Study endpoints

The primary endpoint was the presence of residual neuromuscular blockade, defined as a TOF ratio <0.9 on arrival to the PACU.

The key secondary endpoint was the time from start of study medication administration, to the time the patient was ready for discharge from the operating room, defined as the time point deemed by the providing anaesthesiologist medically appropriate for the patient to leave the operating room. Based on the standard of care at the clinical site, the patients were required to have a regular breathing pattern, with stable oxygen saturation and stable haemodynamics to be considered discharge-ready.

Exploratory endpoints relating to surgical efficiency parameters were also measured.

Safety assessments

Safety assessments were conducted by a blinded safety assessor. Each patient underwent a physical examination at screening and at the post-anaesthetic visit (at least 10 h after administration of sugammadex or neostigmine/glycopyrrolate). Vital signs were recorded at screening. Beats min^{-1} and bp were recorded at regular intervals and changes of >20% from baseline were considered significant. Continuous electrocardiogram and oxygen saturation (Sp_{O_2}) monitoring were performed throughout anaesthesia and postoperatively, in accordance with standard clinical practice. In the PACU, vital signs were recorded on admission, at 5 min and 15 min after admission, and then every 15 min thereafter until 120 min, or discharge from the PACU. Any possible indications of partial neuromuscular blockade (e.g. change in respiratory rate or decrease in Sp_{O_2} level attributed to residual neuromuscular blockade) occurring during the time between administration of the reversal agent until PACU discharge were recorded.

The safety assessor, blinded to both study drug and efficacy measurement results, followed-up on all patients for adverse events (AEs), and serious AEs. The assessor visited the patient in the PACU and on postoperative day 1 and followed-up with the patient 7 days after surgery, either in person or on the telephone.

Statistics

All analyses were conducted for the intention-to-treat population, which comprised all patients who received a dose of study medication. For the primary endpoint, patients were also required to have a reliable TOF ratio measurement at PACU entry for analysis.

For the primary analysis of the primary endpoint, the odds ratio of having residual neuromuscular blockade was analysed for sugammadex *vs* usual care, with the exact 95% confidence interval (CI) for the odds ratio and *P* value calculated by Pearson χ^2 test.[22]

For the key secondary endpoint analysis, time from start of study drug administration to the patient being considered ready for operating room discharge, was analysed with analysis of covariance, where the assigned treatment group was the main predictor in the model, and age, ASA Class, BMI, comorbidity index, and length of surgical procedure were added as covariates. Times were log transformed before inclusion in the model, as these times are considered to follow an approximately lognormal distribution. Non-parametric analysis using the Wilcoxon rank-sum test was performed as a secondary (sensitivity) analysis. This test was also used to compare TOF values before reversal between the two groups.

Categorical data were presented as percentage (frequency) and continuous data as mean, standard deviation (SD), unless otherwise specified. All time intervals were presented as geometric means and associated 95% CI. A sample size of 71 patients per treatment group was determined to have a power of 85%, showing a significant difference (α=0.05) in the incidence of TOF ratio <0.9 between both groups. It was assumed that TOF ratio <0.9 incidence would be 5% in the sugammadex group and 22% in the usual care group.[6 23] The investigators aimed to enrol 75 patients for both groups in case of missing data.

All statistical analyses and tests were performed using SAS (v 9.1.3, Cary, NC). A two-sided *P*-value of <0.05 was considered statistically significant.

Results

In total, 74 patients received sugammadex and 77 patients received usual care and were included in the all-patients-as-treated analysis (Fig. 1, Table 1).

Residual neuromuscular blockade at PACU entry

A TOF ratio for assessment of recovery from neuromuscular blockade was obtained at PACU arrival for all patients in the sugammadex arm (*n*=74) and for all patients except one in the usual care arm (*n*=76). This patient was admitted to ICU after surgery, instead of the PACU.

A total of 33 patients had residual neuromuscular blockade at PACU entry, all of whom were in the usual care group (0% *vs* 43% comparing sugammadex with usual care, *P*<0.0001) (Fig. 2). The exact 95% CI for the odds ratio of residual neuromuscular blockade with sugammadex *vs* usual care was 0.00 to 0.06. A TOF ratio of ≤0.7 at PACU entry was reported for eight (10.5%) patients from the usual care group (Fig. 2).

Similarly, the average level of neuromuscular blockade recovery upon PACU entry was significantly higher in the sugammadex group compared with the usual care group, demonstrated by a mean (SD) TOF ratio of 1.07±0.09 *vs* 0.90±0.17, *P*=<0.0001 (Fig. 3).

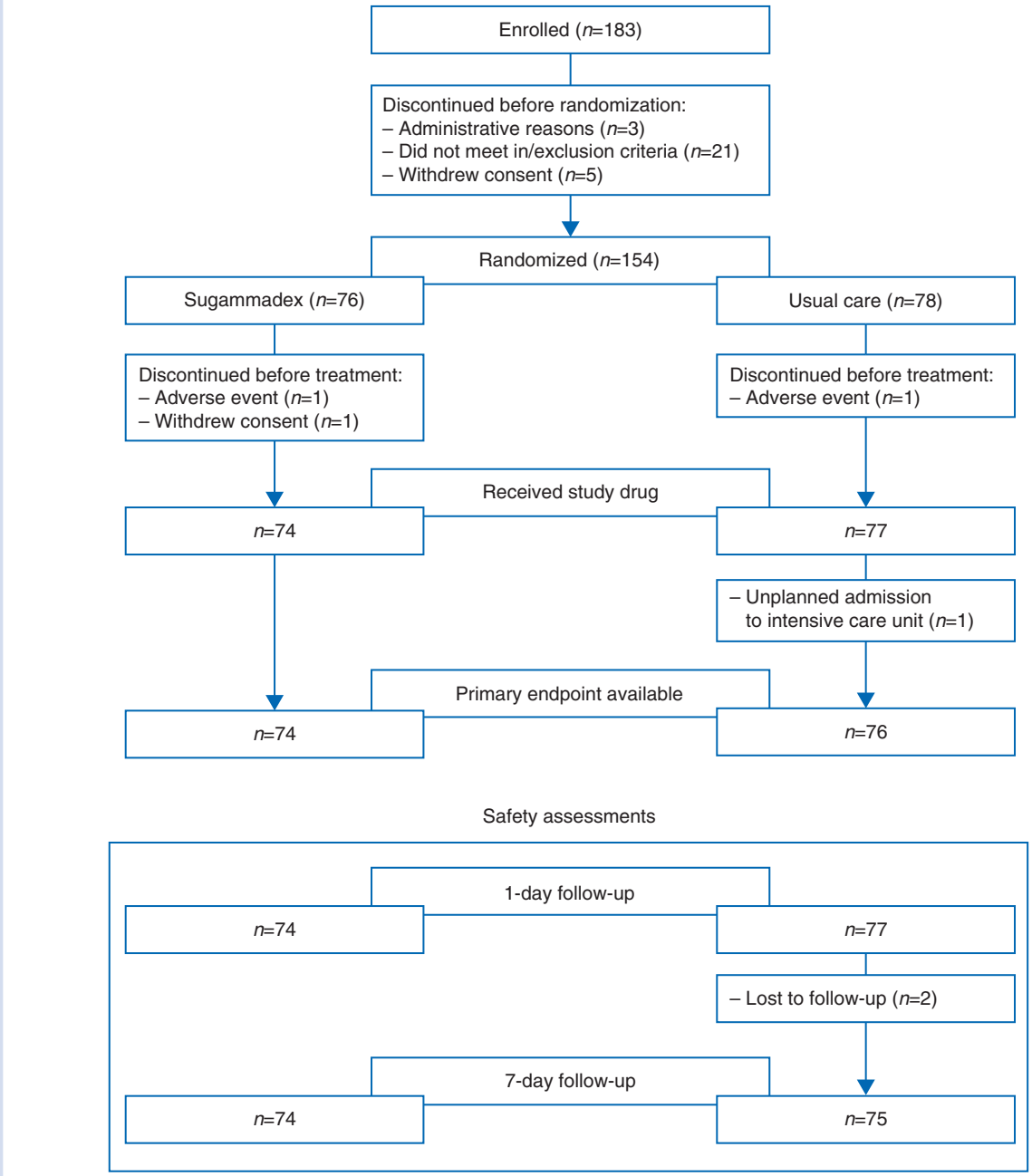

Fig 1 Patient flow chart (in accordance with CONSORT guidelines).

Geometric mean (95% CI) times from study drug administration to operating room discharge readiness were 14.7 (13.1–16.4) min and 18.6 (16.6–20.8) min, for sugammadex *vs* neostigmine, respectively P=0.02).

Intra-operative neuromuscular monitoring before reversal of the blockade was recorded in 87% of the patients. There was no significant difference in median (inter quartile range) levels of neuromuscular blockade before reversal between the two groups (median TOF count 2.5 (1–4) *vs* 3.0 (2–4), comparing sugammadex with usual care, P=0.312, Table 1). In 32% of patients in the usual care group and in 42% of patients in the sugammadex group (P=0.17), reversal was given either in the absence of documented TOF-count or at a documented deep neuromuscular block (TOF-count 0 or 1).

Results of the exploratory endpoints relating to timings of surgery and drug administration are presented in Table 2.

Safety

Overall, at least one AE was reported for 39 patients (53%) in the sugammadex group and for 41 (53%) patients in the usual care group. Frequently observed AEs are listed in Table 3. For the

Table 1 Patient characteristics (mean, standard deviation unless otherwise stated) and summary of administered doses of study medication [median (range)] for dosing variables and percentage (frequency), unless otherwise specified. ASA, American Society of Anesthesiologists; TOF, Train-of-four. *Geometric mean (95% confidence interval); †n=72. Charlson Comorbidity score was calculated based on previous publication.[24] #Train-of-four monitoring at any time during surgery but before administration of the reversal agent recorded in the anaesthesia chart

	Sugammadex (*n*=74)	Usual care (*n*=77)
Age, yr (SD)	56.4 (12.8)	57.0 (12.7)
Male (*n*, %)	47 (64)	43 (56)
Weight, kg (SD)	95.7 (23.7)	87.7 (23.8)
BMI, kg m^{-2} (SD)	32.9 (8.0)	30.2 (7.0)
Charlson comorbidity score (median, range)	2 (0–11)	2 (0–8)
ASA score (*n*, %)		
ASA I	1 (1)	0 (0)
ASA II	59 (80)	63 (82)
ASA III	14 (19)	14 (18)
Moderate renal impairment (*n*, %)	5 (7)	3 (4)
Duration of surgery (min)*	168 (152–185)	177 (160–195)
Intubation rocuronium dose (mg kg^{-1})	0.59 (0.06–1.56)	0.63 (0.26–1.23)
Mean maintenance dose of rocuronium (mg kg^{-1})	0.14 (0.07–0.81)†	0.15 (0.04–0.59)†
Number of maintenance doses of rocuronium	3 (1–12)†	3 (1–12)†
TOF monitoring before reversal (*n*, %)#	64 (86)	67 (87)
TOF count of 0 (*n*, %)	3 (4)	2 (3)
TOF count of 1 (*n*, %)	18 (24)	12 (16)
TOF count of 2 (*n*, %)	11 (15)	9 (12)
TOF count of 3 (*n*, %)	2 (3)	12 (16)
TOF count above 3 (*n*, %)	30 (41)	32 (42)
Sugammadex (mg kg^{-1})	4.00 (2.93–4.19)	0
Neostigmine (μg kg^{-1})	0	51.6 (17.1–84.8)
Glycopyrrolate (μg kg^{-1})	0	7.9 (2.1–17.0)

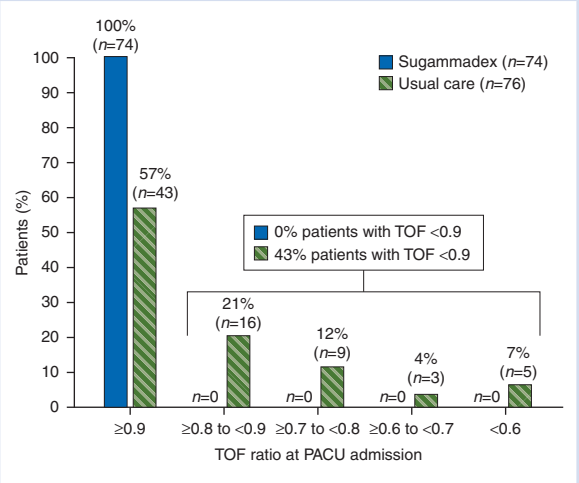

Fig 2 Recovery from neuromuscular blockade, as shown by the train-of-four (TOF) ratio at post-anaesthesia care unit (PACU) arrival.

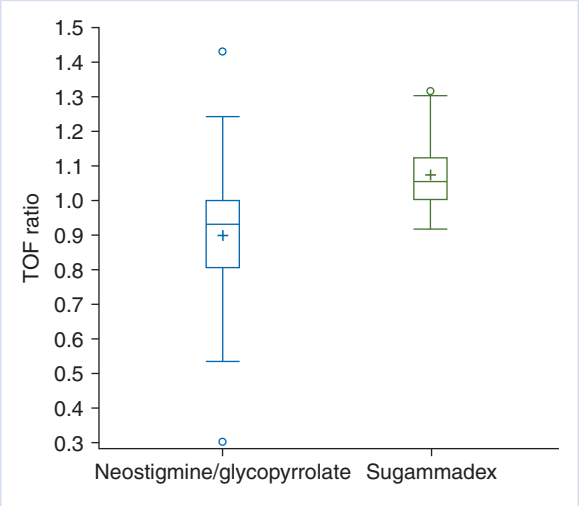

Fig 3 Recovery from neuromuscular blockade, as shown by the train-of-four (TOF) ratio at post-anaesthesia care unit entry. Figure shows mean (+), median (horizontal line in box), interquartile range (upper and lower box edges), and most extreme values within 1.5 interquartile ranges (whiskers).

majority of AEs, the clinical severity was considered as mild or moderate. The most frequently observed AE in the sugammadex group was hypertension, and occurred at a higher rate in the sugammadex *vs* usual care group (13.5% *vs* 2.6%, respectively). Events of hypertension were generally transient and responded to routine treatments, with AE duration between 0.6 and 2.5 h for seven of 10 patients, two events lasting 6 and 8 h, respectively, and for one patient lasting beyond 1 day. Nine of the AEs started within the first hour after study drug administration and one 24 h later. Two of these 10 patients had already been receiving treatment for hypertension before the start of the study and 4 patients intra-operatively before administration of the study drug. All 10 patients with hypertension after sugammadex dosing, were

Table 2 Endpoints related to timings of surgery and drug administration. *ANCOVA without covariate length of surgery (as time interval is overlapping with or part of the duration of surgery); †n=74 for sugammadex and n=75 for usual care. CI, confidence interval; OR, operating room; PACU, post-anaesthesia care unit. **t-test on log-transformed time intervals

	Sugammadex (n=74)	Usual Care (n=77)	P-value t-test** (Wilcoxon)	P-value ANCOVA
Geometric mean times in mins (95% CI), median				
Last rocuronium dose to last stitch	39 (34–45) (median: 40)	49 (41–57) (median: 50)	0.040 (0.033)	0.063*
Study drug administration to extubation	11.0 (9.4–12.9) (median: 11)	15.2 (13.2–17.5) (median: 14)	0.003 (0.003)	0.014
Study drug administration to OR discharge ready	14.7 (13.1–16.4) (median: 13.5)	18.6 (16.6–20.8) (median: 17)	0.004 (0.003)	0.021
Study drug administration to actual OR discharge	19.9 (18.1–21.8) (median:19)	24.1 (21.9–26.5) (median: 23)	0.005 (0.006)	0.020
First incision to extubation	180 (164–197) (median: 187)	190 (172–209) (median: 203)	0.42 (0.23)	0.52*
First incision to actual OR discharge	188 (173–205) (median: 195)	199 (181–218) (median: 212)	0.41 (0.22)	0.49*
Last stitch to extubation	8.6 (7.1–10.3) (median: 11)	9.5 (8.0–11.2) (median: 10)	0.43 (0.80)	0.58
Last stitch to actual OR discharge	17.7 (16.2–19.4) (median: 18)	18.4 (16.6–20.4) (median: 17)	0.57 (0.86)	0.72
PACU admission to PACU discharge ready	135 (120–151) (median: 134)	132 (117–148) (median:130)	0.75 (0.61)	0.63
PACU admission to PACU discharge†	209 (184–237) (median:180)	235 (206–268) (median: 216)	0.20 (0.13)	0.22

Table 3 Safety summary of adverse events (AEs) occurring for at least four subjects in either treatment group, and serious AEs

n (%)	Sugammadex (n=74)	Usual Care (n=77)
Subjects with AEs	39 (52.7)	41 (53.2)
Bradycardia	0 (0)	4 (5.2)
Hypertension	10 (13.5)	2 (2.6)
Hypotension	4 (5.4)	6 (7.8)
Ileus	3 (4.1)	6 (7.8)
Nausea	1 (1.4)	5 (6.5)
Pneumonia	1 (1.4)	4 (5.2)
Pyrexia	7 (9.5)	6 (7.8)
Tachycardia	1 (1.4)	4 (5.2)
Vomiting	1 (1.4)	5 (6.5)
Subjects with serious AEs	7 (9.5)	8 (10.4)
Acute myocardial infarction	0 (0)	1 (1.3)
Diarrhoea	1 (1.4)	1 (1.3)
Gastrointestinal haemorrhage	0 (0)	1 (1.3)
Ileus	3 (4.1)	3 (3.9)
Ileus paralytic	1 (1.4)	0 (0)
Nausea	0 (0)	1 (1.3)
Vomiting	0 (0)	1 (1.3)
Pyrexia	1 (1.4)	0 (0)
Pneumonia	0 (0)	1 (1.3)
Wound infection	0 (0)	1 (1.3)
Delayed recovery from anaesthesia	0 (0)	1 (1.3)
Post-procedural haemorrhage	1 (1.4)	0 (0)
Post-procedural myocardial infarction	1 (1.4)	0 (0)
Procedural haemorrhage	0 (0)	1 (1.3)
Back pain	1 (1.4)	0 (0)
Delirium	1 (1.4)	0 (0)
Urinary retention	0 (0)	1 (1.3)
Haemorrhage	1 (1.4)	0 (0)

considered to be of mild or moderate intensity, and all incidences were considered by the investigator unlikely to be related to the study drug.

Throughout the study, 15 patients experienced at least one serious AE; seven (9.5%) in the sugammadex group, and eight (10.4%) in the usual care group. The majority of serious events were in the gastrointestinal disorder category with five patients in each group experiencing an event in this category: ileus (three patients in each group), nausea (usual care, n=1); vomiting (usual care, n=1); paralytic ileus (sugammadex, n=1); gastrointestinal haemorrhage (usual care, n=1) and diarrhoea (one patient in each group).

There were no significant differences in vital signs data between the groups.

Two patients with evidence of clinically significant neuromuscular weakness were reported in the usual care group. The first corresponding AE was termed 'partial paralysis' by the investigator and was of moderate intensity. This patient received 150 mg rocuronium intra-operatively. Fifteen min before reversal, a TOF count of 2 was documented. During emergence, 5 min after administration of 5 mg neostigmine the patient started to develop respiratory distress, received propofol and was extubated 15 min later. A TOF-ratio of 0.53 was measured upon arrival to the PACU, suggesting that respiratory distress during emergence was in part related to residual neuromuscular blockade. The second patient who had 'inadequate reversal of NMB' as termed by the safety assessor, was of severe intensity. This patient received 140 mg rocuronium intra-operatively and had a TOF count of 0, measured 53 min before administration of 3.5 mg neostigmine. There was no additional documentation of the level of neuromuscular blockade in the operating room. At arrival to the PACU a TOF ratio of 0.74 was measured. The AE started 57 min after administration of neostigmine and lasted 10 min. This patient received a second dose of neostigmine in the PACU to treat the AE, and the signs and symptoms of muscle weakness recovered promptly, such that she did not need any further treatment or airway management. Both patient conditions were considered by the investigator to be probably related to the study drug. No patients with clinical evidence of residual neuromuscular blockade or recurrence of neuromuscular blockade were reported in the sugammadex group.

AEs from the system organ class 'respiratory, thoracic and mediastinal disorders', occurring in the postoperative period (i.e. within 3 days of surgery), were observed in one (1.4%) sugammadex patient *vs* five (6.5%) usual care patients. In the

sugammadex group, the AE was cough, of mild intensity. In the usual care group, there were seven AEs in this class: one patient each with transient apnoea (3 min), cough, hypoventilation, obstructive airways disorder, oropharyngeal discomfort, and two patients with rales; all of mild or moderate intensity. Findings of decreased Sp_{O_2} were observed for one (1.4%) patient in the sugammadex group, *vs* two (2.6%) in the usual care group.

No AEs led to discontinuation of a treated patient from the study. Furthermore, no serious AEs suggestive of hypersensitivity and/or suspected events of anaphylaxis were reported, and no deaths, serious trial procedure-related, or medical device-related events were reported during the study.

Discussion

The use of sugammadex for neuromuscular blockade reversal at the end of surgery was shown to eliminate residual blockade at PACU admission while, in contrast, 43% of patients treated with neostigmine/glycopyrrolate had a TOF ratio <0.9 at PACU arrival, 11% even a TOF ratio <0.7. The mean (SD) TOF ratio at PACU entry was significantly higher in the sugammadex group, compared with neostigmine (1.07±0.09 *vs* 0.90±0.17, respectively; $P<0.0001$).

The TOF-Watch-derived diagnosis of residual blockade translated into clinically significant symptoms of muscular weakness in two patients in the usual care group, considered probably drug-related by the investigator. While clinical signs of residual neuromuscular block may not always be reliable, clinical diagnosis of postoperative muscle weakness could be attributed to residual neuromuscular blockade, because signs and symptoms of muscle weakness were associated with TOF ratios of 0.53 and 0.74, respectively, at PACU arrival.[21] After a total dose of 140 mg rocuronium, one patient developed signs and symptoms of respiratory distress, 57 min after the first administration of 3.5 mg neostigmine. The last TOF count measured and documented before reversal was 0. A previous study demonstrated that the maximum effect of neostigmine reversal decreases by about 25% within an hour.[25] We speculate that recurrence may have been a contributing mechanism of respiratory distress in this patient, based on the combination of high-dose rocuronium, development of muscle weakness one h after neostigmine, and prompt improvement of symptoms after a second dose of neostigmine.

In the second patient, the effects of high-dose rocuronium (150 mg) were intended to be antagonized with high dose neostigmine (5 mg). For this patient a TOF-count of 2 was documented 15 min before reversal. These two patients underline the clinical relevance of residual neuromuscular blockade and the importance of using neuromuscular transmission monitoring, to document recovery of neuromuscular transmission before extubation. No patients with clinical evidence of residual neuromuscular blockade or recurrence of neuromuscular blockade were reported in the sugammadex group.

The use of modern intermediate acting NMBs has been shown to be associated with an increased risk of postoperative residual neuromuscular blockade in the PACU,[7 26] which can represent a considerable safety risk in patients recovering from surgery. Residual neuromuscular blockade has previously been shown to be present in 45% of patients arriving at the PACU, after a single dose of an intermediate-acting NMB.[27] Lingering effects of NMBs may increase the risk of developing respiratory complications in the PACU, particularly in susceptible patients.[5] Residual blockade leads to dysfunction of the respiratory muscles and functional impairment of the muscles of the pharynx and upper oesophagus, and a reduced ventilator response to hypoxia.[5 8–10 28] Traditionally, acetylcholinesterase inhibitors such as neostigmine have been used to reduce residual neuromuscular blockade in the postoperative period. However, Grosse-Sundrup and colleagues[5] found that use of neostigmine in a real-world scenario of a busy operating room, increased the risk of oxygen desaturation in the early postoperative period.[5 15] This may be attributable to the attempts of antagonizing deep blockade that typically result in incomplete recovery,[15] as neostigmine cannot effectively antagonize deep levels of neuromuscular blockade.[12] Sugammadex is not known to be associated with any respiratory complications. In contrast to neostigmine, which significantly impaired upper dilator muscle when given for neuromuscular blockade reversal, sugammadex was associated with no such respiratory side effects.[29] Sugammadex is registered for use in more than 70 countries worldwide and has been approved in the European Union since 2008. Sugammadex has been shown to result in 3 to 18 times faster reversal of rocuronium-induced neuromuscular blockade, compared with neostigmine[12 18 30] and 69 times faster *vs* placebo.[20]

A weakness of the current study was that it was not sufficiently powered to identify differences in incidence of postoperative respiratory complications. The incidence of severe respiratory complications is generally low after surgery; an example is postoperative respiratory failure requiring re-intubation, which was recently found to be 0.41%.[31] Conservatively assuming an incidence of 6% in the neostigmine group *vs* 3% in the sugammadex group, it is estimated that, for a power of 80% to statistically detect a difference in postoperative respiratory complications between patients administered sugammadex *vs* usual care, a total of ≥1600 subjects would be required.

Our study design might have contributed to our finding a lower incidence of residual neuromuscular blockade in the sugammadex group compared with the neostigmine group. In fact, anaesthesia providers were given directions on how to use sugammadex, whereas neostigmine dosing was kept at the discretion of the anaesthesiologist. In one third of patients in the neostigmine group, the reversal agent was administered in an unwarranted fashion,[16] defined as administration either in the absence of a documented TOF-count, or at a documented deep neuromuscular blockade (TOF-count 0 or 1).[16] This inadequate use of neostigmine may translate to postoperative respiratory failure.[16] Other data suggest that it is possible that anaesthesia providers use sugammadex in an unwarranted fashion (e.g. without TOF-monitoring, or by using an inadequate dose). It was reported in an effectiveness study that residual neuromuscular blockade occurred in about 5% of patients after sugammadex administration without TOF-monitoring.[32] Of note, recurarisation or incomplete reversal after sugammadex, can only occur when the number of circulating sugammadex molecules is not sufficient to bind to a critical number of rocuronium molecules, present in the body. One molecule of sugammadex encapsulates one molecule of rocuronium: for instance, 200 mg of sugammadex i.v. binds to 55 mg of rocuronium i.v. When a large dose of rocuronium is given followed by an inadequate dose of sugammadex, it is possible that previously redistributed rocuronium might be mobilized, to produce delayed neuromuscular blockade, as has been previously described by Plaud and co-workers.[33] Accordingly, the absence of evidence of residual blockade after sugammadex, as shown in our study, does not implicate evidence of absence of any risk of residual paralysis when sugammadex is given. Quantitative neuromuscular transmission monitoring is the only way to exclude residual neuromuscular blockade at the end of the procedure.

We performed TOF-measurements in awake patients. We cannot exclude the possibility that these measurements were influenced by either voluntary or non-voluntary movements of the patient to which the thumb may be subject.[34] TOF-ratio measurements in awake patients have been assessed in several prior studies.[6 35] Furthermore, in our clinical practice, clinical decisions of diagnosis of residual neuromuscular blockade in the PACU are made based on TOF-ratio measurements in awake patients. To minimize the risk for potential bias the patient and TOF assessor were blinded to the study drug.

In the present study, the time between reversal agent administration and operating room discharge-readiness was shorter for sugammadex *vs* usual care, indicating accelerated neuromuscular function recovery in the operating room and increased surgical efficiency. Rapid and complete reversal of neuromuscular blockade may be cost-effective, if rapid recovery of muscle strength can be translated into a reduction of recovery time in routine clinical practice,[24] although further studies are needed.

In summary, in this trial reversal of neuromuscular blockade with sugammadex eliminated residual neuromuscular blockade and associated clinically meaningful symptoms of partial paralysis.

Authors' contributions

B.B. and N.S. contributed to data acquisition and writing of the manuscript. P.G., M.K.L. and A.K.S-R. contributed to the statistical analysis and writing of manuscript. T.W. contributed to the study design and writing of the manuscript. J.de B. and M.E. contributed to the study design, data acquisition and writing of the manuscript. M.M., J.L., J.K., R.P., A.S.S and F. McG. contributed to data acquisition and writing of manuscript. All of the authors read and approved the final manuscript.

Acknowledgements

Editorial assistance was provided by Melanie More of Prime Medica Ltd., Knutsford, Cheshire, UK. This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA.

Funding

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA provided financial support to the study.

Declaration of interest

M.K.L. and T.W. are employees of Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA, and P.G. is an employee of MSD Oss, The Netherlands, all of whom may own stock and/or hold stock options in the Company. J.de B. was formerly an employee of Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA. M. E., B.B., M.M., J.L., J.K., A.S.S., F.McG., N.S., and R.P. work for institutions which received research funding for the conduct of the study from Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA.

The sponsor was responsible for site monitoring and quality assurance. The clinical site was responsible for data collection. The clinical site had full access to all data, both original and data on file. The clinical site investigators prepared the manuscript. The sponsor had the right to review and comment, but no veto right existed.

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Handling editor: J. P. Thompson