Residual Neuromuscular Blockade at Extubation: A Randomized Comparison of Sugammadex and Neostigmine Reversal of Rocuronium-Induced Blockade in Patients Undergoing Abdominal Surgery

Daniel Sabo1*, R. Kevin Jones2, James Berry3, Tod Sloan4, Jin-Yi Chen5, Jovino B Morte5 and Scott Groudine6

1University of Pittsburgh Medical Center, Pittsburgh, PA, USA
2Saddleback Memorial Medical Center, Laguna Hills, CA, USA
3Vanderbilt University Medical Center, Nashville, TN, USA
4University of Colorado at Denver, Aurora, CO, USA
5Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA
6Department of Anesthesiology, Albany Medical Center, Albany, NY, USA

Abstract

Background: Residual neuromuscular blockade (NMB) is associated with increased risk of post-operative critical respiratory events. We compared incidence of residual NMB at tracheal extubation after reversal of rocuronium-induced NMB with sugammadex versus neostigmine.

Methods: Adult patients of American Society of Anesthesiologists Class 1-3, scheduled to undergo open abdominal surgery were included. Patients were randomized to receive sugammadex 4.0 mg/kg at ≥1-2 post-tetanic counts after last rocuronium dose, or neostigmine 50 μg/kg + glycopyrrolate 10 μg/kg, according to usual care practices at each institution. Neuromuscular function was assessed using TOF-Watch® SX. Anesthesiologists were blinded to the TOF-Watch recording, except to ask the TOF-Watch operator whether ≥1 PTC had been reached before administering reversal. Use of a peripheral nerve stimulator was permitted. Clinical criteria defined by the institution were used to determine when to perform extubation. Primary efficacy variable was incidence of residual NMB (train-of-four [TOF] ratio <0.9) at extubation. Safety parameters were assessed by a blinded safety assessor.

Results: The intent-to-treat group comprised 97 patients (sugammadex, n=51; neostigmine, n=46). Among patients with valid TOF data, a TOF ratio of ≥0.9 was reached at or before extubation in 48 of 50 (96.0%) sugammadex and 17 of 43 (39.5%) neostigmine patients (P<0.0001). One sugammadex (2.0%) and 15 neostigmine patients (34.9%) were extubated at TOF ratios ≤0.7. Median (95% CI) time from study drug administration to recovery to a TOF ratio ≥0.9 was 2.0 (1.8-2.5) minutes for sugammadex (n=49) versus 8.0 (3.8-16.5) minutes for neostigmine (n=18) (P<0.0001). Safety was comparable between groups, with no clinical evidence of recurrence of NMB.

Conclusions: Significantly more sugammadex-treated patients recovered to a TOF ratio ≥0.9 at extubation and did so significantly faster than neostigmine-treated patients. This study confirms that sugammadex is more effective than neostigmine in reducing potential for residual blockade in the absence of objective NMB monitoring.

Keywords: Neostigmine + glycopyrrolate; Residual neuromuscular blockade; Rocuronium; Sugammadex; TOF-Watch® SX

Introduction

Postoperative residual paralysis remains a common occurrence following the use of neuromuscular blocking agents (NMBAs), despite the use of pharmacological agents to reverse neuromuscular blockade (NMB) towards the end of surgery [1-3]. Residual NMB is associated with an increased risk of critical respiratory events in the post-anesthesia care unit (PACU), [4,5] as well as other significant morbidity [6,7]. Additionally, residual blockade may delay postoperative patient discharge from the recovery room [8].

In order to reduce such risks, it is recommended that objective or quantitative methods are routinely used for monitoring reversal of NMB, [9,10] with acceleromyography offering the best combination of versatility, ease of use, and precision for NMB monitoring in clinical practice [10]. There is good evidence that acceleromyography improves detection and prevention of postoperative residual paralysis compared with clinical tests and subjective methods of evaluation [11]. Nevertheless, many anesthesiologists still do not employ objective monitoring in ‘real world’ clinical practice, [12,13] and there is a need for additional data and guidance in this area.

The modified γ-cyclodextrin sugammadex is the first in a new class of selective relaxant binding agents [14]. Sugammadex has been shown to provide predictable, complete and rapid reversal of both moderate and deep rocuronium- and vecuronium-induced NMB [15-18].

In this multicenter study, we compared the incidence of residual NMB (train-of-four [TOF] ratio <0.9) at the time of tracheal extubation after reversal of rocuronium-induced NMB using sugammadex 4.0 mg/kg administered at a target of ≥1-2 post-tetanic counts (PTC) with that of neostigmine 50 μg/kg administered according to the usual care

*Corresponding author: Daniel Sabo, UPMC Presbyterian Shadyside Hospital, Shadyside Campus, 5230 Centre Avenue, Pittsburgh, PA 15232, USA, Tel: 412 623 2167; Fax: 412 623 4188; E-mail: sabodp@anes.upmc.edu

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practices at each institution. Time of extubation was determined by clinical criteria defined by the investigational site.

Methods
Study design

This was a multicenter, randomized, parallel-group, safety-assessor-blinded and anesthesiologist-TOF-Watch® SX-blinded Phase IV study, named the Lightspeed study.

In this study, acceleromyography (TOF-Watch® SX, Organon Ireland Ltd., a subsidiary of Merck and Co., Inc., Swords, Co. Dublin, Ireland) was used to assess neuromuscular function. Sites selected for this study had to demonstrate proficient use of the TOF-Watch® SX, with test TOF traces required to be quality-assessed and approved by the study sponsor.

Patients were allocated to treatment using a Web Randomization System prepared centrally by the study sponsor, whereby patients were randomly allocated to receive either sugammadex or neostigmine in a 1:1 ratio.

The trial protocol was conducted in accordance with principles of Good Clinical Practice. Ethical approval was provided by the appropriate institutional review boards (IRBs) and regulatory agencies.

Blinding

The anesthesiologists administering the anesthesia were not blinded to the study drug as they needed to be able to adjust the anesthetic regimen according to the treatment group. They were, however, blinded to the specific depth of NMB based on the TOF-Watch® SX recording at administration of reversal agent, and the degree of neuromuscular recovery based on the TOF-Watch® SX recording at tracheal extubation.

The use of standard qualitative NMBA monitors was not prohibited. The safety assessor was blinded to the treatment group and did not observe preparation of the trial medications.

Patients

Adults aged ≥18 years and ≤65 years, of American Society of Anesthesiologists (ASA) Class 1–3 who were scheduled to undergo elective open abdominal surgery under general anesthesia requiring the use of an NMBA, and in a position that would not interfere with the use of the TOF-Watch® SX, were eligible for enrolment.

Patients were excluded if they had a neuromuscular disorder that complicated NMB assessment; a history of malignant hyperthermia; use of an NMBA, and in a position that would not interfere with the use of the TOF-Watch® SX, were eligible for enrolment.

Patients were excluded if they had a neuromuscular disorder that complicated NMB assessment; a history of malignant hyperthermia; significant renal (creatinine clearance <30 mL/min) or hepatic dysfunction; an allergy to opioids, muscle relaxants, or other medication used during general anesthesia; or were pregnant, breast feeding, or of childbearing potential and not using an adequate method of contraception.

All study subjects provided written informed consent.

Anesthesia and NMB

Anesthesia was induced with intravenous (IV) propofol, opioids, and/or nitrous oxide, and maintained with sevoflurane, IV opioids, and/or nitrous oxide with oxygen. Doses of anesthetic agents were consistent with the needs of the patient and the usual care practices at each institution and no other anesthetic agents were permitted. Rocuronium 0.6 mg/kg IV was given for intubation, with additional single doses of 0.15 mg/kg if clinically indicated to maintain NMB.

Repetitive TOF stimulation was applied every 15 sec at the ulnar nerve until the end of anesthesia or at least until recovery of the TOF ratio to 0.9. PTC stimulation commenced when the first twitch response from the TOF stimulation mode disappeared; a 5-sec, 50 Hz tetanic stimulation was delivered. After a 3 sec pause, stimulations were applied at a frequency of 1 Hz for 15 sec with the cycle repeated every 6 min until a PTC of 1 or 2 was reached. Use of the PTC button was prevented by the TOF-Watch® SX for 2 min following a previous successful operation of PTC.

According to randomization, patients received, after the last dose of rocuronium, either sugammadex 4.0 mg/kg IV at a target of ≥1–2 PTC, or neostigmine 50µg/kg IV with glycopyrrolate 10µg/kg IV, each administered as per the usual care practices at each institution. Study drugs were given at the time the anesthesiologist considered the patient ready for reversal of NMB. Although blinded to the specific TOF-Watch® SX recording, the anesthesiologist could ask the TOF-Watch® SX operator whether the patient had recovered to at least 1-2 PTC before administering the reversal agent.

Tracheal extubation was performed at the discretion of the attending anesthesiologist and using standard clinical criteria defined by the institution. The anesthesiologist was allowed to use a device such as a peripheral nerve stimulator to help determine when to extubate, but was not permitted to use any other device to quantitatively monitor neuromuscular transmission.

Efficacy analysis

The primary efficacy variable was the incidence of residual NMB at the time of tracheal extubation. Secondary efficacy variables were the time from the start of administration of sugammadex 4.0 mg/kg or neostigmine 50µg/kg to recovery of the TOF ratio to 0.7, 0.8 and 0.9.

Additional variables included depth of NMB at the time of administration of the reversal agent.

Safety assessments

All adverse events (AEs), serious adverse events (SAEs) and vital signs were recorded for the safety analysis. AEs were assessed for a period up to 7 days after surgery follow-up by the blinded safety assessor and were coded using Medical Dictionary for Regulatory Activities (MedDRA version 11.1; International Federation of Pharmaceutical Manufacturers and Associations, Chantilly, Virginia, USA).

Vital signs (blood pressure and heart rate) were recorded at screening, before rocuronium administration, before administration of the study drug, at 2, 5, 10, 15 and 30 minutes after administration of the study drug, every 15 minutes thereafter until discharge from the PACU, and at the post-anesthetic visit up to 7 days after surgery. Respiratory rate, central body temperature and oxygen saturation were also recorded. Evaluations were performed by the blinded safety assessor within 7 days before surgery and at the post-anesthetic visit.

Patients were monitored for any evidence of residual NMB or recurrence of NMB either clinically (respiratory problems), or by a significant decrease in the monitored TOF ratio.

Statistical analysis

For the sample size calculation, which was based upon the anticipated difference in time to recovery to a TOF ratio of ≥0.9 between the two groups, it was assumed that tracheal extubation would occur 2–3 minutes after administration of sugammadex, and 2-12 minutes after administration of neostigmine. Based on data from the previous...
sugammadex studies in which a dose of 4.0 mg/kg was administered at 1-2 PTC, it was estimated that for approximately 71% of patients in the sugammadex group, the TOF ratio would recover to ≥0.9 in ≤3 minutes. For the neostigmine group, it was estimated that for approximately 35% of patients, the TOF ratio would recover to ≥0.9 in ≤12 minutes, when administered at re-appearance of the second twitch (T₂). Using a Chi-square test and a two-sided significance level of 5%, it was calculated that a sample size of 44 patients per treatment group would be required to provide a power of 90%. This equated to the randomization of 48 patients per group based on an anticipated withdrawal rate of 5-7%. In order to distribute enrolment evenly across 10 study sites, the intended sample size was increased to 50 patients per group.

The primary efficacy analysis was based on the intent-to-treat (ITT) group, which comprised all randomized subjects who had received sugammadex or neostigmine and had at least one efficacy measurement. The all-subjects-treated (AST) group, which consisted of all the subjects who were randomized and received a dose of study medication, was used for the safety analysis.

Efficacy results are presented for patients with valid TOF data available. In addition, missing TOF ratios at extubation were imputed using a highly conservative approach for the sugammadex group, and the imputed dataset were considered from a statistical perspective to represent the primary efficacy analysis, as per study protocol. Data obtained using the imputation technique were compared with the group of patients in whom the respective values were available.

For patients in the sugammadex group for whom data for the TOF ratio at extubation were unavailable, the 5th percentile of this parameter from the sugammadex patients with available data was used. In contrast, the 95th percentile of the neostigmine group was used for neostigmine patients with missing TOF ratio data at extubation.

For imputation of missing times from the start of administration of the study drug to recovery of the TOF ratio to 0.7, 0.8 and 0.9, a worst-case scenario was also applied for sugammadex, and a best-case scenario applied for neostigmine. The imputation method applied has been described previously and differed according to the amount of data available for a given patient [15,17].

The geometric mean is robust against extreme observations arising from data with a skewed distribution and is therefore more relevant to the current study [19]. In contrast, the arithmetic mean is prone to sampling error because extreme observations may impact significantly upon the arithmetic mean. Therefore, in the current study, geometric mean times to recovery were calculated in addition to arithmetic mean and median.

TOF ratios at the time of extubation were categorized into the following groups: ≤0.6, >0.6 to ≤0.7, >0.7 to ≤0.8, and >0.8 to <0.9, and the incidence of residual NMB at extubation assessed for treatment effect using Fisher’s Exact test. Recovery time data were analyzed by analysis of variance (ANOVA) on logarithm-transformed data, with ANOVA also used to determine any center or treatment by center interaction effects.

Results

A total of 106 patients were randomized (sugammadex 4.0 mg/kg, n=54; neostigmine 50μg/kg + glycopyrrolate 10μg/kg, n=52), of whom 100 received treatment (sugammadex, n=51; neostigmine + glycopyrrolate, n=49; AST group) (Figure 1). Three patients in the neostigmine group did not have any efficacy assessment, and thus the ITT group comprised 97 patients in total. Baseline characteristics were comparable between the two treatment groups (Table 1). Patients underwent surgeries in the following categories, classified according to Nordic Medico-Statistical Committee (NOMESCO) guidelines: digestive system and spleen, female genital organs, and urinary system (Table 1). All patients but one underwent open abdominal surgery. One patient in the sugammadex group underwent a laparoscopic transverse colectomy, classified according to NOMESCO guidelines within the

| Gender          | Sugammadex 4.0 mg/kg (n=54) | Neostigmine 50 μg/kg (n=52) |
|-----------------|----------------------------|----------------------------|
| Male, n (%)     | 22 (43)                    | 18 (37)                    |
| Female, n (%)   | 29 (57)                    | 31 (63)                    |
| Mean (SD) age, years | 49 (11)                  | 52 (9)                     |
| Mean (SD) weight, kg | 75 (16)                  | 80 (13)                    |
| Mean (SD) height, cm | 171 (10)                 | 169 (10)                   |

| Race             | Sugammadex 4.0 mg/kg (n=51) | Neostigmine 50 μg/kg (n=49) |
|------------------|-----------------------------|-----------------------------|
| White, n (%)     | 44 (86)                     | 42 (86)                     |
| Black, n (%)     | 3 (6)                       | 2 (4)                       |
| Asian, n (%)     | 1 (2)                       | 1 (2)                       |
| Other, n (%)     | 3 (6)                       | 4 (8)                       |

| Ethnicity, n (%) | Sugammadex 4.0 mg/kg (n=51) | Neostigmine 50 μg/kg (n=49) |
|------------------|-----------------------------|-----------------------------|
| Hispanic/Latino  | 49 (96)                     | 47 (96)                     |
| Non-Hispanic/Latino | 2 (4)                    | 2 (4)                       |

| ASA Class, n (%)  | Sugammadex 4.0 mg/kg (n=51) | Neostigmine 50 μg/kg (n=49) |
|-------------------|-----------------------------|-----------------------------|
| 1                 | 3 (6)                       | 8 (16)                      |
| 2                 | 37 (73)                     | 33 (67)                     |
| 3                 | 11 (22)                     | 8 (16)                      |

*Classified according to Nordic Medico-Statistical Committee guidelines; ASA: American Society of Anesthesiologists.

Table 1: Summary of patient baseline characteristics (all-subjects-treated group; n=100).
digestive system and spleen category.

All but one patient received propofol for anesthesia induction with the remaining patient (in the sugammadex group) receiving sevoflurane for induction. Anesthesia was maintained with sevoflurane in all patients except one in the sugammadex group and two in the neostigmine group who were all maintained under propofol anesthesia. The median (range) intubation dose of rocuronium was 0.6 (0.57–0.61) and 0.6 (0.57–0.71) mg/kg in the sugammadex and neostigmine groups, respectively. In total, 43 patients in the sugammadex group and 40 patients in the neostigmine group received one or more maintenance doses of rocuronium 0.15 mg/kg. The median (range) number of maintenance doses given in the two groups was 4 (1–9) and 2.5 (1–8), respectively.

Patients in whom data were available for efficacy analysis

Eight of 51 and seven of 46 subjects in the ITT group for sugammadex and neostigmine, respectively, were already waking up and moving before extubation and, as a consequence, the monitor was switched off and no TOF ratios were recorded at extubation. In all but three of these patients (one sugammadex and two neostigmine), a TOF ratio of ≥0.9 was reached during the assessment period, before the TOF-Watch® SX was switched off and were thus included in the efficacy analyses.

The last recorded TOF ratios for the three patients not reaching TOF 0.9 were 0.8 in the sugammadex patient and 0.5 and 0.6, respectively, in the neostigmine patients. Additionally, one subject's TOF ratio in the neostigmine group was declared unreliable by the Central Independent Adjudication Committee because of unstable recording. Excluding these four patients, the ITT population for those in a WHO group was recorded at or before extubation comprised 93 patients (n=50 in the sugammadex group and n=43 in the neostigmine + glycopyrrolate group [Table 2]).

Efficacy analysis

At the time of extubation, a TOF ratio of ≥0.9 had been reached in 48 of the 50 (96.0%) patients in the sugammadex group, compared with only 17 of the 43 (39.5%) patients in the neostigmine group (P<0.0001 [Table 2]). Fifteen (34.9%) neostigmine patients were extubated at a TOF ratio of ≥0.7 (Table 2). Of the two sugammadex-treated patients who did not reach a TOF ratio of 0.9 at extubation, one was extubated at a TOF ratio of 0.89. The other patient was extubated at a TOF ratio of 0.38; however, background noise/artifacts resulted in this patient's TOF trace being very difficult to assess.

The median TOF ratio at the time of tracheal extubation was 1.03 (95% CI 1.00 to 1.06) and 0.76 (95% CI 0.68 to 0.89) for the sugammadex and neostigmine groups, respectively (P<0.0001 [Table 3]). Moreover, the median TOF ratios at the time of extubation within the two treatment groups were similar for each of the three surgical categories (Table 3).

Figure 2 shows the cumulative percentage of patients with available data who achieved a TOF ratio of ≥0.9 at or before extubation. Not only had more patients overall reached a TOF ratio of ≥0.9 by the time of extubation in the sugammadex group than the neostigmine group, but on average they did so in a faster time.

Including all patients who reached a TOF ratio of ≥0.9 during the assessment period (n=49 in the sugammadex group and n=18 in the neostigmine group), the median (95% CI) time from administration of study drug to recovery of the TOF ratio to 0.9 was 2.0 (1.8–2.5)
minutes in the sugammadex group and 8.0 (3.8-16.5) minutes in the neostigmine + glycopyrrolate group (P<0.0001 [Figure 3]). Faster recovery times with sugammadex, as well a much lower degree of variability between patients, were also observed for the TOF ratios of 0.7 and 0.8 (Figure 3). Moreover, on average, it also took longer to progress from TOF 0.7 to TOF 0.9 with neostigmine + glycopyrrolate compared with sugammadex (Figure 3).

For the sugammadex group, median (95% CI) time to TOF 0.9 was similar across the digestive system and spleen, female genital organs, and urinary system categories (2.1 [1.6–3.3], 2.0 [1.8–3.1] and 1.9 [1.3–4.0] min, respectively). In the neostigmine group, however, variation across the three surgical categories was observed, with corresponding median (95% CI) times to TOF 0.9 of 4.1 (1.3–18.4), 16.5 (5.9–23.2) and 6.8 (1.8–13.5) minutes, respectively.

Results of the imputed data analysis

For the analysis of the median TOF ratio at extubation, data were imputed for eight patients in each group, including those in whom the TOF-Watch® SX was switched off early before extubation. The imputed data set population, therefore, comprised all 97 ITT patients (n=51 in the sugammadex group and n=46 in the neostigmine + glycopyrrolate group). Results for this dataset analysis were of a similar magnitude to those in the analysis including patients with observed data only. Thus, the median TOF ratio at the time of tracheal extubation was 1.00 (95% CI 0.96 to 1.05) in the sugammadex group compared with 0.85 (95% CI 0.74 to 0.92) in the neostigmine + glycopyrrolate group (P<0.0001).

Because only 18 of 46 patients in the neostigmine group reached a TOF ratio ≥0.9 during the entire assessment period, this meant that times to neuromuscular recovery were imputed for 28 patients in this group. Of these, 24 were extubated before a TOF ratio of 0.9 was reached, and TOF assessment was discontinued. Maximum recorded TOF ratios in these 24 patients ranged from 0.13 to 0.89. In the remaining four patients, the TOF-Watch® SX was switched off before TOF 0.9 in three patients because patient movement precluded the acquisition of any further useful information, and data for one patient were considered unreliable. In contrast, 49 of 51 evaluable patients in the sugammadex group reached a TOF ratio ≥0.9 during the TOF assessment period and, thus, data were imputed for only two patients, both of whom were extubated before a TOF ratio of 0.9 was reached. The median time from administration of the study drug to recovery of the TOF ratio ≥0.9 remained significantly faster in the sugammadex group (2.1 minutes [95% CI 1.8 to 2.6]) compared with the neostigmine + glycopyrrolate group (5.6 minutes [95% CI 1.8 to 10.2]; P<0.0001), despite the analysis using a worst-case scenario for sugammadex and a best case scenario for neostigmine.

For the TOF ratio at tracheal extubation, there was no statistically significant treatment by center interaction effect. In addition, no statistically significant interaction between center and treatment group was observed for time to recovery of the TOF ratio to 0.9, 0.8 and 0.7 (P=0.32, 0.54 and 0.43, respectively). These results imply that the treatment effect of sugammadex versus neostigmine was homogeneous across participating centers.

Safety analysis

All patients in both treatment groups (100%) had at least one AE. Table 4 shows AEs occurring in ≥10% of patients in either treatment group, regardless of relationship to study drug. Of the common AEs occurring with at least a modest (>4%) difference between treatment groups, pyrexia and dizziness occurred more frequently in the sugammadex group and vomiting, incision site pain, headache and pruritus occurred more frequently in the neostigmine group. Most AEs were of mild or moderate intensity. The most commonly reported AEs in both groups were procedural pain and nausea. A total of thirteen SAEs were experienced by 10 patients (sugammadex 4.0 mg/kg, n=4; neostigmine 50 μg/kg, n=6), but all were considered to be unrelated or unlikely related to the study drug. There were no deaths during the trial, and none of the subjects discontinued due to an AE.

Nine possibly drug-related AEs were experienced by eight patients in the sugammadex group (nausea [n=5], procedural pain [n=1], procedural hypotension [n=1], hypotension [n=1] and generalized rash [n=1]). All were classified as mild or moderate except for the procedural pain, which was classified as severe. Eight possibly drug-related AEs occurred in the neostigmine + glycopyrrolate group (nausea [n=5], dyspepsia [n=5], somnolence [n=1] and abdominal pain [n=1]), which were all of mild or moderate intensity, with the exception of one case of severe dyspepsia.

There was no clinical evidence of recurrence of NMB in either group, and recurrence of NMB was not reported as an AE. Furthermore, there was no evidence of recurrence of NMB when defined as a decline in TOF ratio from ≥0.9 to <0.8 on at least three consecutive TOF measurements. Of patients with data available, two out of 50 (4.0%) had residual NMB (TOF <0.9) at the time of extubation in the sugammadex group, compared with 26 out of 43 (60.5%) in the neostigmine group, although there was no clinical evidence (i.e., respiratory problems) of residual NMB in either group.

Table 4: Adverse events occurring in at least 10% of patients in either treatment group, regardless of relationship to study drug (all-subjects-treated group, n=100).

| Adverse event, n (%) | Sugammadex 4.0 mg/kg (n=51) | Neostigmine 50 μg/kg (n=49) |
|----------------------|-----------------------------|---------------------------|
| Procedural pain | 11 (21.6) | 18 (36.7) |
| Nausea | 26 (51.0) | 24 (49.0) |
| Vomiting | 9 (17.6) | 11 (22.4) |
| Incision-site pain | 7 (13.7) | 9 (18.4) |
| Constipation | 6 (11.8) | 6 (12.2) |
| Headache | 3 (5.9) | 7 (14.3) |
| Pyrexia | 7 (13.7) | 2 (4.1) |
| Dizziness | 6 (11.8) | 2 (4.1) |
| Pruritus | 3 (5.9) | 5 (10.2) |

Figure 3: Time from start of administration of sugammadex or neostigmine to recovery of the train-of-four (TOF) ratio to 0.7, 0.8, and 0.9 (intent-to-treat group with data available).

1Includes two patients (one from each group) who reached a TOF ratio of 0.9 after extubation. *P-value of <0.0001 for sugammadex versus neostigmine.
No clinical signs of a possible interaction of sugammadex with endogenous or exogenous compounds other than rocuronium were recorded.

Discussion

This is the first randomized study comparing the incidence of residual NMB (TOF ratio <0.9) at the time of tracheal extubation after reversal of rocuronium-induced NMB by sugammadex 4.0 mg/kg or neostigmine 50µg/kg + glycopyrrolate 10µg/kg.

In this study, usual clinical criteria were employed by the treating anesthesiologist to determine when to extubate the trachea. The anesthesiologist administering the anesthesia was free to manage the case as he/she felt appropriate with respect to re-dosing of rocuronium, time of reversal, and time of extubation, but was blinded to the specific TOF-Watch® SX results, which therefore functioned as a ‘hidden monitor’. That is, even though the anesthesiologist was free to extubate when he/she considered it appropriate, significantly more sugammadex-treated patients were shown to have TOF ratios ≥0.9 at or before extubation compared with neostigmine + glycopyrrolate treated patients (n=48 [96.0%] vs. n=17 [39.5%], respectively, P<0.0001). This suggests that a more rapid and predictable reversal agent may provide important benefits when using only clinical/qualitative assessment methods to determine the most appropriate time for extubation. Moreover, the median TOF ratio at extubation was 1.03 in the sugammadex group, and considerably lower in the neostigmine group (0.76; patients with observed data P<0.0001).

The results observed in this study suggest that without the use of quantitative neuromuscular monitoring, patients treated with neostigmine + glycopyrrolate are more likely to experience residual NMB, which may place them at risk of postoperative critical respiratory events, [4,5] and other significant morbidity. [6,7] Furthermore, residual NMB and recurrence of NMB can result in subjective feelings of muscle weakness which, in addition to associated safety implications, may be unpleasant for the patient. Quantitative neuromuscular monitoring is known to more accurately reflect neuromuscular recovery than clinical methods. [9,10] Given the limitations of the assessments permitted for use by the attending anesthesiologist in this study intended to mimic ‘real world’ practice, it is not surprising that more patients were extubated after complete recovery to a TOF ratio of >0.9 with sugammadex than neostigmine, due to the more predictable and rapid reversal profile of sugammadex. Therefore, should a given practitioner elect to use clinical qualitative neuromuscular monitoring, the use of sugammadex will ensure that a high proportion of patients have a TOF ratio of ≥0.9 at the time of extubation. A previous sugammadex study [20] showed that under the defined conditions (administration of sugammadex 15 min after rocuronium) time to recovery of the fourth twitch was similar regardless of whether a peripheral nerve simulator or acceleromyography was used. In the present study, two sugammadex-treated patients were reported as not having reached a TOF ratio of 0.9 at extubation. However, one of these was extubated at a TOF ratio of 0.89. In the other patient, there were technical issues with neuromuscular monitoring, such that background noise/artifacts made the TOF trace very difficult to assess. Thus, the observed TOF ratio of 0.38 may not reflect the true value.

Results were consistent across the individual surgery types included; all of which were abdominal procedures, where the maintenance of deeper blockade throughout the procedure may be considered beneficial. Not only did patients who received sugammadex, on average, achieve a higher TOF ratio at extubation, they also demonstrated significantly faster recovery to an optimal TOF ratio of 0.9 (median [95% CI] 2.0 [1.8-2.5] vs. 8.0 [3.8-16.5] minutes, for sugammadex vs. neostigmine, respectively). Moreover, 47 of 49 (96%) patients in the sugammadex group reached a TOF ratio of 0.9 in <5 minutes, with the remaining two patients recovering in 5.1 and 5.4 minutes, respectively, indicating a predictable response to sugammadex (Figure 2). This comparison is based upon those patients with valid TOF data in the ITT population who reached a TOF ratio of 0.9 during TOF assessment (which continued after extubation in some patients): 49 out of 51 (96%) sugammadex patients, compared with only 18 out of 46 (39%) neostigmine patients. These findings are consistent with those from previous studies showing that sugammadex provides rapid recovery from deep rocuronium-induced NMB [15,21].

In this study, sevoflurane was administered for maintenance of anesthesia. Volatile anesthetics are known to potentiate the blocking effect of NMBAs and, while use of these anesthetics are not expected to affect the efficacy of sugammadex [22,23], recovery times with neostigmine may be prolonged [16], and use of sevoflurane should be therefore be considered as a contributing factor towards the slow and variable recovery times of neostigmine in this study.

Of note, missing data in the study analyses were addressed by utilizing an imputation technique for the recovery time analyses. This highly conservative approach produces a worst-case scenario for sugammadex with regards to efficacy results, and a best-case scenario for neostigmine. Despite this approach the imputed dataset provided results of a similar magnitude to the analysis including only those patients with all data available.

The lack of blinding of the anesthesiologist to the reversal agent being given might be considered a limitation of the study. However, it was the intention to mimic the likely use of sugammadex and neostigmine in usual clinical practice. These two agents have very different mechanisms of action, and neostigmine requires some degree of spontaneous recovery to be effective [15,18]. In contrast, sugammadex 4 mg/kg is effective when administered during deep blockade [15,18]. Thus, neostigmine was given according to the usual care practices in each institution, whereas it was intended that sugammadex would be given during deep blockade and the anesthesiologist needed to be aware of the drug being administered to make the distinction in treatment.

Sugammadex was shown to be well tolerated, and the safety profile of the two treatment groups was largely comparable. There were numerically greater percentages of patients with pyrexia and dizziness in the sugammadex group compared with those treated with neostigmine, although no cases were considered to be drug-related. It is possible that events reflect increased atelectasis secondary to gastrointestinal surgery, since many patients in the sugammadex group who experienced these conditions underwent such procedures (Table 1).

Eight patients from each group experienced possibly drug-related AEs. One patient in the sugammadex group experienced a mild generalized rash, which started approximately 25.5 hours after sugammadex administration and ended 11.5 hours later. This was considered by the investigator to be possibly drug-related. In all cases of possibly drug-related AEs, whether considered associated with sugammadex or neostigmine + glycopyrrolate, the patient recovered. There was no clinical evidence of recurrence of NMB reported after initial recovery to TOF 0.9 in either group.

Conclusions

When sugammadex 4.0 mg/kg was given at a target of ≥1-2 PTC
(deep NMB) and neostigmine 50μg/kg + glycopyrrolate 10μg/kg given at the time the anesthesiologist considered appropriate for routine reversal, significantly more sugammadex patients recovered to an optimal TOF ratio ≥0.9 at the time of tracheal extubation (determined by clinical criteria according to usual practice at the investigational site) compared with neostigmine patients. Moreover, for those patients who did reach an optimal TOF ratio of ≥0.9, they did so, on average, significantly faster with sugammadex, compared with neostigmine (P<0.0001).

Approximately two thirds of neostigmine patients were extubated at a TOF ratio <0.9, indicating that it is often difficult to determine the optimal time for extubation by clinical criteria. This study demonstrates that sugammadex is more effective than neostigmine in reducing the potential for residual blockade in the absence of objective neuromuscular monitoring.

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