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# Reversal with Sugammadex in the Absence of Monitoring Did Not Preclude Residual Neuromuscular Block

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**BACKGROUND:** In Japan, routine clinical care does not normally involve the use of a monitoring device to guide the administration of neuromuscular blocking drugs or their antagonists. Although most previous reports demonstrate that sugammadex offers more rapid and reliable antagonism from rocuronium-induced neuromuscular blockade, this advantage has not been confirmed in clinical settings when no neuromuscular monitoring is used. In this multicenter observational study, we sought to determine whether sugammadex reduces the incidence of postoperative residual weakness compared with neostigmine when the administration of rocuronium and its antagonists is not guided by neuromuscular monitoring.

**METHODS:** This study was conducted in two 5-month periods that preceded and followed the introduction of sugammadex into clinical practice in Japan. Five university-affiliated teaching hospitals participated in this study. Neostigmine was used to antagonize rocuronium-induced neuromuscular blockade in the first phase, and sugammadex was used in the second phase. The timing and doses of rocuronium, neostigmine, and sugammadex were determined by the attending anesthesiologists without the use of neuromuscular function monitoring devices. To ascertain the incidence of postoperative residual neuromuscular weakness, the train-of-four ratio (TOFR) was determined acceleromyographically after tracheal extubation. Since our practice also does not usually involve calibration and normalization of accelerographic responses, both TOFR <0.9 and TOFR <1.0 were used as the criteria for defining postoperative residual weakness.

**RESULTS:** In the first phase, 109 patients received neostigmine (average dose 33 μg/kg) and 23 patients were considered (by clinical criteria) to have adequate recovery and did not receive neostigmine (spontaneous recovery group). In the second phase, 117 patients received sugammadex (average dose 2.7 mg/kg) for antagonism of rocuronium-induced blockade. The incidence (95% confidence interval) of TOFR <0.9 under spontaneous recovery, after neostigmine, and after sugammadex, was 13.0% (2.8%–33.6%), 23.9% (16.2%–33.0%), and 4.3% (1.7%–9.4%), respectively. The incidence (95% confidence interval) of TOFR <1.0 in these groups was 69.6% (47.1%–86.6%), 67.0% (57.3%–75.7%), and 46.2% (36.9%–55.6%), respectively. The use of sevoflurane in the neostigmine group and the short interval between the administration of the last doses of rocuronium and sugammadex were associated with a higher incidence of postoperative residual weakness.

**CONCLUSIONS:** This study demonstrated that the risk of TOFR <0.9 after tracheal extubation after sugammadex remains as high as 9.4% in a clinical setting in which neuromuscular monitoring (objective or subjective) was not used. Our finding underscores the importance of neuromuscular monitoring even when sugammadex is used for antagonism of rocuronium-induced neuromuscular block. (Anesth Analg 2013;117:345–51)

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Postoperative residual weakness or postoperative residual block poses a significant risk of morbidity in postoperative patients.[1–4] Conventionally, an anticholinesterase has been used to antagonize nondepolarizing neuromuscular blocking drugs (NMBDs); however, this type of reversal sometimes results in slow and incomplete recovery of neuromuscular function.[5–9] Therefore, the use of quantitative monitoring of neuromuscular function has been strongly advocated. Unfortunately, neuromuscular monitors, whether objective or subjective, are not used routinely in the authors' institutions due to lack of financial incentives and lack of professional guidelines. Several surveys have demonstrated that this practice is not an isolated

phenomenon to Japan.[10–13] Sugammadex (Bridion, Merck Sharp & Dohme, Whitehouse Station, NJ) became available in several countries, including Japan.[14–16] The unique ability of this selective γ-cyclodextrin to irreversibly encapsulate either rocuronium or vecuronium molecules enables rapid and reliable antagonism of various degrees of neuromuscular blockade. Therefore, one might expect that reversal of rocuronium with sugammadex would eliminate the risk of postoperative residual weakness, even when neuromuscular monitoring is not used in the clinical setting. The purpose of this study was to investigate whether sugammadex would eliminate the occurrence of postoperative residual weakness when no peripheral nerve stimulators or monitors were used to guide the management of rocuronium-induced neuromuscular block.

## METHODS

This 2-stage, prospective, observational study was conducted at 5 urban, university-affiliated teaching hospitals in Tokyo, Japan. The study protocol conformed to the Journal's requirements for human trials and was approved by the IRBs in each participating hospital; written informed consent was obtained from each participant. ASA physical status I to III patients older than 18 years who received rocuronium during their anesthetic care were eligible for inclusion in this study. The exclusion criteria included patients with neuromuscular disease, patients known or suspected of having an allergy to NMBDs, or those receiving medication in a dose and/or schedule known to interfere with NMBDs (such as antibiotics, anticonvulsants), Written informed consent was obtained from more than the planned number of enrollment at each study center. One investigator at each study center, who was not involved in patient care, was responsible for the selection of patients, assessment of neuromuscular recovery, and data collection regarding postoperative complications.

The first phase of the study was from October 2009 to February 2010. In all patients, anesthesia was maintained with either sevoflurane or target-controlled infusion of propofol. The intraoperative anesthetic management was at the discretion of the attending anesthesiologist who was unaware that the patient had been included in the study. Rocuronium (0.6–0.9 mg/kg) was used to facilitate tracheal intubation, and supplemental doses of 0.1 to 0.2 mg/kg were administered as required for maintaining surgical relaxation. Standard monitoring was used, and core rectal or bladder temperature was maintained above 36.0°C throughout surgery and in the postanesthesia care unit (PACU) with the use of either a forced-air warmer or water blanket. The timing of the administration of rocuronium or the reversal drug was determined by the attending anesthesiologist by clinical criteria without using peripheral nerve stimulators or neuromuscular function monitors. After the conclusion of surgery, the attending anesthesiologist determined the adequacy of neuromuscular transmission by clinical signs. The clinical signs consisted of the presence of either bucking against the endotracheal tube, spontaneous breathing, or movement of extremities in response to commands. When the attending anesthesiologist judged that there was adequate spontaneous recovery from neuromuscular blockade, neostigmine supplemented with atropine sulfate was administered. Otherwise, the administration of neostigmine was delayed until these criteria were met. The dose of neostigmine was also at the discretion of the attending anesthesiologist, but the ratio of neostigmine and atropine sulfate (mg:mg) was fixed at 2:1. The decision to remove the tracheal tube was also made by the attending anesthesiologist based on assessment of clinical tests such as tidal volume, negative inspiratory force, grip force, and ability to sustain head lift. One of the coauthors at each study center randomly selected the study patients from the pool of consented patients and made quantitative assessment of neuromuscular function with the use of acceleromyography (TOF-Watch SX, Organon Ireland Ltd, a division of MSD, Dublin, Ireland). Since recent involvement could have modified neuromuscular management by the attending anesthesiologist, care was taken not to select study patients if the attending anesthesiologist was involved in this study within the previous 7 days. The accelerographic response of the adductor pollicis muscle to a 50-mA train-of-four (TOF) stimulation (train-of-four ratio, TOFR) was recorded. The hand adaptor was used in all measurements to ensure a constant preload, but the TOF-Watch SX was not calibrated or normalized before patient testing. Two consecutive TOF measurements (separated by 15 seconds) were obtained, and the average of the 2 values was noted. If the 2 measurements differed by >10%, up to 4 additional TOF measurements were obtained and the median of all the values was recorded.[2]

In the second phase of the study, which was from November 2010 to March 2011, the incidence of postoperative residual weakness after reversal with sugammadex was investigated. The management of neuromuscular block was similar to that in the first phase. The attending anesthesiologists administered 2 mg/kg sugammadex at the conclusion of surgery if bucking against the tracheal tube, spontaneous breathing, or movement of extremities were noted. If these signs were not present, 4 mg/kg sugammadex was administered IV. After tracheal extubation, TOFR was determined in the same fashion as described earlier.

During both study phases, patients with TOFR between 0.8 and 0.9 were observed in the PACU by one of the coauthors until the TOFR recovered to >0.9 and were subsequently transferred to the ward. Patients with TOFR <0.8 received additional reversals with the same drugs the patients had initially received. They were observed in the PACU until the TOFR exceeded 0.9 and then transferred to the ward.

The primary outcome of this study was the incidence of postoperative residual weakness after tracheal extubation. In this study, we used 2 different definitions of postoperative residual weakness. First, the conventional threshold of TOFR <0.9 was used according to previous reports.[4,17–19] Additionally, a more strict threshold of TOFR <1.0 was used since several studies demonstrated that this criteria is more appropriate than conventional TOFR <0.9 of residual weakness when uncalibrated acceleromyographic measurement is used.[20–23] The secondary outcome was the incidence of critical respiratory events and postoperative pulmonary complications at hospital discharge or during the first postoperative week. These complications are defined as follows: upper airway obstruction requiring

intervention, bronchospasm, aspiration of gastric or oropharyngeal contents, hypoxemia requiring supplemental oxygen administration, need for tracheal reintubation, and pneumonia.[2,24] The nursing staff in the PACU or ward was asked to record whether any of the signs and symptoms described above were present during the observation period. These data were later collected by the one of the coauthors at each study center.

Power analysis and logistic multivariate regression were conveyed by StatMate 2 (Graphpad software, San Diego, CA) and PASW statistics (ver.18, SPSS, Chicago, IL), respectively. Other data were analyzed with Prism (ver 5.0c, Graphpad software). Although we hypothesized that the use of sugammadex would eliminate postoperative residual weakness regardless of the use of a monitoring device, we selected the sample size to detect a 50% reduction in the incidence of residual neuromuscular block (defined as a TOFR <0.9 in studies that calibrated and normalized responses) after sugammadex compared with neostigmine for practical reasons. The incidence of TOFR <0.9 after neostigmine without objective monitoring was reported to be 32%[2]; therefore, a sample size of 110 patients in each phase would provide statistical power of >80% to detect a difference if the incidence of residual block after sugammadex was assumed to be 16% with an α of 0.05. Data are expressed as mean ± SD or the point estimate and 95% confidence interval unless otherwise specified. The incidence of primary and secondary outcomes was compared using $\chi^2$ test. To explore the contributing factors of postoperative residual weakness, several variables from the patients with or without postoperative residual weakness were compared with unpaired *t* test, Mann-Whitney *U* test, or Fisher exact test, as appropriate. Multivariate logistic regression analysis was also used to define risk factors of postoperative residual weakness when possible. A *P* value <0.05 was considered statistically significant.

## RESULTS

Seven to 14 attending anesthesiologists were involved in the management of intraoperative neuromuscular blockade in each study center during the first phase of this study. Five to 14 attending anesthesiologists were involved during the second phase of this study. During the first phase, 132 patients (of the 304 patients who were initially screened and consented for the study) were actually studied. Of those, 23 patients did not receive neostigmine (spontaneous recovery group) and the remaining 109 patients received neostigmine (neostigmine group). During the second phase, 287 patients were initially screened and gave informed consent, of which 117 were studied. All patients studied during the second phase received sugammadex for reversal (sugammadex group). The demographics, the dose and timing of rocuronium administration, reversal administration, and TOFR measurement are summarized in Table 1. The patients in the sugammadex group underwent significantly shorter surgical procedures. The total dose of rocuronium per body weight and per surgical duration was significantly higher in patients in the sugammadex group. The patients in the sugammadex group received the reversal drug and were assessed for adequacy of recovery significantly earlier than the patients in the neostigmine group.

The incidence (95% confidence interval) of TOFR <0.9 was 13.0% (2.8%–33.6%) (3 patients), 23.9% (16.2%–33.0%) (26 patients), and 4.3% (1.7%–9.4%) (5 patients) in the spontaneous recovery, neostigmine, and sugammadex groups, respectively ($P < 0.001$). The incidence (95% confidence interval) of TOFR <1.0 was 69.6% (47.1%–86.6%) (16 patients), 67.0% (57.3%–75.7%) (73 patients), and 46.2% (36.9%–55.6%) (54 patients) in the spontaneous recovery, neostigmine, and sugammadex groups, respectively ($P = 0.003$).

Demographics, rocuronium use, and reversal drug use in patients with or without postoperative residual weakness defined as TOFR <0.9 and TOFR <1.0 in the neostigmine and sugammadex group are summarized in Tables 2 and 3, respectively. The age, gender, types of maintenance

**Table 1. Patient Demographics and Use of Rocuronium and Reversal Drugs**

| | Spontaneous recovery group (*n* = 23) | Neostigmine group (*n* = 109) | Sugammadex group (*n* = 117) |
|---|---|---|---|
| Sex (male/female) | 15/8 | 44/65 | 43/74 |
| Age (y) | 47.0 ± 19.0 | 56.0 ± 16.0 | 58.0 ± 18.0 |
| Height (cm) | 164.1 ± 10.0 | 160.0 ± 9.0 | 159.4 ± 9.0 |
| Weight (kg) | 64.7 ± 13.0 | 57.8 ± 11 | 55.2 ± 11.0 |
| ASA physical status (I/II/III) | 17/6/0 | 49/60/0 | 52/65/0 |
| Duration of surgery (min) | 147.8 ± 49.0 | 202.1 ± 122.0 | 158.4 ± 112.0 (*P* < 0.0001) |
| Maintenance anesthetics (sevoflurane/propofol) | 17/6 | 73/36 | 80/37 |
| Intubation dose of rocuronium (mg) | 48.5 ± 9.6 | 43.3 ± 9.3 | 43.4 ± 10.0 |
| Supplemental dose of rocuronium (mg) | 15.6 ± 12.6 | 28.9 ± 29.6 | 29.5 ± 30.4 |
| Total dose of rocuronium (mg) | 62.6 ± 17.4 | 72.2 ± 32.0 | 72.9 ± 33.7 |
| Total dose of rocuronium (mg/kg) | 1.02 ± 0.28 | 1.26 ± 0.54 | 1.33 ± 0.56 |
| Total dose of rocuronium (mg/kg/h) | 0.44 ± 0.22 | 0.45 ± 0.20 | 0.68 ± 0.45 (*P* < 0.0001) |
| Dose of reversal drug | n/a | 32.9 ± 8.7(μg/kg) | 2.7 ± 1.0 (mg/kg) |
| Duration between final administration of rocuronium and reversal administration (min) | n/a | 87.3 ± 51.4 | 71.5 ± 42.2 (*P* = 0.012) |
| Duration between reversal administration and TOFR measurement (min) | n/a | 11.5 ± 8.0 | 8.0 ± 4.0 (*P* < 0.0001) |

Data are expressed as mean ± SD or numbers.
n/a = not applicable; TOFR = train-of-four ratio.
A *P* value is in parenthesis if there are statistical differences versus spontaneous group and neostigmine group with analysis of variance and Bonferroni post hoc test or versus neostigmine group with unpaired *t* test.

**Table 2. Characteristics of Patients with TOFR Below and Above 0.9 After Tracheal Extubation in the Neostigmine and Sugammadex Group**

| | Neostigmine group | | Sugammadex group | |
|---|---|---|---|---|
| | TOFR <0.9 (*n* = 26) | TOFR ≥0.9 (*n* = 83) | TOFR <0.9 (*n* = 5) | TOFR ≥0.9 (*n* = 112) |
| Gender (male/female) | 13/13 | 31/52 | 1/4 | 42/70 |
| Age (y) | 63.2 ± 12.9* | 53.7 ± 16.8 | 64.4 ± 21.9 | 57.7 ± 18.2 |
| Height (cm) | 159.0 ± 8.6 | 160.3 ± 9.0 | 156.8 ± 8.4 | 159.5 ± 8.8 |
| Weight (kg) | 56.5 ± 8.1 | 58.2 ± 12.0 | 51.0 ± 3.1 | 55.4 ± 11.3 |
| ASA physical status (I/II/III) | 7/19/0* | 42/41/0 | 2/3/0 | 50/62/0 |
| Duration of surgery (min) | 236.6 ± 135.9 | 191.4 ± 115.6 | 199.0 ± 155.9 | 156.6 ± 110.5 |
| Maintenance anesthetics (sevoflurane/propofol) | 22/4* | 51/32 | 5/0 | 75/37 |
| Intubation dose of rocuronium (mg) | 43.8 ± 8.0 | 43.2 ± 9.7 | 36.0 ± 8.9 | 43.7 ± 9.9 |
| Supplemental dose of rocuronium (mg) | 41.5 ± 29.9* | 24.9 ± 28.6 | 40.0 ± 41.2 | 29.1 ± 30.0 |
| Total dose of rocuronium (mg) | 85.4 ± 31.1* | 68.1 ± 31.4 | 76.0 ± 42.8 | 72.8 ± 33.5 |
| Total dose of rocuronium (mg/kg) | 1.54 ± 0.62* | 1.18 ± 0.48 | 1.48 ± 0.77 | 1.32 ± 0.55 |
| Total dose of rocuronium (mg/kg/h)[a] | 0.47±0.19 | 0.45±0.20 | 0.51±0.17 | 0.68 ± 0.46 |
| Dose of reversal drug (mean ± SD, median [range]) | 29.7 ± 10.7* μg/kg<br>31.3 [14.1–54.0] μg/kg | 33.9 ± 7.8 μg/kg<br>33.8 [17.1–51.3] μg/kg | 2.0 ± 0.1 mg/kg<br>2.0 [1.9–2.0] mg/kg | 2.7 ± 1.0 mg/kg<br>2.1 [1.7–5.7] mg/kg |
| Interval between final administration of rocuronium and reversal administration (min) | 65.5 ± 18.4* | 94.9 ± 55.6 | 66.6 ± 19.5 | 71.7 ± 43.0 |
| Interval between reversal administration and TOFR measurement (min) | 11.8 ± 10.1 | 11.5 ± 7.7 | 6.8 ± 3.0 | 8.0 ± 4.0 |

Data are expressed as numbers or mean ± SD unless otherwise specified.
TOFR = train-of-four ratio.
[a]Total dose of rocuronium (mg/kg/h) was calculated per body weight and surgical duration.
*$P < 0.05$ versus patients with TOFR ≥0.9 with unpaired *t* test or $\chi^2$ test.

anesthetics, the dose of reversal drug per body weight, interval between the last rocuronium administration and TOFR measurement, as well as the interval between the reversal administration and TOFR were used to construct a multivariate logistic regression model for the risk of TOFR <1.0 (Table 4). The linearity of log-transformed odds ratio of each explanatory variable was confirmed. In the neostigmine group, use of sevoflurane significantly increased the risk of residual muscle weakness compared with the use of propofol for maintenance of anesthesia. In the sugammadex group, the longer the interval between last dose of rocuronium administration and TOFR measurement, the lower the incidence of TOFR <1.0.

Three patients in the neostigmine group whose TOFR was <0.8 after initial reversal received an additional 2 mg neostigmine and 1 mg atropine sulfate. The dose of neostigmine used for the initial reversal was 18, 17, and 22 μg/kg, respectively. The other patients whose TOFR <0.9 were closely observed without receiving additional reversal. These patients remained in the PACU and were transferred to the ward after TOFR >0.9 was confirmed. No critical respiratory event was noted during this extended observational

**Table 3. Characteristics of Patients with TOFR Below and Above 1.0 After Tracheal Extubation in the Neostigmine and Sugammadex Groups**

| | Neostigmine group | | Sugammadex group | |
|---|---|---|---|---|
| | TOFR <1.0 (*n* = 73) | TOFR ≥1.0 (*n* = 36) | TOFR <1.0 (*n* = 54) | TOFR ≥1.0 (*n* = 63) |
| Gender (male/female) | 31/42 | 13/23 | 22/32 | 21/42 |
| Age (y) | 56.3 ± 15.7 | 55.3 ± 17.8 | 61.9 ± 18.8 | 53.9 ± 17.0 |
| Height (cm) | 160.1 ± 8.6 | 159.7 ± 9.6 | 158.6 ± 8.8 | 160.3 ± 9.1 |
| Weight (kg) | 57.6 ± 9.0 | 58.3 ± 14.8 | 54.9 ± 10.2 | 55.9 ± 12.4 |
| ASA physical status (I/II/III) | 36/37/0 | 13/23/0 | 20/34/0 | 32/31/0 |
| Duration of surgery (min)* | 221.3 ± 135.5* | 163.4 ± 74.5 | 173.0 ± 123.2 | 155.8 ± 101.6 |
| Maintenance anesthetics (sevoflurane/propofol) | 59/14* | 14/22 | 41/13 | 39/24 |
| Intubation dose of rocuronium (mg) | 42.7 ± 8.1 | 44.7 ± 11.3 | 45.6 ± 11.0 | 42.0 ± 8.3 |
| Supplemental dose of rocuronium (mg) | 34.5 ± 32.6* | 17.6 ± 17.9 | 35.8 ± 33.1 | 25.8 ± 28.2 |
| Total dose of rocuronium (mg) | 77.1 ± 34.9 | 62.4 ± 22.4 | 81.4 ± 37.0 | 67.9 ± 28.9 |
| Total dose of rocuronium (mg/kg) | 1.35 ± 0.6* | 1.08 ± 0.32 | 1.47 ± 0.59 | 1.23 ± 0.50 |
| Total dose of rocuronium (mg/kg/h)[a] | 0.45 ± 0.19 | 0.46 ± 0.21 | 0.69 ± 0.47 | 0.63 ± 0.43 |
| Dose of reversal drug (mean ± SD, median [range]) | 32.5 ± 9.0 μg/kg<br>32.6 [14.0–54.0] μg/kg | 33.7 ± 8.3 μg/kg<br>34.5 [17.1–51.3] μg/kg | 2.60 ± 0.92 mg/kg<br>2.1 [1.9–5.3] mg/kg | 2.69 ± 0.89 mg/kg<br>2.1 [1.7–5.7] mg/kg |
| Interval between final administration of rocuronium and reversal administration (min) | 80.9 ± 45.1* | 101.9 ± 59.0 | 60.5 ± 32.4* | 85.0 ± 49.6 |
| Interval between reversal administration and TOFR measurement (min) | 12.2 ± 9.2 | 10.2 ± 6.1 | 8.1 ± 4.3 | 8.4 ± 3.7 |

Data are expressed as numbers or mean ± SD unless otherwise specified.
TOFR = train-of-four ratio.
[a]Total dose of rocuronium (mg/kg/h) was calculated per body weight and surgical duration.
*$P < 0.05$ versus patients with TOFR ≥1.0 with unpaired *t* test or $\chi^2$ test.

**Table 4. Risk Factors of Postoperative TOFR Below 1.0 in Neostigmine and Sugammadex Group**

| | Neostigmine ($n$ = 109) | | | Sugammadex ($n$ = 117) | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% CI | $P$ value | Odds ratio | 95% CI | $P$ value |
| Age (y) | 0.99 | 0.964–1.024 | 0.67 | 1.00 | 0.982–1.026 | 0.75 |
| Male gender | 0.91 | 0.348–2.400 | 0.86 | 1.26 | 0.556–2.871 | 0.58 |
| Sevoflurane maintenance | 2.54 | 1.585–3.900 | 0.0001 | 1.81 | 0.225–1.360 | 0.20 |
| Dose of reversal drug per body weight[a] | 0.77 | 0.216–2.747 | 0.69 | 0.99 | 0.626–1.556 | 0.96 |
| Interval between final administration of rocuronium and reversal administration (min) | 0.99 | 0.984–1.002 | 0.11 | 0.98 | 0.975–0.997 | 0.015 |
| Interval between reversal administration and TOFR measurement (min) | 1.05 | 0.973–1.135 | 0.20 | 1.00 | 0.903–1.125 | 0.88 |

The odds ratio, 95% confidence interval (CI), and $P$ value of each explanatory variable were summarized. The predictive accuracy of each analysis was 0.789 and 0.624, respectively. Hosmer-Lemeshow test confirmed the adequacy of the modeling in both groups.
TOFR = train-of-four ratio.
[a]The unit of this variable was μg/kg for the neostigmine group and mg/kg for the sugammadex group.

period. Furthermore, no postoperative pulmonary complications occurred during the patients' hospital stay.

## DISCUSSION

In this study, we investigated the incidence of postoperative residual weakness after spontaneous recovery or assisted recovery from rocuronium with neostigmine or sugammadex when no form of intraoperative neuromuscular monitoring was used. After the use of rocuronium, the point estimate (95% confidence interval) of TOFR <0.9 was 13.0% (2.8%–33.6%), 23.9% (16.2%–33.0%), and 4.3% (1.7%–9.4%) in the spontaneous recovery, neostigmine, and sugammadex groups, respectively. Furthermore, the incidence of TOFR <1.0 was 69.6% (47.1%–86.6%), 67.0% (57.3%–75.7%), and 46.2% (36.9%–55.6%) in the spontaneous recovery, neostigmine, and sugammadex groups, respectively. This study demonstrated that the risk of TOFR <0.9 in the PACU remains at least 1.7% and may be as high as 9.4% after reversal with sugammadex when no form of intraoperative neuromuscular monitoring is used.

The clinical implications of postoperative residual weakness after the administration of NMBDs have been repeatedly demonstrated even in the case of NMBDs with intermediate duration.[4,17,18,25] Since no clinical signs enable anesthesia practitioners to confirm this level of recovery,[25,26] the quantitative monitoring of neuromuscular function is strongly advocated to prevent postoperative residual weakness and its clinical consequences.[1,27–31] However, quantitative neuromuscular monitoring is not yet widely used.[13] For example, a survey in the United Kingdom showed that only 9.4% of respondents routinely used quantitative neuromuscular monitors.[10] Also, a survey in Italy revealed that 73% of the respondents depend on the clinical signs of recovery, rather than objective measurements of neuromuscular function.[11] In the United States, only 22.7% of survey respondents reported that quantitative TOF monitors were even available.[12]

Contrary to neostigmine, sugammadex quickly reverses rocuronium- or vecuronium-induced neuromuscular blockade in a dose-dependent manner. Almost all clinical trials have demonstrated the advantage of sugammadex over neostigmine in various settings.[32–37] These studies collectively suggest that sugammadex may preclude the possibility of postoperative residual weakness, as long as an adequate dose is used. We therefore investigated whether reversal with sugammadex would eliminate postoperative residual weakness in a real-world clinical scenario in which neuromuscular monitoring is not used routinely.

We found that reversal with sugammadex failed to eliminate the occurrence of postoperative residual weakness. Additionally, we found a surprisingly high number of patients who had residual weakness after reversal with either neostigmine or sugammadex. Our multivariate logistic regression analysis yielded different risk factors after reversal with neostigmine and sugammadex. First, the effect of sevoflurane on increasing the risk of postoperative weakness was only demonstrated in the neostigmine group. This finding is in accordance with previous reports on the effects of volatile anesthetic drugs on antagonism of neuromuscular blockade.[38–41] Second, the short interval between the last dose of rocuronium and sugammadex administration was found to be associated with an increased risk of residual weakness after sugammadex. Since previous studies universally demonstrated that sugammadex provides rapid and complete recovery of neuromuscular function when the dose is adequately matched with the degree of neuromuscular blockade, our findings underscore the lack of reliability of clinical signs for assessment of neuromuscular recovery.[42–44]

This study has several limitations. First, the study was observational and was performed at 2 different time intervals. It is possible that practice patterns regarding neuromuscular blockade and its recovery might have been modified between the 2 study phases, possibly due to the publications that demonstrated better efficacy and safety profiles of sugammadex. For example, sugammadex may be more liberally administered since it lacks serious side effects. However, this design allows us to evaluate the incidence of postoperative residual weakness in terms of our routine clinical practice since the attending anesthesiologists who provided intraoperative care were not aware of study enrollment. Second, variation of the interval between sugammadex administration and the TOFR measurement may play a role in the incidence of postoperative residual weakness, at least in patients receiving sugammadex. Although there was no statistical difference between the patients with TOFR <1.0 and with TOFR ≥1.0 in the sugammadex group, some patients with TOFR <1.0 at the time of measurement may have recovered from neuromuscular blockade within several minutes. Third, the criteria and data collection of postoperative pulmonary complication may not have been sufficiently sensitive to find minor but

clinically relevant complications caused by postoperative residual weakness. Despite these limitations, we believe our data clearly demonstrate the importance of quantitative monitoring of neuromuscular monitoring to assure adequate recovery at the end of anesthesia.

In conclusion, this study demonstrated that sugammadex decreased the incidence of postoperative residual weakness compared with neostigmine (4.3% vs 23.9% for TOFR <0.9 and 46.2% vs 67.0% for TOFR <1.0). However, the risk of TOFR <0.9 in the PACU remained at least 1.7% and may be as high as 9.4% even with sugammadex in a clinical setting when no neuromuscular monitoring is used routinely.

## DISCLOSURES

**Name:** Yoshifumi Kotake, MD, PhD.
**Contribution:** This author helped design and conduct the study, analyze the data, and write the manuscript.
**Attestation:** Yoshifumi Kotake has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
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