ANESTHESIOLOGY

A Dose-finding Study of Sugammadex for Reversal of Rocuronium in Cardiac Surgery Patients and Postoperative Monitoring for Recurrent Paralysis

T. Andrew Bowdle, M.D., Ph.D., F.A.S.E.,
Kishanee J. Haththotuwegama, B.S.,
Srdjan Jelacic, M.D., F.A.S.E., Sharon T. Nguyen, B.S.,
Kei Togashi, M.D., M.P.H., Kelly E. Michaelsen, M.D., Ph.D.

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ABSTRACT

Background: The dose of sugammadex recommended by the manufacturer for reversal of rocuronium is 2 mg/kg when the train-of-four count is 2 or more and 4 mg/kg when it is less than 2 but there is a posttetanic count of at least 1. The purpose of this dose-finding study was to titrate sugammadex to produce a train-of-four ratio 0.9 or greater at the conclusion of cardiac surgery, and to continue monitoring neuromuscular blockade in the intensive care unit to identify recurrent paralysis. The hypothesis was that many patients would require less than the recommended dose of sugammadex, but that some would require more, and that recurrent paralysis would not occur.

Methods: Neuromuscular blockade was monitored using electromyography during cardiac surgery. Administration of rocuronium was at the discretion of the anesthesia care team. During sternal closure, sugammadex was titrated in 50-mg increments every 5 min until a train-of-four ratio 0.9 or greater was obtained. Neuromuscular blockade was monitored with electromyography in the intensive care unit until sedation was discontinued before extubation or for a maximum of 7 h.

Results: Ninety-seven patients were evaluated. The dose of sugammadex required to achieve a train-of-four ratio of 0.9 or greater varied from 0.43 to 5.6 mg/kg. There was a statistically significant relationship between the depth of neuromuscular blockade and the sugammadex dose required for reversal, but there was a large variation in dose required at any depth of neuromuscular blockade. Eighty-four of 97 patients (87%) required less than the recommended dose, and 13 (13%) required more. Two patients required additional sugammadex administration for recurrent paralysis.

Conclusions: When sugammadex was titrated to effect, the dose was usually less than the recommended dose, but it was more in some patients. Therefore, quantitative twitch monitoring is essential for ascertaining that adequate reversal has taken place after sugammadex administration. Recurrent paralysis was observed in two patients.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Sugammadex is effective for reversing neuromuscular blockade produced by rocuronium or vecuronium
- The manufacturer has recommended that a sugammadex dose of 2 mg/kg be administered if at least two twitches are present in response to a train-of-four stimulus, or 4 mg/kg if there are less than two twitches but a posttetanic count of more than 0

What This Article Tells Us That Is New

- The hypothesis that many patients would require less than the recommended dose of sugammadex, but that some would require more, and that recurrent paralysis would not occur was tested in a prospective dose-finding study of 97 cardiac surgery patients administered rocuronium in whom neuromuscular blockade was monitored using an electromyography-based twitch monitor
- The sugammadex dose required for an individual patient could not be predicted with certainty based on the train-of-four twitch response immediately before reversal
- Two patients had recurrent paralysis during the postoperative monitoring period
- Quantitative twitch monitoring is essential to evaluate the effectiveness of reversal with sugammadex

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T. Andrew Bowdle, M.D., Ph.D., F.A.S.E.: Department of Anesthesiology, University of Washington, Seattle, Washington.

Kishanee J. Haththotuwegama, B.S.: Department of Anesthesiology, University of Washington, Seattle, Washington.

Srdjan Jelacic, M.D., F.A.S.E.: Department of Anesthesiology, University of Washington, Seattle, Washington.

Sharon T. Nguyen, B.S.: Department of Anesthesiology, University of Washington, Seattle, Washington.

Kei Togashi, M.D., M.P.H.: Department of Anesthesiology and Perioperative Care, University of California-Irvine, Irvine, California; Department of Anesthesiology, University of Washington, Seattle, Washington.

Kelly E. Michaelsen, M.D., Ph.D.: Department of Anesthesiology, University of Washington, Seattle, Washington.

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Sugammadex, a γ-cyclodextrin molecule, is effective for reversing aminosteroid neuromuscular blocking drugs by binding the neuromuscular blocking drugs stoichiometrically, each molecule of sugammadex binding a molecule of rocuronium or vecuronium. The manufacturer has recommended that a sugammadex dose of 2 mg/kg actual body weight should be administered if at least two twitches are present in response to a train-of-four stimulus, or 4 mg/kg if there are less than two twitches but more than a posttetanic count of 0. This two-tiered approach to dosing is generally supported by data from several dose-finding studies.[1–14] Nevertheless, it is also apparent from these data that in some patients, reversal to a train-of-four ratio of at least 0.9 can be achieved with less than the recommended dose. However, the safety of using less than the recommended dose of sugammadex has been questioned because of concerns about possible recurrent paralysis (also known as "recurarization"), whereby a patient who has achieved a train-of-four ratio of at least 0.9, subsequently over a period of minutes or hours experiences increased neuromuscular blockade and a train-of-four response that is less than a train-of-four ratio of 0.9.[2,3,7,15–17] In addition, some patients may require more than the recommended dose of sugammadex. For example, Ortiz-Gomez *et al.* reported a case in which rocuronium neuromuscular blockade in a patient with a train-of-four count of 1 could not be reversed after 9.7 mg/kg of sugammadex; they could not find an explanation for this, finally concluding that the patient was a dose-response "outlier."[18]

We conducted a prospective dose-finding study to further investigate the dose-response relationship between sugammadex and the train-of-four twitch response and the possibility of recurrent neuromuscular blockade. Cardiac surgery patients were studied because they routinely remain intubated for at least several hours after surgery. In addition, our medical center's cardiac surgery fast-track extubation protocol includes quantitative twitch monitoring and reversal of neuromuscular blocking drugs at the conclusion of surgery.

The hypothesis was that many patients would require less than the recommended dose of sugammadex, but that some patients would require more, and that recurrent paralysis would not occur.

Methods

Participants

This dose-finding study was approved by the Institutional Review Board of the University of Washington (Seattle, Washington). Patients were approached for the study between February 2022 and July 2022 and gave written informed consent. The study was registered at ClinicalTrials.gov (NCT05246397; Dr. Bowdle, February 18, 2022) before patient enrollment; the study was carried out as described except for minor modifications. Patients aged 18 yr or older undergoing cardiac surgery fit the inclusion criteria. Exclusion criteria were allergies or other contraindications to the use of sugammadex. The study was carried out at a single center.

Quantitative Neuromuscular Blockade Monitoring and Sugammadex Administration

Reversal or recovery from paralysis was defined as a train-of-four ratio greater than or equal to 0.9. Neuromuscular blockade was monitored using an electromyography-based twitch monitor (TwitchView, Blink DC, USA) with stimulating current set to 80 mA at a 300-ms pulse width (The default settings for the TwitchView are 65 mA at 300-ms pulse width. When testing quantitative neuromuscular blockade monitors, we utilize the maximum current output of the monitor, which is typically 60 to 80 mA.[19–21] This approach has also been taken by others.[22] We take this approach because our clinical and laboratory experience is that lower currents, including the supramaximal current, sometimes fail to produce a large enough twitch amplitude for accurate measurement of the train-of-four count or the train-of-four ratio under real world clinical conditions). The TwitchView electrode array was applied to stimulate the ulnar nerve and measure the muscle action potential at either the adductor pollicis or the first dorsal interosseous muscle. The administration of neuromuscular blocking drugs was at the discretion of the clinical anesthesia team; however, rocuronium was the nondepolarizing neuromuscular blocking drug used in all cases. Anesthesia consisted of isoflurane and opioids (including fentanyl, sufentanil, hydromorphone, and methadone); isoflurane was administered during cardiopulmonary bypass. At the end of surgery, a propofol infusion was administered for postoperative sedation. After induction of anesthesia but before administration of any neuromuscular blocking drugs, and before tucking the arm at the patient's side, a baseline train-of-four measurement was made to verify that the monitor and electrode array were functioning properly. Near the end of the surgery, when the sternum had been reapproximated, the response to a train-of-four stimulus was determined, and sugammadex titration was performed under the supervision of the investigators unless the train-of-four ratio had spontaneously recovered to at least 0.9. A 200-mg, 2-ml vial of sugammadex was diluted in a syringe to a total of 20 ml with saline to facilitate the administration of sugammadex in 50-mg (5-ml) boluses. Five minutes after each sugammadex dose of 50 mg, the response to the train-of-four stimulus was determined. Sugammadex dosing was continued until a train-of-four ratio of at least 0.9 was achieved, before patient transport to the intensive care unit (ICU).

Postoperative Assessment of Neuromuscular Blockade

Electromyography-based twitch monitoring by the investigators was continued in the ICU every 15 min for the first

hour after arrival and then hourly for up to 7 h or until propofol sedation was discontinued in preparation for extubation. If the train-of-four ratio was less than 0.9 during the monitoring period in the ICU, additional sugammadex doses of 50 mg were administered until the patient regained a train-of-four ratio 0.9 or greater.

Primary and Secondary Outcomes

The primary outcome was the response to train-of-four stimulation just before sugammadex administration and the total dose of sugammadex required to achieve a train-of-four ratio of at least 0.9. The secondary outcome was the incidence of recurrent paralysis during the postoperative monitoring period, defined as a train-of-four ratio less than 0.9 after first having achieved successful reversal to a train-of-four ratio 0.9 or greater.

Statistical Analysis

Sample size was based on previous sugammadex dose-finding studies. The sample size in this study was similar to the largest previous sugammadex dose-finding studies. Descriptive statistics are presented as number (%) for categorical variables or mean ± SD for continuous variables. Outcome variables (sugammadex dose) were compared among twitch response groups using two-sample Student's *t* test with the assumption of unequal variance (Satterthwaite's degrees of freedom), ANOVA, two-sample test of proportions, Wilcoxon rank-sum test and Pearson's chi-square test as appropriate. All *P* values were two-sided, and statistical significance was defined as a *P* value <0.05. All statistical analyses were performed with STATA 11.0 (Stata Corp LP, USA). Patient and procedure characteristics were analyzed with R 4.2.1s (R Foundation for Statistical Computing, Austria).

Results

One hundred forty-five patients eligible for the study were approached preoperatively, and 126 were enrolled. One hundred patients (of the 126 enrolled) required reversal with sugammadex. The remaining 26 patients recovered spontaneously to a train-of-four ratio of at least 0.9 at the time of sternal reapproximation. Three patients of 100 who received sugammadex were excluded from the study: 1 patient received an incorrect dose of sugammadex during titration (200 mg instead of 50 mg), 1 patient had probable anaphylaxis to sugammadex and the titration was discontinued, and 1 patient received an additional dose of sugammadex after reversal to train-of-four ratio 0.9 or greater. Patient enrollment is further depicted in figure 1. The characteristics of the 97 patients who received sugammadex and were evaluable are shown in table 1. Of these 97 patients, there were 4 whose post-reversal monitoring period was shorter than intended (2 patients required additional rocuronium after successful reversal, and 2 patients were extubated in the operating room), but these patients were not excluded from the study.

The total dose of sugammadex required to achieve a train-of-four ratio of at least 0.9 is shown in figure 2A for each patient, along with the response to the train-of-four stimulus just before sugammadex administration. The sugammadex dose on a per kilogram actual body weight

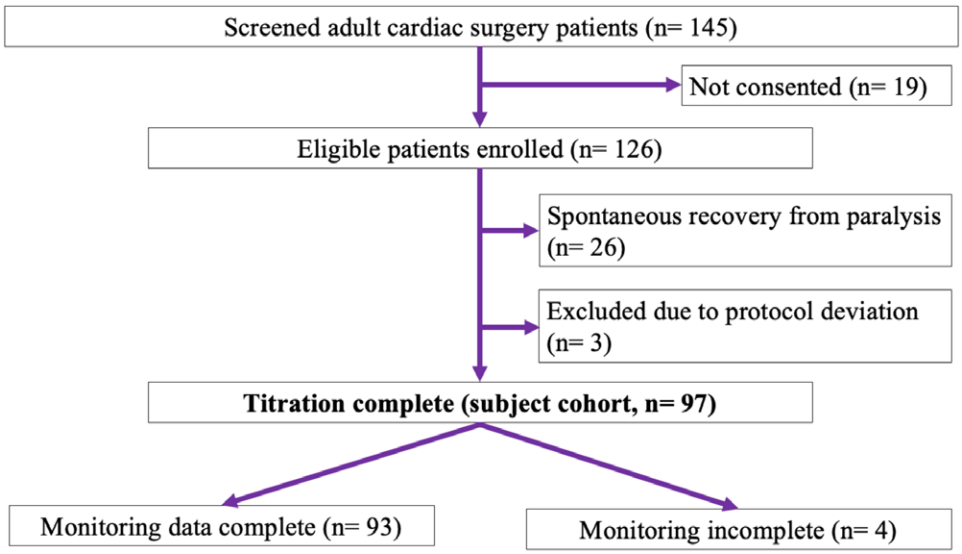

Fig. 1. Flowchart depicting the enrollment of patients.

Table 1. Patient Characteristics*

	All Patients, N = 97	Prereversal Train-of-four Count < 2, N = 29	Prereversal Train-of-four Count ≥ 2, N = 68	*P* Value between Dosing Group†
Age, yr	58 (15)	57 ± 15.0	59 (16)	0.622
Sex				0.857
Female	23 (24%)	6 (21%)	17 (25%)	
Male	73 (75%)	23 (79%)	50 (74%)	
Other	1 (1%)	0 (0%)	1 (1.5%)	
Weight, kg	80 [73–95]	81 [75–105]	80 [73–94.0]	0.505
BMI, kg/m^2	27.3 (4.7)	28.2 (5.3)	26.9 (4.3)	0.248
Race				0.600
Asian	8 (8%)	4 (14%)	4 (6%)	
White	77 (79%)	23 (79%)	54 (79%)	
Other	12 (12%)	2 (7%)	10 (15%)	
Creatinine, mg/dl‡	0.9 [0.8–1.1]	0.9 [0.8–1.0]	1.0 [0.9–1.1]	0.105
Hemoglobin, g/dl§	9.2 (1.6)	9.1 ± 1.4	9.3 (1.7)	0.881
Proportion with deep hypothermic cardiac arrest	19 (20%)	5 (17%)	14 (21%)	0.704
Minimum temperature on bypass, °C‖	34.2 [32.1–35.3]	34.2 [32.0–34.8]	34.3 [32.1–35.3]	0.432
Temperature at time of reversal#	36.3 [35.9–36.7]	36.3 [35.8–36.7]	36.4 [35.9–36.8]	0.517
Procedure duration	329.1 (91.6)	323.3 ± 72.6	331.6 (99.0)	0.909
Time between last rocuronium dose and first sugammadex dose	138 [66–269]	62 [24–142]	169 [107–276]	< 0.001
Postoperative monitoring time	113 [86–204]	109 [83–234]	115 [90–195]	0.694

*Continuous variables are presented as mean ± SD for normally distributed data or median [interquartile range]. †Pearson's chi-square test; Wilcoxon rank-sum test. ‡Preoperative value. §Value at time of sugammadex administration. ‖Data missing for three patients. #Data missing for four patients.

basis is shown in figure 2B. A box-and-whisker plot is shown in figure 3A for the two subgroups of patients that would require either 2 mg/kg or 4 mg/kg sugammadex based on the manufacturer's dosing recommendations; four patients with a posttetanic count of 0 were included in the 4 mg/kg subgroup although the manufacturer does not specify a dose for patients with a posttetanic count of 0. There was a significant difference in mean sugammadex dose requirement between the 2 mg/kg and 4 mg/kg recommended dose groups ($P < 0.001$), and this difference was maintained whether or not the four patients with a posttetanic count of 0 were included (table 2). A box-and-whisker plot is shown in figure 3B for subgroups of patients with a posttetanic count (including a posttetanic count of 0), a train-of-four count of 1, 2, or 3, a train-of-four ratio less than 0.4, or a train-of-four ratio 0.4 or greater before sugammadex administration. There was a significant difference in the mean sugammadex dose requirement between the subgroups with different train-of-four stimulus responses before sugammadex ($P < 0.001$; table 2).

The mean dose requirements were less than the manufacturer's recommended dose for each subgroup; however, there was substantial variation in dose requirement between patients. While many patients required less than the recommended dose, some patients required more than the recommended dose. Of the 68 patients starting the sugammadex titration with a train-of-four count of at least 2, whose manufacturer's recommended dose would be 2 mg/kg, 11 required more than 2 mg/kg to achieve a train-of-four ratio of at least 0.9. Of the 29 patients starting the sugammadex titration with a train-of-four count of 1 or less, whose manufacturer's recommended dose would be 4 mg/kg, 2 required more than 4 mg/kg to achieve reversal. Although four patients had a posttetanic count of 0 and therefore fell outside of the manufacturer's dose recommendations, none required more than 4 mg/kg for reversal; they required 0.9, 1.7, 2.6, or 3.8 mg/kg.

Ninety-five out of 97 patients (98%) did not have recurrent paralysis during the postoperative monitoring period, which averaged 2.5 h and ranged between 3 min and just greater than 7 h. One patient weighing 74 kg had a train-of-four ratio of 0.47, received 100 mg sugammadex, and achieved a train-of-four ratio greater than 0.9, but 5 min later, while still in the operating room, had a train-of-four ratio of 0.87. Two additional 50-mg doses of sugammadex were administered before achieving a train-of-four ratio greater than 0.9; the train-of-four ratio remained above 0.9 during 175 min of postoperative monitoring (fig. 4A). One patient weighing 78 kg had a posttetanic count of 0, received 250 mg sugammadex to produce a train-of-four ratio greater than 0.9, but after 45 min in the ICU had a train-of-four ratio of 0.81. An additional 50-mg dose of sugammadex produced a train-of-four ratio greater than 0.9, which was maintained during the remaining 181 min of postoperative monitoring (fig. 4B). Both patients had normal renal function.

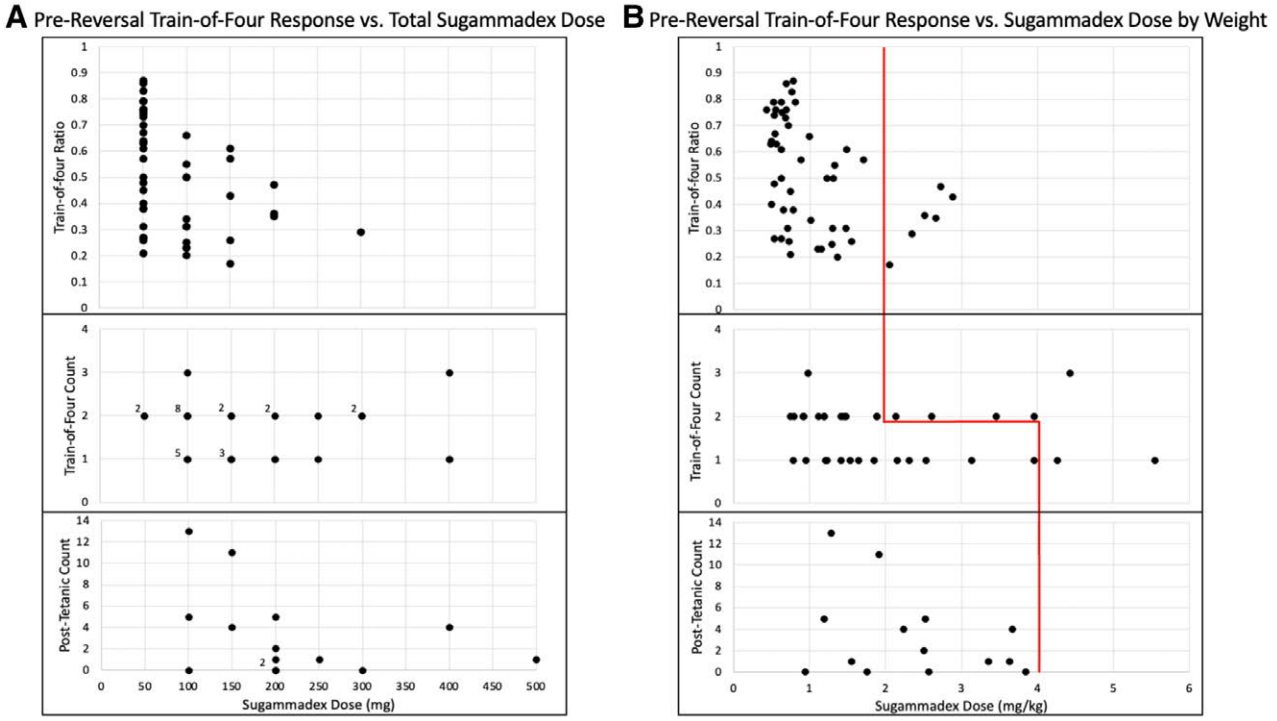

Fig. 2. The dose of sugammadex required to produce a train-of-four ratio of at least 0.9 is plotted against the response to a train-of-four stimulus (posttetanic count, train-of-four count, or train-of-four ratio) just before sugammadex administration. Data are shown for 97 patients. (*A*) The total dose of sugammadex is shown. When *dots* overlap and indicate more than one patient, the number of patients indicated by a dot is shown by a *numeral* next to the dot. (*B*) The dose of sugammadex is expressed normalized for patient weight (mg/kg). The *red line* indicates the manufacturer's recommended dose, 2 or 4 mg/kg based on the response to a train-of-four stimulus. Subjects to the *right* of the red line required doses larger than recommended.

Discussion

The dose of sugammadex required to achieve a train-of-four ratio of at least 0.9 varied from 0.43 mg/kg to 5.55 mg/kg. While there was a statistically significant relationship between the twitch response before reversal and the sugammadex dose required to achieve a train-of-four ratio of at least 0.9, as shown in figure 3, the range of dose requirements between patients with the same twitch response varied greatly. Eighty-four out of 97 patients (87%) required less than the manufacturer's recommended dose, and 13 (13%) required more than the manufacturer's recommended dose. A subgroup analysis of these 13 subjects compared to the other 84 subjects did not reveal clinically significant differences in patient characteristics between the groups. Three patients required more than the manufacturer's recommended dose of 4 mg/kg. Two patients required more than 4 mg/kg (5.55 and 4.26 mg/kg), despite having a train-of-four count of 1 before reversal. The third patient required more than 4 mg/kg (4.43 mg/kg) despite having a train-of-four count of 3 before reversal.

Since the dose required for an individual patient could not be predicted with certainty based on the train-of-four twitch response immediately before reversal, we conclude that quantitative twitch monitoring is essential to evaluate the effectiveness of reversal with sugammadex. Even if sugammadex had been administered at 4 mg/kg to all patients, some patients would not have attained a train-of-four ratio of at least 0.9.

Previous studies of reversal of rocuronium with sugammadex have utilized experimental designs with substantial differences from this study, making direct comparisons problematic (see table in Supplemental Digital Content 1, https://links.lww.com/ALN/D134). In previous studies, sugammadex was typically given at several fixed doses, such as 0.5, 1, 2, or 4 mg/kg, and the time required to reach a train-of-four ratio of 0.9 was measured. In some of these studies, sugammadex was administered when a train-of-four count of 2 was reached.[1,6–9,11,12] In some other studies, sugammadex was administered when neuromuscular blockade was profound, such as a posttetanic count of 1 or 2.[2–5,10] In other studies, small doses of sugammadex, 1 mg/kg or less, were administered when the train-of-four ratio reached 0.2 or 0.5.[13,14] Most previous studies utililzed acceleromyography, without normalization. While a dose of sugammadex of 2 mg/kg for a train-of-four count of 2 or 4 mg/kg

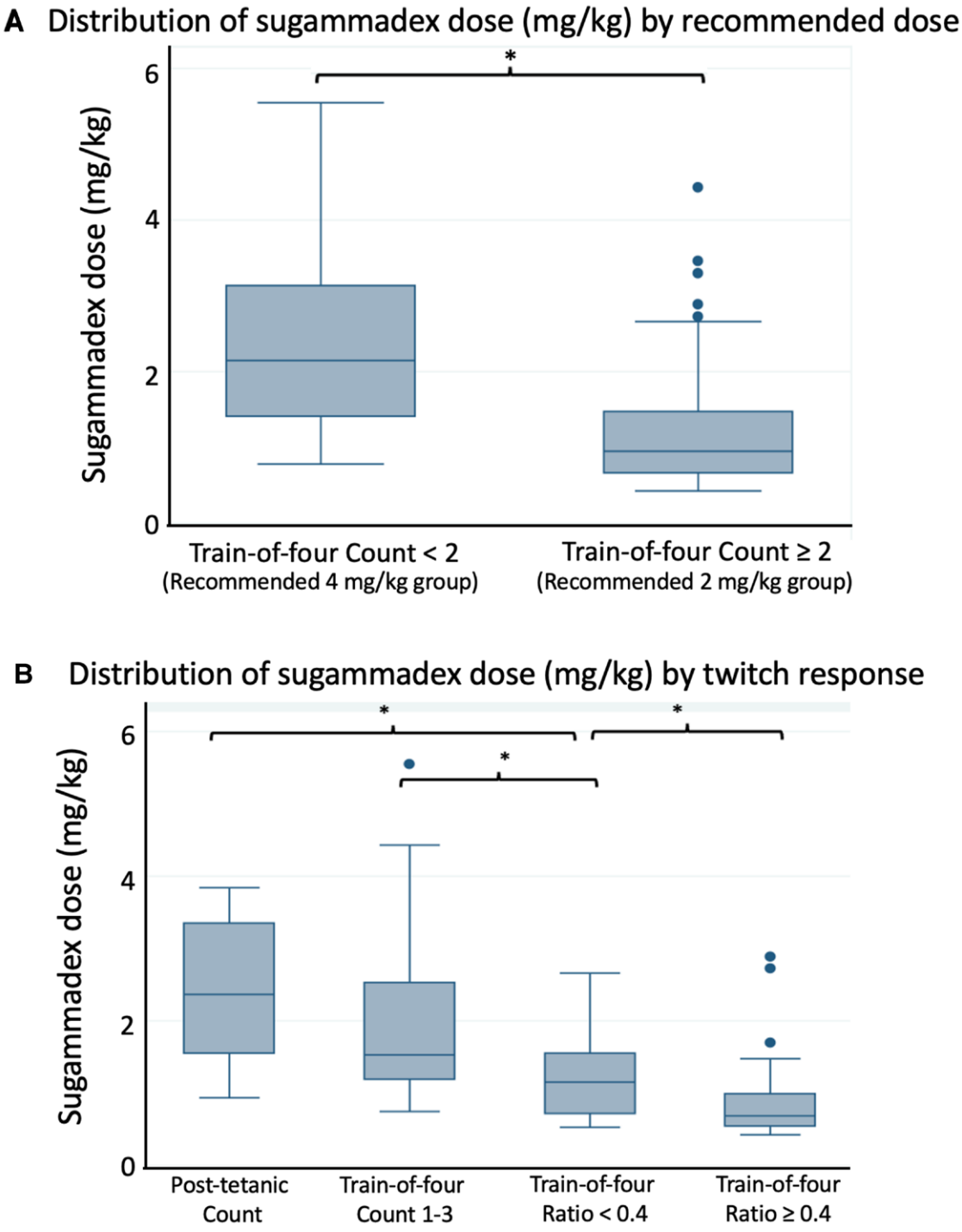

Fig. 3. The dose of sugammadex (mg/kg) required to produce a train-of-four ratio of at least 0.9 is shown in box and whisker plots[23] with patients divided into cohorts based on the response to the train-of-four stimulus just before reversal. The *box* depicts the median and interquartile range (25–75). The *whiskers* depict the minimum and maximum data points that occur within 1.5 times the interquartile range of the first and third quartiles. The *solid circles* depict outliers. (*A*) Patients were assigned to cohorts based on the manufacturer's recommended dose of sugammadex. Patients with a train-of-four count of 2 or more were assigned to the 2 mg/kg group. Patients with a train-of-four count of less than 2 were assigned to the 4 mg/kg group. (*B*) Patients were assigned to cohorts as shown. Patients with a train-of-four ratio were divided into 2 groups, those with a train-of-four ratio less than 0.4 and those with a train-of-four ratio 0.4 or greater. This division was chosen because patients with shallow neuromuscular blockade (train-of-four ratio 0.4 or greater) may be promptly reversed using neostigmine.[24] An *asterisk* and *bracket* indicate a statistically significant difference ($P < 0.05$) between groups.

Table 2. Sugammadex Dose Requirement for Different Twitch Responses before Reversal

Twitch Response before Reversal	Sugammadex Dose Requirement, mg/kg, Mean ± SD	*P* Value
Posttetanic count	2.35 ± 0.98	< 0.0001
Train-of-four count 1, 2, or 3	2.01 ± 1.22	
Train-of-four ratio < 0.4	1.29 ± 0.67	
Train-of-four ratio ≥ 0.4	0.90 ± 0.60	
Train-of-four count < 2*	2.30 ± 1.18	< 0.0001
Train-of-four count ≥ 2†	1.24 ± 0.83	

*Manufacturer's recommended dose of sugammadex is 4 mg/kg. †Manufacturer's recommended dose of sugammadex is 2 mg/kg.

for a posttetanic count of 1 or 2 usually resulted in a train-of-four ratio of 0.9 in less than 5 min in these studies, there were outliers. For example, Jones *et al.* reported that when the posttetanic count was 1 or 2, the time required to reach a train-of-four ratio of 0.9 after administering sugammadex 4 mg/kg ranged from 0.9 to 16.1 min; in addition, one patient did not reach a train-of-four ratio of 0.9 "during the observation period."[5] When the posttetanic count was 1 or 2 and a dose of sugammadex less than 4 mg/kg was administered, the time required to reach a train-of-four ratio was highly variable. For example, Duvaldestin *et al.* found that in patients receiving rocuronium with a posttetanic count of 1 or 2, a dose of sugammadex at 1 mg/kg achieved a train-of-four ratio of at least 0.9 in a median time of fewer than 10 min but required as much as nearly 120 min.[3] Groudine *et al.* found that in patients receiving rocuronium with a posttetanic count of 1 or 2, a dose of sugammadex at 1 mg/kg achieved a train-of-four ratio of at least 0.9 in a mean time of 19 min. However, the range was 5 to 33 min.[4] Sugammadex, 2 mg/kg, achieved a train-of-four ratio of at least 0.9 in a median time of 5 min, but the range was 2 to 15 min.

Most previous studies of sugammadex dose-response for reversal of neuromuscular blockade have utilized acceleromyography and have reported raw train-of-four ratio data without normalization. Using acceleromyography without normalization will tend to produce a nonnormalized train-of-four ratio of 0.9 with either smaller doses of sugammadex or shorter time intervals, as many patients have a baseline train-of-four ratio of greater than 1 with acceleromyography.[25,26] A train-of-four ratio of 0.9 with acceleromyography may not represent adequate reversal in patients with a baseline train-of-four ratio greater than 1. As this study utilized electromyographic twitch monitoring, which is not complicated by baseline train-of-four "overshoot," the doses of sugammadex and the time required to achieve a train-of-four ratio of at least 0.9 may be greater than found with acceleromyography.

There were two patients with mild recurrent paralysis, one with a posttetanic count of 0 before reversal, which is outside of the manufacturer's dosing recommendations. The other patient with recurrent paralysis had a train-of-four ratio of 0.47 before reversal and received 100 mg sugammadex. The train-of-four ratios at the time of recurrent paralysis were 0.81 and 0.87, respectively. While these train-of-four ratios do not represent severe recurrent paralysis, they were nevertheless less than 0.9. There have been numerous case reports of imputed recurrent paralysis after sugammadex, as well as some data from clinical trials (see table in Supplemental Digital Content 2, https://links.lww.com/ALN/D135).[2,3,7,15–17] The circumstances from these reports are highly variable and, in some cases, are obviously related to either failure to achieve reversal to a train-of-four ratio of at least 0.9 or to the lack of quantitative twitch monitoring. Determination of the response to a train-of-four stimulus after surgery can be complicated by patient discomfort when using the same stimulating current commonly used intraoperatively (approximately 45 to 80 mA).[27,28] As the stimulating current is reduced to avoid patient discomfort, ulnar nerve depolarization may be incomplete, resulting in a diminished twitch response compared to that which would occur at a higher current.[27] In this study, we performed quantitative twitch monitoring in sedated, intubated patients at 80 mA, the same current utilized for intraoperative monitoring, to ensure an adequate twitch response. Taken as a whole, the literature concerning recurrent paralysis after reversal with sugammadex suggests that achieving a train-of-four ratio of at least 0.9 does not, by itself, guarantee that recurrent paralysis will not occur.

Interestingly, a well-conducted study of reversal of vecuronium by sugammadex at the reappearance of the fourth twitch of the train-of-four found recurrent paralysis in 9 of 27 (33%) patients. These instances of recurrent paralysis occurred during 60 min of quantitative twitch monitoring in the recovery room using the same stimulating current used in the operating room (Laszlo Asztalos, M.D., Ph.D., Department of Anesthesiology and Intensive Care, University of Debrecen, Debrecen Hungary; written communication, July 16, 2022). Recurrent paralysis was observed in patients receiving sugammadex doses at 0.5 (3 of 9 patients), 1.0 (4 of 8 patients), or 2.0 (2 of 10 patients) mg/kg.[15] Vecuronium is not as avidly bound by sugammadex as rocuronium.[29] Further research may be needed to characterize the conditions in which recurrent paralysis occurs after sugammadex administration for reversal of vecuronium, which may differ from reversal of rocuronium.

This study has several limitations. We deliberately studied cardiac surgery patients because of the opportunity to measure train-of-four twitch response for several hours after surgery in sedated, intubated patients. This enabled the use of an 80-mA stimulation current throughout the study, which is not feasible in awake patients due to discomfort. In addition, the protocol for fast-track extubation of cardiac

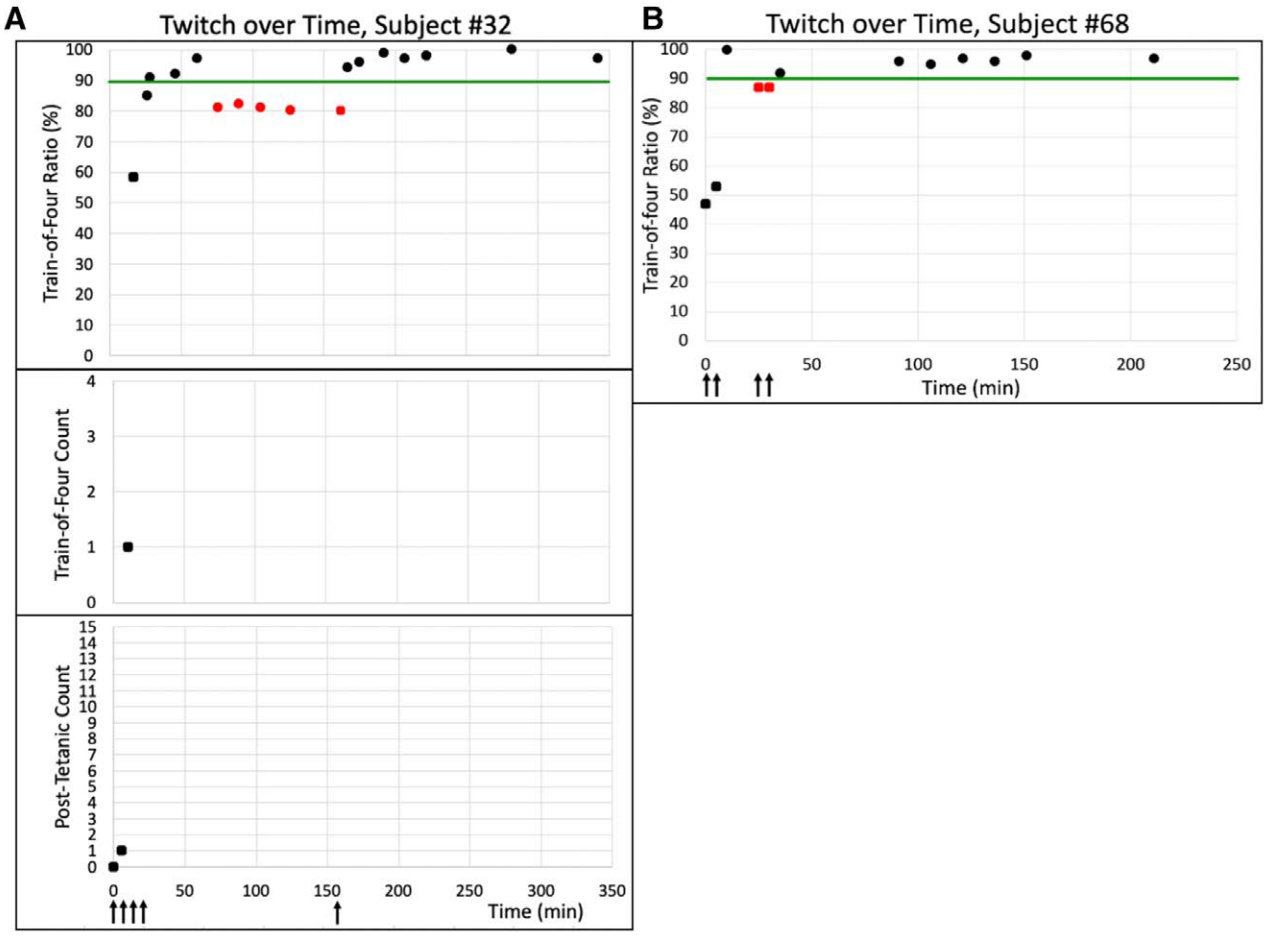

Fig. 4. Two subjects had recurrent paralysis defined as a train-of-four ratio less than 0.9 after having previously achieved a train-of-four ratio 0.9 or greater. The *vertical arrows* below the *x axis* designate 50-mg doses of sugammadex. A *horizontal line* at a train-of-four ratio of 0.9 designates the threshold for recovery. (*A*) Subject 32 had a posttetanic count of 0 and received 250 mg sugammadex before achieving a train-of-four ratio 0.9 or greater. While being monitored in the intensive care unit, the train-of-four ratio declined to a value less than 0.9 until an additional 50-mg dose of sugammadex was administered. (*B*) Subject 68 had a train-of-four ratio of 0.47 and received 100 mg sugammadex to achieve a train-of-four ratio 0.9 or greater. While still in the operating room, the train-of-four ratio declined to a value less than 0.9 until an additional 100-mg dose of sugammadex was administered.

surgery patients utilized by our medical center recommends the reversal of neuromuscular blockade at the conclusion of surgery. The patients underwent cardiopulmonary bypass with a variable extent of deliberate hypothermia, although the patients were rewarmed at the time of sugammadex administration (table 1). Whether this influences the reversal of rocuronium with sugammadex and whether the results would be the same in noncardiac surgery patients is uncertain. However, we are unaware of any specific reasons the results would not apply to noncardiac surgery patients.

Because we titrated sugammadex in 50 mg increments every 5 min, administration of larger doses of sugammadex required more time than would be the case if the entire dose were administered as a single bolus. For example, administration of sugammadex 400 mg would have required more than 40 min. Throughout the sugammadex administration, rocuronium clearance is ongoing, which would likely reduce the total dose of sugammadex required. Therefore, for the larger doses of sugammadex given in this study, the amount required for reversal could be an underestimate of the dose that would have been required had the entire dose been administered as a single bolus.

Additionally, all of the patients in this study received rocuronium. Because rocuronium is bound more avidly to sugammadex than vecuronium, the results and conclusions of this study may not apply to vecuronium. The time interval between sugammadex doses, 5 min, may have influenced the result. An argument could be made that in some cases, the maximum effect of sugammadex may not be seen within 5 min. However, clinical trial data

suggest that sugammadex reversal to a train-of-four ratio of at least 0.9 frequently occurs within 5 min. Also, from a practical perspective, it seemed unlikely that anesthesia providers in a real-world setting would be willing to wait longer than 5 min before giving additional sugammadex if reversal were not achieved. Finally, the choice of an incremental sugammadex dose of 50 mg may have influenced the result. This dose was chosen from a practical perspective, given that a vial of sugammadex contains 200 mg in 2 ml; dilution of this vial to a total of 20 ml with saline makes the administration of 50-mg increments reasonably accurate.

In conclusion, sugammadex was titrated in 50-mg increments every 5 min until a train-of-four ratio of at least 0.9 was reached at the conclusion of cardiac surgery, and quantitative twitch monitoring was continued postoperatively in the ICU while the patients remained sedated and intubated. The sugammadex dose requirement for reversal was generally less than the manufacturer's recommended doses. However, there was a wide range of dose requirements for individual patients, and some patients required more than the recommended dose. Therefore, quantitative twitch monitoring is required to determine whether a train-of-four ratio of at least 0.9 has been reached, even at a sugammadex dose of 4 mg/kg. There were two cases of mild recurrent paralysis, suggesting that recurrent paralysis after sugammadex requires additional study.

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Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Bowdle: Mail Stop 356540, Department of Anesthesiology, University of Washington, Seattle, Washington 98195. bowdle@uw.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

Supplemental Digital Content

Supplemental Digital Content 1—Sugammadex dose-finding clinical trials, https://links.lww.com/ALN/D134
Supplemental Digital Content 2—Case reports and clinical trial recurrent paralysis, https://links.lww.com/ALN/D135

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