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ARTICLE

Required dose of sugammadex or neostigmine for reversal of vecuronium-induced shallow residual neuromuscular block at a train-of-four ratio of 0.3

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Abstract

Residual shallow neuromuscular block (NMB) is potentially harmful and contributes to critical respiratory events. Evidence for the optimal dose of sugammadex required to reverse vecuronium-induced shallow NMB is scarce. The aims of the present study were to find suitable doses of sugammadex and neostigmine to reverse a residual vecuronium-induced NMB from a time of flight (TOF) ratio of 0.3–0.9 and evaluate their safety and efficacy. In total, 121 patients aged 18–65 years were randomly assigned to 11 groups to receive placebo, sugammadex (doses of 0.125, 0.25, 0.5, 1.0, or 2.0 mg/kg), or neostigmine (doses of 10, 25, 40, 55, or 70 μg/kg). The reversal time of sugammadex and neostigmine to antagonize a vecuronium-induced shallow residual NMB (i.e., TOF ratio of 0.3) and related adverse reactions were recorded. Several statistical models were tested to find an appropriate statistical model to explore the suitable doses of sugammadex and neostigmine required to reverse a residual vecuronium-induced NMB. Based on a monoexponential model with the response variable on a logarithmic scale, sugammadex 0.56 mg/kg may be sufficient to reverse vecuronium-induced shallow residual NMB at a TOF ratio of 0.3 under anesthesia maintained with propofol. Neostigmine may not provide prompt and satisfactory antagonism as sugammadex, even in shallow NMB.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Sugammadex 4 and 2 mg/kg can effectively reverse deep and moderate neuromuscular blockade (NMB) induced by aminosteroidal NMB agents, respectively.

Jing He and Huan He contributed equally to this work.

IRB contact information: General Hospital of Southern Theatre Command of PLA Medical Ethics Committee (Tel: +86–20–88653625, E-mail: gzjqzyy@163.com).

This study was conducted with written informed consent from the study subjects.

The study was registered prior to patient enrollment.

Clinical trial number and registry URL: ClinicalTrials.gov (NCT03656614) https://www.clinicaltrials.gov/ct2/show/NCT03656614?term=NCT03656614.

The optimal dose of sugammadex required to reverse vecuronium on shallow NMB has not yet been evaluated, and whether neostigmine can provide the same satisfactory antagonism as sugammadex in vecuronium-induced shallow NMB remains unknown.

WHAT QUESTION DID THIS STUDY ADDRESS?

This analysis of a single-center, randomized, double-blind trial evaluated biological models to find an appropriate model to explore suitable doses of sugammadex and neostigmine to reverse residual vecuronium-induced NMB from a time of flight (TOF) ratio of 0.3 to 0.9.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Sugammadex 0.56 mg/kg may be sufficient to reverse vecuronium-induced shallow residual NMB at a TOF ratio of 0.3 under anesthesia maintained with propofol. Neostigmine may not provide antagonism as satisfactory as the sugammadex dose due to its less stable recovery time and higher incidence of recurarization even in shallow NMB.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

A small dose of sugammadex—0.56 mg/kg—can satisfactorily reverse vecuronium-induced shallow NMB at a TOF ratio of 0.3. If doctors use the required dose of sugammadex, it will promote rational drug use and avoid some side effects of excessive medication.

INTRODUCTION

Residual neuromuscular block (NMB) contributes to postoperative respiratory complications, such as hypoventilation, hypoxia, aspiration pneumonia, and even death.[1,2] Moreover, residual NMB is commonly observed during the postoperative period and may affect up to 45% of patients, most of whom have shallow degrees of NMB.[3,4] This is partly because shallow NMB is easily ignored by anesthesiologists. As an intermediate-acting aminosteroidal muscle relaxant, vecuronium is widely used in muscle relaxation due to its lack of histamine release and lack of ganglion and vagal nerve blockade.[5] Furthermore, residual NMB induced by vecuronium is also commonly observed during the postoperative period.

At present, the most widely used muscle relaxation antagonists include acetylcholinesterase inhibitors and sugammadex. Sugammadex is a modified γ-cyclodextrin that promptly reverses different degrees of neuromuscular blockade by forming a complex with steroidal nondepolarizing neuromuscular blockers at a 1:1 ratio.[6]

However, to date, there are few data exploring the optimal dose of sugammadex required for the reversal of vecuronium-induced shallow NMB.[7] Studies of sugammadex reversing residual shallow NMB are only about rocuronium.[6] The potency and affinity of vecuronium with sugammadex are quite different from those of rocuronium. The affinity between sugammadex and rocuronium is almost 3.1-fold that of vecuronium (1.79×10^7 mol/L vs. 5.72×10^6 mol/L).[7] Although the molecular weights of the two muscle relaxants are similar (637 vs. 610 Da), vecuronium is greater than 6 times more potent than rocuronium (ED95 = 0.05 vs. 0.30 mg/kg were determined using cumulative dose-response curves by bolus injections of vecuronium or rocuronium).[8] Thus, the results for rocuronium cannot be directly applied to vecuronium.

In addition, neuromuscular blockade can reduce the risk of respiratory complications 24 h after surgery, but unreasonable use of muscle relaxation antagonists may also translate to increased postoperative respiratory morbidity.[9–11] The optimal dose of sugammadex or neostigmine required to reverse vecuronium on shallow NMB has not yet been evaluated, and whether neostigmine can provide the same satisfactory antagonism as sugammadex in vecuronium-induced shallow NMB remains unknown. Thus, the aim of this study was to investigate the dose-effect relationship of sugammadex and neostigmine for the reversal of vecuronium-induced shallow residual NMB (i.e., time of flight [TOF] ratio of 0.3) and observed related adverse reactions.

The quality of dose-exploration studies mainly depends on appropriate mathematical models. Previous dose-finding studies for sugammadex used a monoexponential approach with recovery times on a linear scale,[12] but later similar dose-exploration studies considered the biexponential model with time on a logarithmic scale[13] or a monoexponential model on a logarithmic scale[14] to be more suitable. There is no conclusion on which mathematical

model is most suitable for this kind of dose-effect relationship exploring research. Thus, in our study, we tested these biological models to find an appropriate model to explore suitable doses of sugammadex and neostigmine required to reverse residual vecuronium-induced NMB from a TOF ratio of 0.3–0.9.

MATERIALS AND METHODS

Study design and patient selection

This single-center, randomized, parallel-arm, double-blind study was approved by the local ethics committee of the General Hospital of the Southern Theater Command of PLA, and written informed consent was obtained from all patients included in this study. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT03656614; Principal investigator: Bo Xu; Date of registration: July 10, 2018).

The study consisted of 121 patients who underwent routine elective surgery in our hospital between July 2018 and June 2019. The inclusion criteria were as follows: age 18–65 years, American Society of Anesthesiologists (ASA) physical status I–III, body mass index 18.5–25.0 kg/m^2, and undergoing general anesthesia with an expected duration of at least 1 h. The exclusion criteria were as follows: expected difficult airway, neuromuscular disease, significant hepatic or renal dysfunction, a family history of malignant hyperthermia, allergy to any of the drugs used in this trial, taking medication that might interfere with NMB or the antagonist, and glaucoma. Patients who were pregnant or breastfeeding were not included, nor were those who had participated in another study within the previous 30 days. In total, 130 patients were assessed for eligibility, and 121 patients were randomly assigned into 1 of 11 groups to receive placebo, a sugammadex dose of 0.125, 0.25, 0.5, 1.0, or 2.0 mg/kg, or a neostigmine dose of 10, 25, 40, 55, or 70 μg/kg combined with atropine at half doses of neostigmine.

Procedure

On arrival in the operating room, an intravenous cannula was inserted in the forearm vein of the patient on the side opposite to that used for the electromyograph (EMG). Vital signs were monitored, such as electrocardiography, blood oxygen saturation (SpO_2) level, and noninvasive blood pressure. Anesthesia was induced and maintained with a target-controlled infusion of propofol 3–5 μg/ml using the Marsh pharmacokinetic model and remifentanil at 4–6 ng/ml using the Minto pharmacokinetic model. The patients were artificially ventilated by a face mask until intubation of the trachea to maintain normocapnia and oxygen saturation greater than 96%. Body temperature was maintained between 36.0 and 37.0°C.

Neuromuscular monitoring was performed according to international consensus guidelines.[15] The adductor pollicis muscle response to ulnar nerve stimulation was monitored by a neuromuscular transmission module via the S/5 GE Datex Light monitor (GE Datex Medical Instrumentation, Inc., Tewksbury, MA, USA). The piezoelectric probe of the EMG was attached to the tip of the thumb with a hand adapter that ensured preload of the thumb. After immobilizing the forearm and degreasing the skin, surface skin electrodes were placed over the ulnar nerve proximal to the wrist. Following a 5 s tetanic train of 50 Hz to stabilize the signal, the stimulation was switched to TOF mode (70 mA current; 0.2 ms pulse duration, 2 Hz frequency). Then, calibration of EMG monitoring was commenced to determine the individual supramaximal nerve stimulation. After the signal was stable, repetitive TOF stimulation was applied at the ulnar nerve wrist point every 20 s until the patient recovered from anesthesia. Skin temperature was measured at the site of neuromuscular measurements and maintained at above 32.0°C.

Vecuronium 0.1 mg/kg was administered via an intravenous (i.v.) bolus after stabilization of the EMG twitch response. When the TOF ratio disappeared, the trachea was intubated. During surgery, 0.02 mg/kg vecuronium was administered when two twitches to TOF stimulation returned.

Near the end of surgery, spontaneous recovery from NMB was allowed to a TOF ratio of 0.3. Study medications, dosed according to randomization, or placebo were administered via an i.v. bolus within 10 s into the forearm vein. Neuromuscular monitoring was continued for at least 30 min after the TOF ratio reached 0.9. Reoccurrence of NMB was defined as the reappearance of a TOF ratio of less than 0.8. After the patient had recovered from anesthesia, the trachea was extubated.

The patients were kept in the post-anesthesia care unit (PACU) for a minimum of 60 min under close surveillance for any signs of reoccurrence of muscle weakness or other adverse events (AEs). In the PACU, every 15 min until discharge, the patients were required to open their eyes for 5 s and perform a 5 s head-lift test, a 5 s leg-lift test, and swallow saliva to check for clinical evidence of any muscle weakness. Moreover, the patient's level of consciousness was assessed using Ramsay scores if he or she was uncooperative. Oxygen saturation, heart rate, noninvasive blood pressure, and respiratory rate were routinely monitored, and oxygen was delivered via a nasal cannula. After discharge from the PACU, the patients were monitored for 24 h to detect any late AEs.

Data management and statistical analysis

Previous guidelines[12–14,16] have suggested that a biological model, such as a monoexponential model (Equation 1), biexponential model (Equation 2), or fractional polynomial model can be applied to analyze these types of dose-response relationships. The fractional polynomial models consisted of one (FP1) (Equation 3), or two degrees (FP2) (Equation 4) with exponents (p, p1, and p2) taken from a predefined set of values and parameters (a1, a2, and a3).[17] It has not been established which biological model is more suitable for research on the relationship between sugammadex and neostigmine dosing and recovery times. The mathematical model formulas are as follows:

$$\Delta t\,(\text{dose}) = a1 + a2 \cdot e^{-a3 \cdot \text{dose}} \quad (1)$$

$$\Delta t\,(\text{dose}) = a1 + a2 \cdot e^{-a3 \cdot \text{dose}} + a4 \cdot e^{-a5 \cdot \text{dose}} \quad (2)$$

$$\text{FP1: } \Delta t\,(\text{dose}) = a1 + a2 \cdot \text{dose}^{p} \quad (3)$$

$$\text{FP2: } \Delta t\,(\text{dose}) = \begin{cases} a1 + a2 \cdot \text{dose}^{p1} + a3 \cdot \text{dose}^{p2} \\ a1 + a2 \cdot \text{dose}^{p1} + a3 \cdot \text{dose}^{p2} \cdot \ln(\text{dose}) \end{cases} \quad (4)$$

To select the optimal mathematical model, we compared these models based on the following three factors. First, the adjusted *R*-Square (Equation 5), adjusted for the different number of parameters in the models, denoted R^2_{adj}, should be close to 1. A larger R^2_{adj} means that the model fits better. Second, the Akaike information criterion (AIC) (Equation 6), which is used to determine the best-fitting model with the lowest complexity within a given set of data, was used. Third, the parameters of the model should be significant.[16] Under the premise that the model parameters are significant, the larger the R^2_{adj} and the smaller the AIC value, the better the model is. To achieve a better fit for the model, considering that recovery times in previous sugammadex dose-finding studies showed a positively skewed distribution, we also compared the recovery times on a logarithmic scale with a linear scale in the four types of models.

$$R^2_{adj} = 1 - \left(1 - R^2\right) \cdot \frac{n-1}{n-k-1} \quad (5)$$

$$\text{AIC} = n \cdot \ln\left(2\pi \frac{\text{RSS}}{n}\right) + n + 2 \cdot (k+1) \quad (6)$$

In the current study, the AIC values were minimal for the fractional polynomial model compared with the other three models, but the R^2_{adj} was relatively small and the parameters were not significant (Tables 1 and 2). Considering these three factors, we selected a monoexponential model as the best-fitting mathematical model for our data. In addition, the recovery time was a better fit on a logarithmic scale than on a linear scale in the dose-response relationship of reversing vecuronium-induced residual NMB (higher R^2_{adj}; Table 1). Hence, we adopted the monoexponential model with the dependent variable on a logarithmic scale.

TABLE 1 Dose estimations for neostigmine and sugammadex using several mathematical models

Reversal agent	Δ*t* Scale	Model	R^2_{adj}	AIC
Neostigmine	Linear	1-exp	0.75	394.2
		2-exp	0.741	397.2
		FP1	0.492	244.0
		FP2	0.47	248.0
	ln	1-exp	0.832	165.9
		2-exp	0.826	169.8
		FP1	0.51	133.1
		FP2	0.487	137.1
Sugammadex	Linear	1-exp	0.757	390.7
		2-exp	0.749	387.1
		FP1	0.575	236.3
		FP2	0.496	238.6
	ln	1-exp	0.863	161.1
		2-exp	0.878	163.3
		FP1	0.706	126.8
		FP2	0.701	130.6

Abbreviations: 1-exp, mono-exponential; 2-exp, bi-exponential; AIC, Akaike information criterion; FP1, fractional polynomial 1 degree; FP2, fractional polynomial 2 degrees.

The monoexponential model with the dependent variable on a logarithmic scale is $\ln\Delta t\,(\text{dose}) = a1 + a2 \cdot e^{-a3 \cdot \text{dose}}$, where $\Delta t\,(\text{dose})$ is the estimated time to recovery of the TOF ratio from 0.3 to 0.9; "a1" represents the fastest achievable recovery time for the average subject; "a2" is the difference in time between mean spontaneous recovery and mean recovery after an infinitely large dose of sugammadex; and "a3" represents the extent of reduction in recovery time with sugammadex.

On the basis that the maximal dose of neostigmine was 70 μg/kg and the mathematical model required five different doses, we adopted an arithmetic progression in which the constant was 15 μg/kg. Given that a low dose of sugammadex might not offer satisfactory reversal of vecuronium-induced NMB,[18] we applied a geometric progression ranging from 0.125 to 2 mg/kg.

The primary outcome measure of the study was an estimate of the dose of sugammadex or neostigmine required to reverse vecuronium-induced NMB from a TOF ratio of 0.3 to

TABLE 2 Parameter estimations and *p* values for neostigmine and sugammadex using several mathematical models

		Estimate				*p* value[a]	
Model	**Parameter**	**SUG**	**95% CI**	**NEO**	**95% CI**	**SUG**	**NEO**
linear_1-exp	a1	2.6864	(2.0980, 3.2748)	4.0578	(3.3786, 4.7371)	<0.0001	<0.0001
	a2	49.2785	(44.7417, 53.8152)	48.1231	(43.5350, 52.7113)	<0.0001	<0.0001
	a3	11.9088	(10.2362, 13.5814)	0.1705	(0.1412, 0.1998)	<0.0001	<0.0001
linear_2-exp	a1	0.4804	(−9.8905, 10.8513)	3.7844	(2.8057, 4.7631)	0.9266	<0.0001
	a2	47.6764	(41.8748, 53.4780)	21.7747	(−18.2192, 61.7687)	<0.0001	0.2807
	a3	13.6207	(10.3102, 16.9311)	0.5482	(−4.2405, 5.3369)	<0.0001	0.8197
	a4	4.1748	(−3.1298, 11.4793)	26.7401	(−12.4231, 65.9033)	0.2578	0.1772
	a5	0.6057	(−2.6242, 3.8356)	0.1123	(0.0040, 0.2206)	0.7092	0.0424
linear_FP1	a1	1.7573	(0.6152, 2.8994)	3.1706	(1.0837, 5.1087)	0.0032	0.0032
	a2	0.6502	(−0.2552, 1.5555)	336.74	(−508.77, 1108.77)	0.1557	0.4600
	p	−1.3655	(−2.0327, −0.6983)	−1.5573	(−2.7293, −0.2811)	0.0001	0.0169
linear_FP2	a1	−34.262	(−959.86, 891.33)	3.1609	(1.1366, 5.1851)	0.9411	0.0028
	a2	36.9482	(−888.82, 962.72)	328.47	(−558.86, 1215.81)	0.9365	0.4573
	a3	−0.0204	(−0.1924, 0.1516)	137.13	(−8557.69, 8831.96)	0.8131	0.9741
	p1	−0.0373	(−0.9760, 0.9013)	−1.5479	(−2.8282, −0.2676)	0.9367	0.0184
	p2	−2.4866	(−6.3469, 1.3737)	−3.9516	(−6.5031, −1.4001)	0.2021	0.0038
ln_1-exp	a1	0.6865	(0.2047, 1.1682)	1.2082	(0.6734, 1.7430)	0.0059	<0.0001
	a2	2.9800	(1.8559, 4.1041)	2.6480	(1.4150, 3.8811)	<0.0001	<0.0001
	a3	3.755	(0.09063, 7.4194)	0.07585	(−0.00834, 0.1600)	0.0448	0.0766
ln_2-exp	a1	−32.7626	(−813.29, 747.76)	1.1755	(0.3861, 1.9648)	0.9334	0.0042
	a2	34.1812	(−746.26, 814.62)	2.3466	(−1.7140, 6.4072)	0.9306	0.2524
	a3	0.0136	(−0.3025, 0.3297)	0.06473	(−0.1052, 0.2346)	0.9318	0.4492
	a4	2.4668	(1.0059, 3.9278)	0.3521	(−4.3588, 5.0630)	0.0013	0.8817
	a5	7.2612	(−1.4492, 15.9716)	2.6149	(n.e.)	0.1007	<0.0001
ln_FP1	a1	−1.5759	(−17.2229, 14.0710)	0.8063	(−2.9236, 4.5362)	0.8407	0.6662
	a2	2.4533	(−13.4013, 18.3078)	9.1027	(−45.8518, 64.0571)	0.7576	0.7409
	p	−0.2228	(−1.4706, 1.0249)	−0.7519	(−4.2329, 2.7290)	0.7217	0.6665
ln_FP2	a1	0.6526	(−7.1086, 8.4138)	0.9087	(−1.5708, 3.3883)	0.8668	0.4654
	a2	0.3093	(−7.5374, 8.1560)	32.6655	(n.e.)	0.9373	<0.0001
	a3	−0.2045	(−6.1901, 5.7812)	10.2062	(−50.2782, 70.6906)	0.9457	0.7363
	p1	−0.8208	(−10.0012, 8.3596)	−488.64	(n.e.)	0.8584	<0.0001
	p2	1.2078	(−32.1552, 34.5709)	−1.1924	(−4.3219, 1.9371)	0.9424	0.448

Abbreviations: CI, confidence interval; SUG, sugammadex; NEO, neostigmine.

[a]The *p* value of all the parameters of the model is less than 0.05, the model is meaningful.

0.9 in 95% of patients within 5 min. The secondary outcome measures were the doses of sugammadex and neostigmine resulting in a slower reversal (5 min for 50% of patients, upper limit of 10 min for 95% of patients). Additional outcome measures were the incidence of recurrence of NMB within the first 60 min and the incidence of AEs during the study.

Sample size calculations for a reliable regression model suggest at least 10 samples per parameter.[19] Assuming that a 10% dropout rate might occur, we enrolled 11 patients in each group (i.e., 121 patients total). Statistical analysis and image processing were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics

The study enrolled 121 patients in total (see Figure S1 for the flow diagram). Five patients were excluded: EMG technical failure occurred in two patients (one each in the placebo and

TABLE 3 Baseline characteristics and treatment of patients

	SUG[a]	NEO[a]	Placebo[a]	*p* value
Sex (M/F)	29/25	29/23	6/4	0.93[b]
Age (years)	37.5 (26.8–49.3)	39.5 (30.5–50.0)	48.5 (27.5–58.3)	0.55[c]
BMI (kg/m^2)	21.6 (20.5–23.5)	22.9 (20.6–24.3)	23.1 (19.9–23.9)	0.17[c]
ASA class (I/II/III)	27/19/8	29/18/5	7/2/1	0.76[b]
Total vecuronium dose, mg/kg	0.14 (0.12–0.17)	0.13 (0.10–0.17)	0.13 (0.12–0.14)	0.17[c]
Duration of surgery, min	97.5 (62.8–153.3)	85.5 (73.0–110.8)	102.0 (53.5–178.0)	0.74[c]
Time from first vecuronium dose to TOF count 0, min	3.0 (2.85–3.50)	3.0 (2.83–3.13)	3.0 (2.58–3.05)	0.42[c]

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; TOF, train-of-four; SUG, sugammadex; NEO, neostigmine.

[a]Medians (interquartile ranges) are shown when data did not meet the assumptions of parametric statistical tests.

[b]Data are from χ^2 tests.

[c]Data are from Kruskal–Wallis analysis of variance (ANOVA).

sugammadex 0.125 mg/kg groups), one patient was excluded due to accidental discharge of drug during injection (neostigmine 10 μg/kg group), the cuff of one patient's endotracheal tube broke (neostigmine 40 μg/kg group), and, in one patient, the TOF ratio did not reach 0.9 due to improper hand fixation (neostigmine 70 μg/kg group). Thus, 116 patients were included in the final analysis. All groups met the criterion of at least 10 samples. There were no significant differences in baseline characteristics (sex, age, body mass index, and ASA physical status score) or treatment (total vecuronium dose, duration of surgery, and time from first vecuronium dose to a TOF count of 0; Table 3) among the groups.

Statistical characteristics

Sugammadex and neostigmine produced a dose-dependent reduction in the time to recovery of the TOF ratio from 0.3 to 0.9. The median time to recovery decreased from 44.0 min (placebo) to 1.7 and 2.8 min in the sugammadex 2.0 mg/kg and neostigmine 70 μg/kg groups, respectively (Table 4).

As the parameters in the exponential part of the model were −3.755 (sugammadex) and −0.07858 (neostigmine), which were significantly different from zero, a dose-reduction effect could be demonstrated. From Figure 1c,d, it was calculated that the fastest recovery time of the upper 95% limit was 3.2 min in the sugammadex group and 5.9 min in the neostigmine group.

Outcome measures

Regarding the primary outcome measure, for an upper limit recovery time of 5 min in 95% of patients, the dose was estimated to be 0.56 mg/kg (sugammadex). Neostigmine could not make 95% of patients recover within 5 min (Figure 1c,d).

TABLE 4 Time from administration of various doses of drugs at a TOF ratio of 0.3 to attaining a TOF ratio of 0.9

	Time intervals of recovery, min[a]	
Treatment group	Median (range)	95% CI
Placebo	44.0 (28.0–103)	34.9–69.6
Sugammadex, 0.125 mg/kg	13.9 (3.7–25.0)	8.1–17.0
Sugammadex, 0.25 mg/kg	5.3 (2.7–8.0)	3.3–6.9
Sugammadex, 0.5 mg/kg	3.3 (2.7–7.7)	3.1–6.7
Sugammadex, 1.0 mg/kg	2.7 (1.7–4.0)	2.7–4.7
Sugammadex, 2.0 mg/kg	1.7 (1.0–2.7)	2.4–4.5
Neostigmine, 10 μg/kg	10.8 (5.7–25.0)	8.1–17.0
Neostigmine, 25 μg/kg	4.7 (3.3–13.0)	3.3–6.9
Neostigmine, 40 μg/kg	4.2 (2.1–11.1)	3.1–6.7
Neostigmine, 55 μg/kg	3.4 (1.5–6.5)	2.7–4.7
Neostigmine, 70 μg/kg	2.8 (2.0–6.0)	2.4–4.5

Abbreviations: CI, confidence interval; TOF, time of flight.

[a]Times are given in minutes. Medians (ranges) are shown when data did not meet the assumptions of parametric statistical tests. The 95% tolerance indicates the time interval during which recovery of 95% of patients can be expected after reversal with the respective dose of drugs.

Regarding the secondary outcome measures, for an upper limit recovery time of 10 min in 95% of patients, the estimated doses were 0.30 mg/kg for sugammadex and 33 μg/kg for neostigmine. For a recovery time of 5 min in 50% of patients, the estimated doses were 0.31 mg/kg for sugammadex and 27 μg/kg for neostigmine (Figure 1c,d).

Regarding the additional outcome measures, the overall incidence of the recurrence of NMB was 19.2% in the neostigmine group and 0% in the sugammadex group. Recurrence of NMB occurred in 10 patients: four in the neostigmine 70 μg/kg group, four in the neostigmine

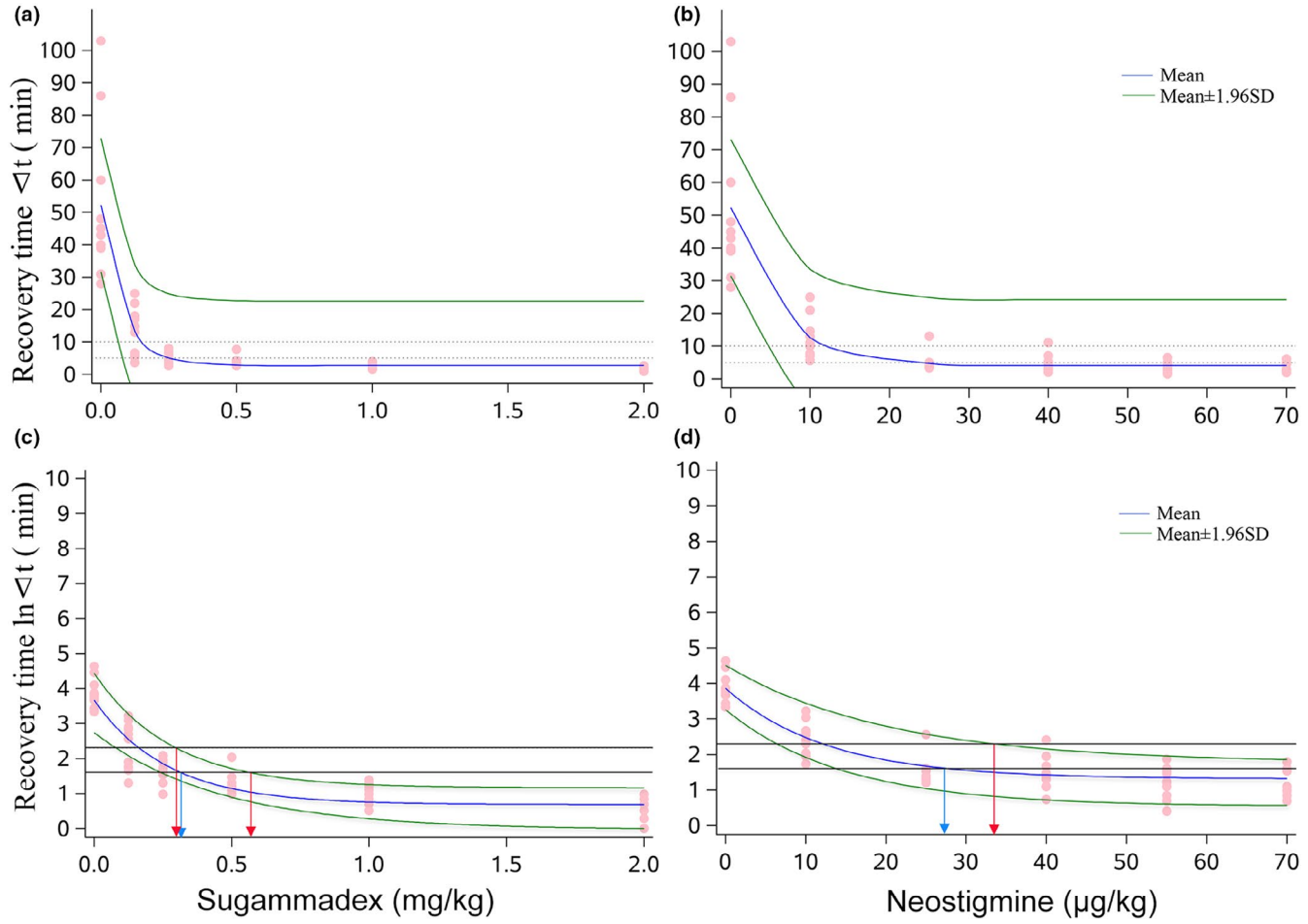

FIGURE 1 Sugammadex and neostigmine dose estimation with a monoexponential model. Recovery time on a linear scale (a and c) or a logarithmic scale (b and d). The points of intersection indicate the dose necessary to reverse a time of flight (TOF) ratio of 0.3–0.9 within 5 min (the lower horizontal line, ln5 = 1.6) and 10 min (the upper horizontal line, ln10 = 2.3) in 95% of patients (red arrow) or in 50% of patients (blue arrow) in both groups. The disadvantage of the linear scale models is evident; the upper 95% curve is too flat to allow an estimation. The prediction formulas are $\ln\Delta t\,(\text{dose}) = 0.69 + 3.0 \cdot e^{-3.8 \cdot \text{dose}}$ (sugammadex) and $\ln\Delta t\,(\text{dose}) = 1.3 + 2.5 \cdot e^{-0.079 \cdot \text{dose}}$ (neostigmine)

55 μg/kg group, one in the neostigmine 40 μg/kg group, and one in the neostigmine 25 μg/kg group.

For clinical muscle function tests, three patients with recurrence of NMB in the operating room complained about muscle weakness (difficulty in opening their eyes and lifting their head) in the PACU. All three patients were in the neostigmine 70 μg/kg group. Two patients in the sugammadex 0.125 mg/kg group suffered from muscle weakness in the PACU. All patients with incomplete reversal in the PACU received rescue therapy (sugammadex 0.5 mg/kg) and returned to normal thereafter.

The assessment of patients' level of consciousness showed no difference between the groups at any time during the postoperative period in the PACU. In our study, one patient in the neostigmine 40 μg/kg group experienced glossoptosis and subsequent hypoxia; SpO_2 increased to normal values after an oropharyngeal airway was inserted. No other serious AEs occurred.

DISCUSSION

In this study, we investigated the dose-response relationship of sugammadex and neostigmine for the reversal of vecuronium-induced NMB at a TOF ratio of 0.3. We found that 0.56 mg/kg sugammadex accelerated recovery from a TOF ratio of 0.3–0.9 within 5 min in 95% of all treated patients. The dose of neostigmine was calculated to be 33 μg/kg for an upper limit of 10 min in 95% of patients. To the best of our knowledge, this might be the first time that the optimal doses of sugammadex and neostigmine required to reverse vecuronium-induced shallow residual NMB at a TOF ratio of 0.3 in patients have been established.

Previous dose-finding studies of sugammadex used a monoexponential approach with recovery times on a linear scale.[12] This process follows linear characteristics; it cannot be transferred to complex data. Therefore, Schaller et al.[13] analyzed a biexponential model with time on a

logarithmic scale to explore the suitable dose when reversing rocuronium-induced NMB. However, Kaufhold et al.[14] found that a monoexponential model with the logarithm of the recovery time as a dependent variable offered the best fit due to the monoexponential model having the lowest AIC. Based on their finding, we considered the lowest AIC; the adjusted coefficient of determinant R^2_{adj} should be close to 1; and the parameters of the model should be significant.[16] Finally, the monoexponential model with the dependent variable on a logarithmic scale was considered the most appropriate model in our study of reversing vecuronium-induced shallow NMB, which is similar to the finding of Kaufhold et al.[14]

A study of sugammadex[20] reversing vecuronium-induced NMB found that 0.5 mg/kg sugammadex cannot reverse a threshold TOF count-of-four NMB to a TOF ratio of 0.9 in 30% of the patients, but they did not calculate what dose is fitted at the degree of TOF count-of-four; thus, they recommended that 1.0 mg/kg adequately reversed this level of block. Research on which dose of sugammadex is suitable to reverse shallow vecuronium-induced residual NMB, especially above the degree of TOF count of four, is scarce; thus, many doctors have applied 1 mg/kg or even 2 mg/kg in clinical practice. Based on the most appropriate model, in our study, it was calculated that 0.56 mg/kg sugammadex reversed 95% of all treated patients within 5 min at a TOF ratio of 0.3 without AEs.

What the present study adds to our knowledge is that 0.56 mg/kg sugammadex could satisfactorily reverse vecuronium-induced residual NMB at a TOF ratio of 0.3. Previous studies showed that at a deeper NMB degree of TOF count-of-four (the reappearance of the fourth twitch of TOF stimulation), 0.5 mg/kg sugammadex adequately reversed rocuronium-induced NMB,[21] but this dose was not effective in vecuronium at TOF count-of-four and a higher dose of 1.0 mg/kg sugammadex is needed.[20] This suggested that at the same degree as NMB, vecuronium-induced NMB might require more sugammadex for reversal than rocuronium-induced NMB. The following reasons may explain this phenomenon. First, sugammadex is more selective for rocuronium than for vecuronium (association constant (Ka) = 1.79×10^7 mol/L and 5.72×10^6 mol/L, respectively),[5] as the complexation is slower with vecuronium than with rocuronium. Second, higher sugammadex concentrations are required for complex formation with vecuronium because the dissociation constant (Kd) of vecuronium is three times that of rocuronium (0.17 vs. 0.055 μM).[5] This means that more sugammadex is required to reverse the same degree of NMB when induced by vecuronium than when induced by rocuronium.

Even with the best-fitting model, the R^2_{adj} of neostigmine (Table 1) was relatively low, and the AIC was high, indicating that the efficacy of neostigmine in reversing vecuronium at a TOF ratio of 0.3 was unstable. Due to a ceiling effect, the recovery speed and effect were not enhanced with increased doses, but the incidence of AEs increased when neostigmine exceeded the maximum dose of 70 μg/kg.[22] Furthermore, in our study, recurrence of NMB was detected in 10 patients; the incidences of NMB in the 55 and 70 μg/kg neostigmine groups were 36% and 40%, respectively. The incidence of re-paralysis increased when neostigmine exceeded the suitable dose. This might be because the doses of 70 and 55 μg/kg are too high for the NMB of a TOF ratio of 0.3. Due to excessive acetylcholine at the neuromuscular junction, the postsynaptic membrane continues to depolarize, and repolarization is blocked, unable to form an effective action potential, which eventually leads to weakened muscle strength.[23,24] Moreover, neostigmine, as an antagonist against nondepolarizing muscle relaxant (NMBA), cannot eliminate NMBA easily but increases the concentration of acetylcholine. Therefore, even if the TOF ratio shows a full recovery, there are still a fair number of acetylcholine receptors that can be captured by NMBA.[24]

In this study, none of the patients in the sugammadex group experienced recurrence of vecuronium-induced residual NMB during EMG monitoring in the operating room (OR). This is similar to the findings of several studies[13,14] that used a small dose of sugammadex to reverse rocuronium-induced shallow residual NMB. However, Pùhringer et al.[12] found that the incidence of rebound of vecuronium- or rocuronium-induced NMB at the reappearance of TOF count-of-two was 8.6%. Asztalos et al.[20] also observed that the overall incidence of vecuronium-induced re-paralysis at a TOF count of four was 18.7%. There are several reasons the results may have differed. First, sevoflurane potentiates the effects of NMB agents, and residual concentrations of sevoflurane reinforce NMB in the postoperative period.[25] Unlike the studies by Asztalos[20] and Pùhringer,[12] we did not use sevoflurane during the study. Second, unlike the TOF count-of-four (the reappearance of the fourth twitch of TOF stimulation), the TOF ratio of 0.3 (the fourth twitch of TOF stimulation is 0.3 times the first), which we investigated, is a shallower residual degree and needs less sugammadex to achieve satisfactory reversal. Nevertheless, two patients in the sugammadex 0.125 mg/kg group experienced muscle weakness (difficulty opening their eyes and lifting their heads) in the PACU, although they did not experience re-paralysis during neuromuscular monitoring in the OR. Muscle weakness might have been attributed to a suboptimal dose (0.125 mg/kg) of sugammadex.

Considering that awake patients might not endure the stimulation of EMG and neuromuscular monitoring may produce bias when patients are transferred to the PACU,

we did not monitor the TOF ratio after patients left the OR. This was a limitation of our study. In addition, our study was a single-center study. The participation of more centers and more patients would add credibility. Our study recruited patients aged 18–65 years, and we did not investigate whether age affected the recovery time. Thus, the potential effect needs further research.

In conclusion, sugammadex 0.56 mg/kg may be sufficient to reverse vecuronium-induced shallow residual neuromuscular block at a TOF ratio of 0.3 under anesthesia maintained with propofol. Neostigmine may not provide antagonism as satisfactory as the sugammadex dose due to its less stable recovery time and higher incidence of recurarization even in shallow NMB. The reliability of reversal acceleration was improved by increasing the dose of sugammadex, but this result was not observed for neostigmine.

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CONFLICTS OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

J.H., X.L., H.H., and B.X. wrote the manuscript. B.X., J.H., and H.H. designed the research. J.H., H.H., M.S., and Z.L. performed the research. J.H., X.L., and B.X. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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