Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Pharmacokinetics and Pharmacodynamics of Sugammadex Dosed by Corrected Body Weight for Reversal of Vecuronium in Obese Patients

Zhihao Lai
The Third Affiliated Hospital of Guangzhou Medical University
Ming Xiong
New Jersey Medical School
Shouping Wang
The Third Affiliated Hospital of Guangzhou Medical University
Weidong Shao
General Hospital of Southern Theatre Command
Liangping Wu
Jinshazhou Hospital of Guangzhou University of Traditional Chinese Medicine
Rui Xiao
General Hospital of Southern Theatre Command
Zhonghua Liu
General Hospital of Southern Theatre Command
Xiaojiang Dai
Jinshazhou Hospital of Guangzhou University of Traditional Chinese Medicine
Wenbin Xi
General Hospital of Southern Theatre Command
Nimisha Shawalker
New Jersey Medical School
Bo Xu
xubo333@hotmail.com

Southern Medical University

Research Article

Keywords: Sugammadex, Obesity, Pharmacokinetics, Pharmacodynamics, Corrected Body Weight, Vecuronium

Posted Date: November 12th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11068106/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Dosing in obese individuals is complicated by obesity-related pathophysiological changes and deserves further investigation.

Objective

This study aimed to find out the influence of obesity on pharmacokinetics (PK) and pharmacodynamics (PD) of sugammadex dosed by corrected body weight (CBW) with different body mass index (BMI).

Methods

This prospective observational cohort study included 48 patients, who were divided into non-obese, obese, and morbidly obese groups (n = 16 per group). At the end of laparoscopic surgical procedures, each patient received 2 mg/kg sugammadex dosed by CBW to reverse vecuronium-induced moderate neuromuscular blockade (NMB) monitored by train-of-four (TOF) setting a primary efficacy of TOF ratio to ≥ 0.9. Blood samples were collected at 2, 3, 5, 10, 15, 20, 30, 60, 120, 240, 360 and 480 min after administering sugammadex. Finally, concentration of sugammadex was identified using ultra-high-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS) and PK parameters of sugammadex were calculated using Phoenix WinNonLin software.

Results

PK and PD data were obtained from 48 patients. C_{max}, T_{max}, $t_{1/2\beta}$, AUC_{0-t}, and $AUC_{0-\infty}$ were significantly different between non-obese and the other two groups ($P < 0.05$), whereas V_d and CL showed no significant differences among three groups ($P > 0.05$). Moreover, the average times to recover from moderate NMB in non-obese, obese and morbidly obese groups were 178 ± 7.52 s, 200 ± 13.2 s and 226 ± 19.9 s respectively and did not significantly differ among three groups ($P > 0.05$).

Conclusion

This study served as supplement to PK and PD of sugammadex in patients with different BMI and demonstrated sugammadex of 2 mg/kg dosed by CBW efficiently reversed vecuronium-induced moderate NMB in obese or morbidly obese patients although some of PK parameters changed with different BMI.

Trial Registration:

The study was registered prior to patient enrollment at clinicaltrials.gov (NCT05328778; principal investigator: Bo Xu; first submitted on 4 March 2022).

Introduction

Overweight and obese population currently accounts for more than one billion individuals worldwide, with a notable proportion in the United States, Mexico, and England [1, 2, 3]. Obesity involves a multitude of pathophysiological modifications such as an increased blood flow and gastrointestinal transit, body composition changes, hepatomegaly, liver and kidney impairments. These physiological differences lead to pharmacokinetic changes of drugs which can significantly impact the doses, the clinical tolerance, and its efficacy [4]. Anesthesia management in obese patients is complicated by increased requirement of anesthesia drugs, management of a difficult airway and abnormalities in pulmonary physiology etc. [5] Moreover, residual neuromuscular blockade (RNMB, also called postoperative residual curarization) following anesthesia can lead to upper airway obstruction, hypoxia, and postoperative pulmonary complications in obese patients [6, 7]. RNMB is commonly monitored using mechanomyography or electromyography. A train-of-four (TOF) ratio can be served as one of the best pharmacodynamic indicators for monitoring muscle relaxation. A TOF ratio of ≥ 0.9 to ulnar nerve stimulation at the adductor pollicis muscle is considered as complete reversal of the neuromuscular relaxant [8, 9].

Sugammadex sodium (sold under the Brand name Bridion; Merck Co., Inc., Kenilworth, NJ, USA), one of the optimal choices to reverse RNMB, is the first selective relaxant-binding agent. Although bradycardia and anaphylaxis were reported in some cases [10], sugammadex reverses rocuronium- or vecuronium-induced neuromuscular blockade during general anesthesia [11] with fewer cardiovascular, arrhythmias, respiratory and digestive adverse effects than neostigmine, which may even require dosing atropine typically with the acetylcholinesterase inhibitors [12]. Studies on PK of sugammadex have mainly focused on subjects for namely healthy, elderly [13], and those with renal dysfunction [14]. However, further investigation is needed to identify PK and PD of sugammadex in obese patients. Several studies have focused on sugammadex to reverse rocuronium-induced neuromuscular blockade because rocuronium is reasonably cardiostable, has a shorter duration of action, and shows minimal cumulative effect with a higher affinity to sugammadex [15]. However, the incidence of the reports containing anaphylaxis terms did not differ between vecuronium and rocuronium in the U.S. but were significantly different for foreign reports (with accounting for 50% of 146 in rocuronium *vs*. 19% of 122 in vecuronium) [16]. Moreover, M. NAGUIB found out rocuronium and vecuronium show no significant changes in either plasma histamine concentrations or haemodynamic variables [17]. With advantage of lower cost [16] and potency of 6 times that of rocuronium [18], sugammadex reverseal of vecuronium deserved further explored.

The regional blood flow and distribution of anesthesia drugs among different tissues may differ in obese patients, leading to alterations in the PK and PD of anesthetic agents [4] including sugammadex, of

which the appropriate weight-based correction scheme remains unexplored in morbidly obese patients. With published work, Kate mostoller et al. [19] had demonstrated to support actual body weight (ABW)-based sugammadex dosing in morbidly obese patients irrespective of the depth of rocuronium- or vecuronium-induced NMB (moderate or deep). Nevertheless, the principle of “do no harm” would direct dosing information on the side of administering the lowest effective dose [20] to avoid excessive and engender side effects. Llaurado et al. [21] reported that the median time taken for the TOF ratio to recover to 0.9 was 113 s for moderate reversed using sugammadex of 2 mg/kg dosed by ideal body weight (IBW), however the percentage of patients that required a second dose of sugammadex because of a lack of recovery of the TOF ratio to > 0.9 after 3 minutes was 23.4%. Horrow et al. [20] mentioned that IBW and ABW differed by a factor of 2 values at the extremes of various dosing paradigms in morbidly obese patients, without addressing whether doses between these two extremes in his prior study. In terms of PK and PD, this study added CBW-based dosage to identifying safe and cost-reducing administration of sugammadex in obese patients.

In this study, we identified PK and PD of sugamadex in non-obese, obese, and morbidly obese patients who underwent laparoscopic gastrointestinal surgery and were administered sugammadex to reverse vecuronium-induced moderate neuromuscular blockade. This study was designed to find out the influence of obesity on PK and PD of sugammadex dosed by CBW with different BMI.

Materials and Methods

Design and study subjects

The study was reported in accordance with STROBE guidelines, a prospective observational cohort pharmacological study approved by the Medical Ethics Committee of General Hospital of Southern Theatre Command (No: NZLLKZ2022041; date: 27 Jan 2022). The trial was registered prior to patient enrollment at ClinicalTrials.gov (NCT05328778; principal investigator: Bo Xu; first submitted on 4 March 2022).

Written informed consent was obtained from all subjects participating in the study. 51 patients who underwent laparoscopic gastrointestinal surgery were recruited between Apr. 2022 and Jan. 2026 from the General Hospital of the Southern Theatre Command.

Inclusion criteria: (1) aged 18 to 65 years, (2) American Society of Anesthesiologists (ASA) physical status: I or II, (3) BMI: ≥18.5 kg/m^2. Exclusion criteria: (1) patients with difficult airway, neuromuscular disorders, renal dysfunction, a family history of malignant hyperthermia or allergies to narcotics, (2) patients taking muscle relaxants, any medication that interferes with general anesthesia, neuromuscular blocking drugs or neostigmine and/or glycopyrrolate, (3) patients having previously enrolled in a sugammadex trial, or female patients who are pregnant or breast feeding or of childbearing age who are taking hormonal contraception or birth control measures. After applying these criteria, 2 patients in the obese group were excluded from the study due to inadequate preoperative preparation and 1 patient in

the morbidly obese group was excluded due to mislabeling of blood samples. All enrolled patients were divided into three study groups (*n* = 16 per group) according to their BMI as follows: non-obese group with BMI = 18.5–29.9 kg/m^2, obese group with BMI = 30–39.9 kg/m^2 and morbidly obese group with BMI ≥ 40 kg/m^2. A flow diagram was presented in the graphical abstract (Fig. 1).

Study protocol

Study protocol

Preoperatively an intravenous cannula was established, then a needle to measure electromyography (EMG) was inserted on forearm and vital signs were monitored using electrocardiography, peripheral blood oxygen saturation, and blood pressure. General anesthesia was induced with sufentanil (0.3–0.5 μg/kg) and propofol (1.5–2.5 mg/kg), followed by endotracheal intubation after 3–5 min oxygen supply with oxygen saturation level ≥ 96% while maintaining body temperature between 36.0°C and 37.0°C. Next, radial artery catheterization was performed and neuromuscular reaction was monitored according to the international consensus guidelines [22] based on the response of the adductor pollicus muscle to ulnar nerve stimulation using a neuromuscular transmission module of the S/5 GE Datex Light monitor (GE Datex Medical Instrumentation, Inc., Tewksbury, MA, USA). This was done using a piezoelectric probe of the EMG which was fixed to the thumb tip using a hand adapter, and the skin electrodes were fixed over the ulnar nerve proximal to the wrist. A 5 s tetanic sequence was performed at 50 Hz to stabilize the signal and then switched the stimulation to the TOF mode with a 70 mA current for 0.2 ms pulse duration at 2 Hz frequency. The EMG monitor was set to assess individual supramaximal nerve stimulation level. After the signal stabilized, the TOF mode was used to repeatedly stimulate at the ulnar nerve point of the wrist every 20 s until the patients woke up. Meanwhile skin temperature was measured at the neuromuscular measurement site and maintained it above 32.0°C. Vecuronium of 0.15 mg/kg dosed by lean body weight was administered intravenously after the EMG convulsion response stabilized. When the TOF ratio disappeared, we performed tracheal intubation. TOF-stimulated convulsions presenting between T_1–T_3 are defined as moderate neuromuscular blockade and an additional dosage of vecuronium (0.02 mg/kg) was administered when T_2 convulsions were recorded during the surgical procedure.

Meanwhile, anesthesia was maintained with continuous infusion of propofol (4–8 mg/kg·h) and remifentanil (0.10–0.25 μg/kg·min) and dosages were adjusted to the bispectral index value of 40–60. Vecuronium was discontinued bolus after surgery. Sugammadex of 2 mg/kg dosed by crrocted body weight [CBW = (ABW - IBW) × 0.4 + IBW] [23, 24] (CBW: corrected body weight, ABW: actual body weight, IBW: ideal body weight) was not administrated until the T_2 count was naturally recovered as monitored by muscle relaxation, followed by extracting the endotracheal tube after ensuring complete reversal of NMB as indicated by the TOF ratio.

Collection and assay of sugammadex level in blood samples

Whole blood samples were collected (3 mL) into heparin tubes from each patient at 2, 3, 5, 10, 15, 20, 30, and 60 min and at 2, 4, 6, and 8 h after administration of sugammadex. Next, these blood samples were centrifuged at 2000 g for 15 min, and 1.5 mL of plasma was collected, and stored at -20°C. An ultra-high-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS) was performed within 15 days of blood sampling to assess the blood level of sugammadex [25]. These plasma samples were pretreated using acetonitrile precipitation and Max SPE purification and loaded the samples into the Phenomenex Kinetex C18 column (100 × 2.1 mm; 2.6 μm) using 0.1% formic acid (v/v) and methanol as the mobile phase; while the sample underwent gradient elution at a flow rate of 0.35 mL/min. The electrospray ion source (ESI) was used as positive ion scanning for multiple reaction monitoring. Thereafter, quantitative analysis of the sugammadex transitions were conducted ranging from 1000 to 963.5 m/z with a linear range of 0.05–50 g/mL and correlation coefficient of 0.9920, resulting in a detection limit of 50 ng/mL, quantification limit of 100 ng/mL, and recovery rate of 82.0–94.2%. In addition, inter- and intraday relative standard deviations were also obtained between 4.3% and 10.4%.

PK analyses of blood samples

PK parameters of sugammadex were calculated with the non-compartmental models using Phoenix WinNonLin software (ver. 8.3 Certara, Princeton, NJ, USA). The PK parameters of sugammadex were listed: the maximum concentration (C_{max}), time to maximum concentration (T_{max}), apparent terminal half-life ($t_{1/2\beta}$), apparent volume of distribution (V_d), total clearance (CL), area under the plasma concentration-time curve from time 0 to the last measurable concentration (AUC_{0-t}), and area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$).

Collection of PD data

The times taken to observe a TOF ratio ≥ 0.9 served in the study was recorded. Additionally, the TOF ratio was also recorded immediately while administering sugammadex, at post 15 s and subsequently every 30 s.

Statistical analyses

The sample size was determined based on previous pharmacokinetic studies of sugammadex in obese and non-obese patients, which typically included 12–20 participants per group to adequately characterize the pharmacokinetic profile. A total of 16 participants per group (48 in total) was therefore considered sufficient to estimate the primary pharmacokinetic parameters with acceptable precision. All statistical analyses were performed using SPSS 26.0 statistical software (IBM Corp., Armonk, NY, USA). Normally distributed continuous data were presented as mean ± standard deviation and compared among the three groups using one-way analysis of variance (ANOVA), followed by Bonferroni post-hoc test for pairwise comparisons. Non-normally distributed data were expressed as median (interquartile range) and compared using the Kruskal-Wallis test, with Dunn's post-hoc test and Bonferroni correction

for multiple comparisons. A two-sided *P* value of < 0.05 was considered statistically significant. GraphPad Prism (ver. 9.5.0, GraphPad Software, San Diego, CA, USA) was used for statistical analysis and graphical visualization.

Results

51 laparoscopic gastrointestinal surgery patients were divided into non-obese, obese and morbidly obese groups. 2 patients in the obese group were excluded from the study due to inadequate preoperative preparation and 1 patient in the morbidly obese group was excluded due to mislabeling of blood samples. Table 1 shows baseline characteristics of this cohort of patients. Overall, these patients had ASA grade I or II and were aged between 18 and 65 years; furthermore, they all had a BMI of ≥ 18.5 kg/m^2 with normal liver and renal functions. There was a significant difference in weight, BMI, CBW and sugammadex dosage among three groups (*P* < 0.05) (Table 1).

Table 1
Clinicopathological features of these patients

Characteristics	Non-obese patients	Obese patients	Morbidly obese patients	*P*-value
Sex M (%)/F (%)	8 (50%)/8 (50%)	8 (50%)/8 (50%)	8 (50%)/8 (50%)	-
Age (year)	35.5 ± 5.50	36.2 ± 9.37	30.1 ± 8.41	0.07
Height (cm)	166 ± 6.61	170 ± 7.00	168 ± 10.1	0.24
Weight (kg)	60.8 ± 8.81[a]	100 ± 19.6[b]	133 ± 23.5[c]	< 0.001
BMI (kg/m^2)	23.0 ± 3.02[a]	34.3 ± 4.67[b]	47.2 ± 5.14[c]	< 0.001
IBW (kg)	60.9 ± 8.42	67.9 ± 9.13	65.1 ± 12.2	0.15
CBW (kg)	60.9 ± 7.36[a]	84.2 ± 13.9[b]	99.3 ± 17.0[c]	< 0.001
Serum creatinine (μg/mL)	73.4 ± 14.3	61.3 ± 15.3	65.1 ± 12.6	0.06
Crystalloid fluid (mL)	1430.00 (1160, 1750)	1500 (1390, 1700)	1500 (1200, 1650)	0.71
Urine (mL)	275 (233, 538)	255 (200, 600)	250 (125, 488)	0.72
Blood loss (mL)	22.5 (20.0, 37.5)	22.5 (20.0, 37.5)	20.0 (20.0, 30.0)	0.62
Sugammadex dosage (mg)	122 ± 14.7[a]	168 ± 27.7[b]	199 ± 34.1[c]	< 0.001

Data with different superscript letters within the same row indicate significant difference (*P* < 0.05).

PK results

After intravenous administration, we found that sugammadex rapidly induced a gradient effect on reducing blood concentration of the neuromuscular blocking agent (e.g., vecuronium) and gradually shifted the neuromuscular blocking agent from the tissues (e.g., neuromuscular junction) to the intravascular space, which is where it bonded and formed a complex. Figure 2 showed the plasma sugammadex level-time curves in three groups. Sugammadex quickly reached peak level within 2 min in non-obese patients *vs.* a peak at 5 min followed by a steep decline at 10 min in the other two groups, indicating a significant difference between non-obese and the other two groups. However, the curves of obese and morbidly obese patients almost overlapped with each other, indicating that sugammadex distribution and elimination were comparable in these two groups. Moreover, the plasma sugammadex level-time curves were consistent after one $t_{1/2\beta}$ (around 120 min) among these three groups and in accordance with the linear non-compartmental model.

PK data after a single intravenous sugammadex injection identified that C_{max}, T_{max}, $t_{1/2\beta}$, AUC_{0-t}, and $AUC_{0-\infty}$ significantly differed between non-obese group and the other two groups ($P < 0.05$) (Table 2). The PK parameters (except V_d and CL) in non-obese patients showed lower values than in obese and morbidly obese patients. However, we were unable to find any differences in V_d or CL among three groups ($P > 0.05$) (Table 2).

Table 2
Pharmacokinetics data on single dose sugammadex injection in the blood samples of patients

Parameters	Non-obese patients	Obese patients	Morbidly obese patients	*P* value
C_{max} (μg/mL)	25.1 (18.9, 35.9)[a]	61.1 (50.6, 68.4)[b]	54.9 (49.1, 68.3)[b]	< 0.001
T_{max} (min)	2.00 (2.00,2.00)[a]	5.00 (5.00, 8.75)[b]	5.00 (5.00, 10.0)[b]	< 0.001
$t_{1/2\beta}$ (min)	106 ± 18.3[a]	124 ± 29.7[b]	129 ± 19.5[b]	0.02
V_d (L)	10.0 (7.02, 12.3)	10.3 (8.01, 16.9)	12.3 (10.2, 14.5)	0.16
CL (mL/min)	67.2 ± 28.0	62.8 ± 15.8	70.9 ± 20.4	0.58
AUC_{0-t} (μg • min/mL)	1990 ± 758[a]	2570 ± 456[b]	2740 ± 630[b]	< 0.001
$AUC_{0-\infty}$ (μg • min/mL)	1960 (1520, 2550)[a]	2640 (2540, 2990)[b]	2800 (2330, 3390)[b]	< 0.001

C_{max}, maximum concentration; T_{max}, time to maximum concentration; $t_{1/2\beta}$, apparent terminal half-life; V_d, apparent volume of distribution; CL, total clearance; AUC_{0-t}, area under the plasma concentration–

time curve from time 0 to the last measurable concentration; $AUC_{0-\infty}$, area under the plasma concentration–time curve from time 0 to infinity. Data with different superscript letters within the same row indicate significant difference ($P < 0.05$).

PD results

The TOF ratio was monitored to assess the muscle relaxation level and the TOF ratio gradually increased following the reversal of muscle relaxation with sugammadex. The recovery of the TOF ratio to 0.9 was defined as complete reversal of the neuromuscular relaxant, which was regarded as an indicator for extubation. Times to recovery of TOF ratio were compared among three groups (Fig. 3) and the TOF ratio began to recover from a T_2 count at 30 s after sugammadex administration, and gradually reached 0.9 after 150 s. However, the average duration of the recovery from the T_2 count to the TOF ratio of 0.9 did not significantly differ among three groups (Fig. 3A). Upon comparing the proportion in three groups with a TOF ratio of > 0.9 following the reversal with sugammadex, all subjects in non-obese group appeared to achieve complete reversal effects more rapidly, followed by obese group, and then below that, morbidly obese group (Fig. 3B), showing that sugammadex administration of recommended dosage 2 mg/kg according to the guidelines was sufficient to reverse the action of muscle relaxant in all patients of three groups.

Discussion

In current study, PK and PD of sugammadex were determined in non-obese, obese, and morbidly obese patients during general anesthesia for laparoscopic gastrointestinal surgery. Our data revealed that sugammadex of 2 mg/kg dosed by CBW efficiently reversed vecuronium-induced moderate neuromuscular blockade in obese or morbidly obese patients, indicating that sugammadex dosed by CBW in vecuronium-induced moderate neuromuscular blockade would keep consistent to some extent with different BMI.

Pharmacokinetics

The PK parameters C_{max}, T_{max}, $t_{1/2\beta}$, AUC_{0-t}, and $AUC_{0-\infty}$ of sugammadex were found to significantly differ between non-obese group and the other two groups ($P < 0.05$), whereas V_d and CL were not significantly different among three groups ($P > 0.05$). C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ all increased in a dose-dependent manner with increasing BMI and CBW, which was most likely due to the increase in sugammadex consumption with increase in weight. According to the results, T_{max} was 2 min in non-obese group but about 5 min in the other two groups, which may be attributed to body weight, high fat deposition, higher dosage of muscle relaxants, and slow metabolic distribution etc., leading to prolonged absorption time. Yuan et al. [26] included 11 Chinese subjects in their study and successively administered 1-, 2-, and 4-mg/kg of sugammadex with a median dosage of T_{max} of 1.8 min in the three groups, which was comparable to the T_{max} of non-obese group (2 min) in our study. Since $t_{1/2\beta}$ is

dependent on both V_d and CL, changes in $t_{1/2\beta}$ reflect changes in V_d or CL or both. V_d is largely dependent on the physicochemical properties of a drug, whereas CL is predominantly dependent on the physiological status of the liver and kidney. It seemed to be a paradox that V_d and CL did not significantly differ among the three groups but $t_{1/2\beta}$ did, which was probably due to the difference between the apparent $t_{1/2\beta}$ and intrinsic ('true') $t_{1/2\beta}$. Researchers have previously pointed out that apparent $t_{1/2\beta}$ values are functions of both the ongoing rate of uptake as well as the rate of elimination, resulting in biased estimation of the intrinsic $t_{1/2\beta}$ [27]. However, failure to explicitly account for ongoing exposure is common in the published literature. The rate of intrinsic elimination can be determined if the influence of ongoing exposure and changes in physiology (such as body weight) are accounted for [28]. Thus, a further study involving more subjects may be needed to develop the population-based PK models [29] which may help to calculate the intrinsic $t_{1/2\beta}$ of sugammadex. However, according to our research so far, we consider that intrinsic $t_{1/2\beta}$ of sugammadex will remain similar despite different BMI (see below).

There was no significant difference in V_d among three groups ($P > 0.05$), suggesting that BMI did not affect the distribution of sugammadex. Volume of distribution is indeed dependent on the physicochemical properties of a drug, but it is also dependent on cardiac output and blood flow distribution to various tissue groups. These are different between non-obese and obese individuals. Although obese subjects have a great deal of adipose tissue, the fact that the adipose tissue is so poorly perfused would make this tissue group relatively inconsequential in the early distribution of drugs. Hanley et al. [30] pointed out that the distribution of non-lipophilic drugs is limited in excess adipose tissue, making the PK volume of the peripheral compartment similar in lean and obese individuals. Abernethy and Greenblatt [31] suggested that the apparent distribution of volume changes in obese individuals may be quite extreme, depending on the physical and chemical properties of drugs. The change in volume of distribution was initially hypothesized to be at least partially related to drug lipophilicity with obese individuals, showing a significant increase in volume of distribution for highly lipophilic drugs while showing only little change in the same for water-soluble drugs. The trends observed for sugammadex, a water-soluble drug, are consistent with this statement.

Besides, it was found that CL in the three groups was lower than its previously reported values in healthy adults (88 mL/min) [32]. CL can be defined as the volume of blood in which the drug is completely cleared within a given distribution time, and for most drugs, liver is the primary organ for drug metabolism. Obesity is associated with non-alcoholic fatty liver disease, and the accumulation of fat in the liver of obese individuals may change the blood flow within the liver. The other major organ involved in drug metabolism and clearance is the kidney, and the process of drug excretion through the kidney includes glomerular filtration, renal tubule secretion, and reabsorption. However, the influence of obesity on these functions remains unclear [30]. It may also be related to the influence of perioperative management on PK, and in particular, the total plasma volume deserves more attention. All patients in this study fasted for 8–12 h preoperatively and received restricted fluid therapy to prevent serious cardiovascular events (particularly for obese patients) during surgery [33]. Crystalloid fluid intake and urine remained consistent, obese patients in this study were likely to have hypovolemia perioperatively.

In formula [34] CL = V × U/P (V: urine volume per minute, U: substance concentration in urine, and P: substance concentration in plasma), creatinine was regarded as substance and sugammadex, with water solubility similar to it, exhibiting very consistent behavior in CL. Moreover, the compression of blood vessels in the abdominal viscera by pneumoperitoneum also contributed to decrease in glomerular filtration rate [35]. Therefore, lower renal perfusion led to decreased CL.

Pharmacodynamics

There was no significant difference among three groups in the average times of TOF > 0.9 ($P > 0.05$), indicating that sugammadex of 2 mg/kg dosed by CBW is effective to reverse vecuronium-induced moderate neuromuscular blockade and it is suitable for individuals with different BMI for laparoscopic gastrointestinal surgery. Subramani et al. [36] systematically evaluated the efficacy and safety of sugammadex *vs.* neostigmine in reversing neuromuscular blockade in morbidly obese patients undergoing bariatric surgery, and their results revealed that sugammadex led to faster reversal and fewer adverse events than neostigmine. And so far, our results have further confirmed the feasibility of sugammadex of 2 mg/kg dosed by CBW to reverse vecuronium-induced moderate neuromuscular blockade in patients with different BMI.

Limitations of this study were as follows: (1) It was a single-center study. (2) Only different BMI was focused without considering other obesity parameters which may affect the PK or PD of sugammadex. (3) Deep neuromuscular blockade in this study was not taken into account.

Conclusion

In conclusion, this study served as supplement to PK and PD of sugammadex in patients with different BMI and demonstrated sugammadex of 2 mg/kg dosed by CBW, efficiently reversed vecuronium-induced moderate neuromuscular blockade in obese or morbidly obese patients. Although certain PKs changed with different BMI, an additional dosage of sugammadex was not required in obese individuals.

Abbreviations

PK
pharmacokinetics
PD
pharmacodynamics
C_{max}
maximum concentration
T_{max}
time to maximum concentration
$t_{1/2\beta}$
apparent terminal half-life
V_d

apparent volume of distribution
CL
total clearance
AUC_{0-t}
area under the plasma concentration–time curve from time 0 to the last measurable concentration
$AUC_{0-\infty}$
area under the plasma concentration–time curve from time 0 to infinity
BMI
body mass index
ABW
actual body weight
CBW
corrected body weight
EMG
electromyography
ESI
electrospray ion source
RNMB
residual neuromuscular blockade
TOF
train-of-four
UHPLC-MS
ultra-high-performance liquid chromatography–tandem mass spectrometry.

Declarations

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of General Hospital of Southern Theatre Command (No: NZLLKZ2022041; date: 27 Jan 2022). The study was conducted according to the Declaration of Helsinki, the Good Clinical Practice guideline and local laws and regulations. Written informed consent was obtained from all subjects participating in the study.

Consent for publication

Not applicable.

Data Sharing Statement

Individual deidentified participant data that underlie the results reported in this article (including text, tables and figures) will be shared. The study protocol, statistical analysis plan and informed consent

form will also be made available upon reasonable request. Data requests should be directed to the corresponding author Bo Xu via email (xubo333@hotmail.com). To gain access, data requestors will need to sign a data access agreement. Data will be shared with researchers who provide a methodologically sound proposal, for the purpose of achieving the aims specified in the approved proposal.

Conflict of interest

The authors report no conflicts of interest in this work

Funding

This study was supported by the National Natural Science Foundation of China (No. 82472110).

Author Contribution

All authors made a significant contribution to the work reported. Z. Lai contributed to the conceptualization, methodology, data curation, and writing of the original draft and its review and editing. M. Xiong, B. Xu, and S. Wang contributed to the conceptualization, formal analysis, and writing-review and editing. W. Shao, L. Wu, Z. Liu, and X. Dai contributed to the investigation and resources. R. Xiao, W. Xi, and N. Shawalker contributed to the data curation and writing-review and editing. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version for publication; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Acknowledgments

The authors would like to thank Dr. Xing Li MD PhD, Dr. Wenxuan Jiang MD PhD and Dr. Ji Jia MD PhD for the language correction of this manuscript and statistical support for this study.

Data Availability

Individual deidentified participant data that underlie the results reported in this article (including text, tables and figures) will be shared. The study protocol, statistical analysis plan and informed consent form will also be made available upon reasonable request. Data requests should be directed to the corresponding author Bo Xu via email (xubo333@hotmail.com). To gain access, data requestors will need to sign a data access agreement. Data will be shared with researchers who provide a

methodologically sound proposal, for the purpose of achieving the aims specified in the approved proposal.

References

1. Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P, St-Onge MP. Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association[J]. Circulation. 2021;143(21):e984–1010.
2. Bleich S, Cutler D, Murray C, Adams A. Why is the developed world obese?[J]. Annu Rev Public Health. 2008;29:273–95.
3. Blüher M. Obesity: global epidemiology and pathogenesis[J]. Nat Rev Endocrinol. 2019;15(5):288–98.
4. Gouju J, Legeay S. Pharmacokinetics of obese adults: Not only an increase in weight[J]. Biomed Pharmacother. 2023;166:115281.
5. Nightingale CE, Margarson MP, Shearer E, Redman JW, Lucas DN, Cousins JM, Fox WT, Kennedy NJ, Venn PJ, Skues M, Gabbott D, Misra U, Pandit JJ, Popat MT, Griffiths R. Peri-operative management of the obese surgical patient 2015: Association of Anaesthetists of Great Britain and Ireland Society for Obesity and Bariatric Anaesthesia[J]. Anaesthesia. 2015;70(7):859–76.
6. Naguib M, Kopman AF, Ensor JE. Neuromuscular monitoring and postoperative residual curarisation: a meta-analysis[J]. Br J Anaesth. 2007;98(3):302–16.
7. Baillard C, Clec'h C, Catineau J, Salhi F, Gehan G, Cupa M, Samama CM. Postoperative residual neuromuscular block: a survey of management[J]. Br J Anaesth. 2005;95(5):622–6.
8. Ortega R, Brull SJ, Prielipp R, Gutierrez A, De La Cruz R, Conley CM. Monitoring Neuromuscular Function[J]. N Engl J Med. 2018;378(4):e6.
9. Naguib M, Brull SJ, Johnson KB. Conceptual and technical insights into the basis of neuromuscular monitoring[J]. Anaesthesia. 2017;72(Suppl 1):16–37.
10. Li D, Wang Y, Zhou Y, Yin C. Efficacy and safety of sugammadex doses calculated on the basis of corrected body weight and total body weight for the reversal of deep neuromuscular blockade in morbidly obese patients[J]. J Int Med Res. 2021;49(1):300060520985679.
11. Miller RD. Sugammadex: an opportunity to change the practice of anesthesiology?[J]. Anesth Analg. 2007;104(3):477–8.
12. Bom A, Bradley M, Cameron K, Clark JK, Van Egmond J, Feilden H, MacLean EJ, Muir AW, Palin R, Rees DC, Zhang MQ. A novel concept of reversing neuromuscular block: chemical encapsulation of rocuronium bromide by a cyclodextrin-based synthetic host[J]. Angew Chem Int Ed Engl. 2002;41(2):266–70.
13. Ledowski T, Szabó-Maák Z, Loh PS, Turlach BA, Yang HS, de Boer HD, Asztalos L, Shariffuddin II, Chan L, Fülesdi B. Reversal of residual neuromuscular block with neostigmine or sugammadex and

postoperative pulmonary complications: a prospective, randomised, double-blind trial in high-risk older patients[J]. Br J Anaesth. 2021;127(2):316–23.

14. Adams DR, Tollinche LE, Yeoh CB, Artman J, Mehta M, Phillips D, Fischer GW, Quinlan JJ, Sakai T. Short-term safety and effectiveness of sugammadex for surgical patients with end-stage renal disease: a two-centre retrospective study[J]. Anaesthesia. 2020;75(3):348–52.
15. Juneja N, Alam MS, Varshney VK, Gogia P, Prasad MK, Jheetay GS. Comparison of Hemodynamic Changes in Patients Undergoing Laparoscopic Cholecystectomy using rocuronium and vecuronium for Intubation and Maintenance under General Anesthesia[J]. Anesth Essays Res. 2022;16(1):133–7.
16. Bhananker SM, O'Donnell JT, Salemi JR, Bishop MJ. The risk of anaphylactic reactions to rocuronium in the United States is comparable to that of vecuronium: an analysis of food and drug administration reporting of adverse events[J]. Anesth Analg. 2005;101(3):819–22.
17. Naguib M, Samarkandi AH, Bakhamees HS, Magboul MA, el-Bakry AK. Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine[J]. Br J Anaesth. 1995;75(5):588–92.
18. Asztalos L, Szabó-Maák Z, Gajdos A, Nemes R, Pongrácz A, Lengyel S, Fülesdi B, Tassonyi E. Reversal of Vecuronium-induced Neuromuscular Blockade with Low-dose Sugammadex at Train-of-four Count of Four: A Randomized Controlled Trial[J]. Anesthesiology. 2017;127(3):441–9.
19. Mostoller K, Wrishko R, Maganti L, Herring WJ, van Zutphen-van Geffen M. Pharmacokinetics of Sugammadex Dosed by Actual and Ideal Body Weight in Patients With Morbid Obesity Undergoing Surgery[J]. Clin Transl Sci. 2021;14(2):737–44.
20. Horrow JC, Li W, Blobner M, Lombard J, Speek M, DeAngelis M, Herring WJ. Actual versus ideal body weight dosing of sugammadex in morbidly obese patients offers faster reversal of rocuronium- or vecuronium-induced deep or moderate neuromuscular block: a randomized clinical trial[J]. BMC Anesthesiol. 2021;21(1):62.
21. Llauradó S, Sabaté A, Ferreres E, Camprubí I, Cabrera A. Sugammadex ideal body weight dose adjusted by level of neuromuscular blockade inlaparoscopic bariatric surgery[J]. Anesthesiology. 2012;117:93–8.
22. Naguib M, Brull SJ, Kopman AF, Hunter JM, Fülesdi B, Arkes HR, Elstein A, Todd MM, Johnson KB. Consensus Statement on Perioperative Use of Neuromuscular Monitoring[J]. Anesth Analg. 2018;127(1):71–80.
23. Van Lancker P, Dillemans B, Bogaert T, Mulier JP, De Kock M, Haspeslagh M. Ideal versus corrected body weight for dosage of sugammadex in morbidly obese patients[J]. Anaesthesia. 2011;66(8):721–5.
24. Subramani Y, Rajarathinam M, Dabirzadeh A, Tawfic Q, Krause S, Avci Y, Nagappa M. Comparison of Different Weight Scalars to Dose Sugammadex for the Reversal of Neuromuscular Blockade in Morbidly Obese Patients: A Systematic Review[J]. Cureus. 2024;16(3):e57057.
25. de Zwart MA, ten Bruggencate-Broeders J, van Hal HJ, Megens RH, Frasa HW. Determination of sugammadex in human plasma, urine, and dialysate using a high-performance liquid

chromatography/tandem mass spectrometry assay[J]. J Chromatogr B Analyt Technol Biomed Life Sci. 2011;879(19):1573–86.

26. Yuan F, Yang M, Chen W, Chen H, Xu H, Li H, Sheng L, Li X, Ellen Wrishko R, Joel Woolf E. Pharmacokinetics of Sugammadex: An Open-Label, 3-Period, Fixed-Sequence, 3-Single-Doses Study in Healthy Chinese Subjects[J]. Clin Pharmacol Drug Dev. 2022;11(3):333–40.
27. Shirai JH, Kissel JC. Uncertainty in estimated half-lives of PCBS in humans: impact on exposure assessment[J]. Sci Total Environ. 1996;187(3):199–210.
28. Russell MH, Waterland RL, Wong F. Calculation of chemical elimination half-life from blood with an ongoing exposure source: the example of perfluorooctanoic acid (PFOA)[J]. Chemosphere. 2015;129:210–6.
29. Ritter R, Scheringer M, MacLeod M, Moeckel C, Jones KC, Hungerbühler K. Intrinsic human elimination half-lives of polychlorinated biphenyls derived from the temporal evolution of cross-sectional biomonitoring data from the United Kingdom[J]. Environ Health Perspect. 2011;119(2):225–31.
30. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans[J]. Clin Pharmacokinet. 2010;49(2):71–87.
31. Abernethy DR, Greenblatt DJ. Drug disposition in obese humans. An update[J]. Clin Pharmacokinet. 1986;11(3):199–213.
32. Gijsenbergh F, Ramael S, Houwing N, van Iersel T. First human exposure of Org 25969, a novel agent to reverse the action of rocuronium bromide[J]. Anesthesiology. 2005;103(4):695–703.
33. Suh SW. Influence of Obesity and Fluid Balance on Operative Outcomes in Hepatic Resection[J]. J Pers Med. 2022;12(11):1897.
34. McIntosh JF, Möller E, Van Slyke DD, STUDIES OF UREA, EXCRETION. III. The Influence of Body Size on Urea Output[J]. J Clin Invest. 1928;6(3):467–83.
35. Nguyen NT, Wolfe BM. The physiologic effects of pneumoperitoneum in the morbidly obese[J]. Ann Surg. 2005;241(2):219–26.
36. Subramani Y, Querney J, He S, Nagappa M, Yang H, Fayad A. Efficacy and Safety of Sugammadex versus Neostigmine in Reversing Neuromuscular Blockade in Morbidly Obese Adult Patients: A Systematic Review and Meta-Analysis[J]. Anesth Essays Res. 2021;15(1):111–8.

Figures

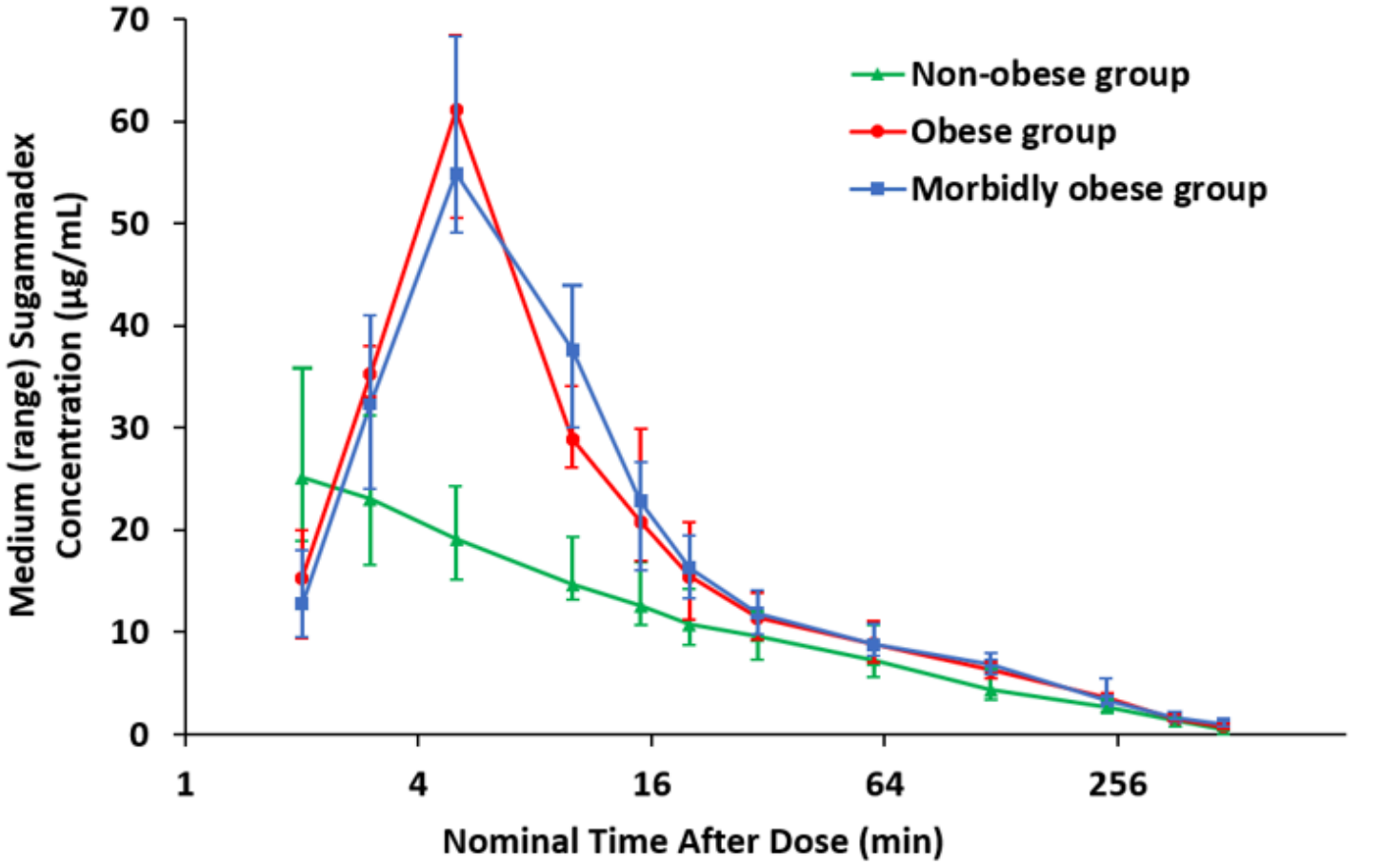


Figure 2

Medium sugammadex plasma concentration-time profiles following the administration of a single dose of sugammadex in each group (*n* = 16)

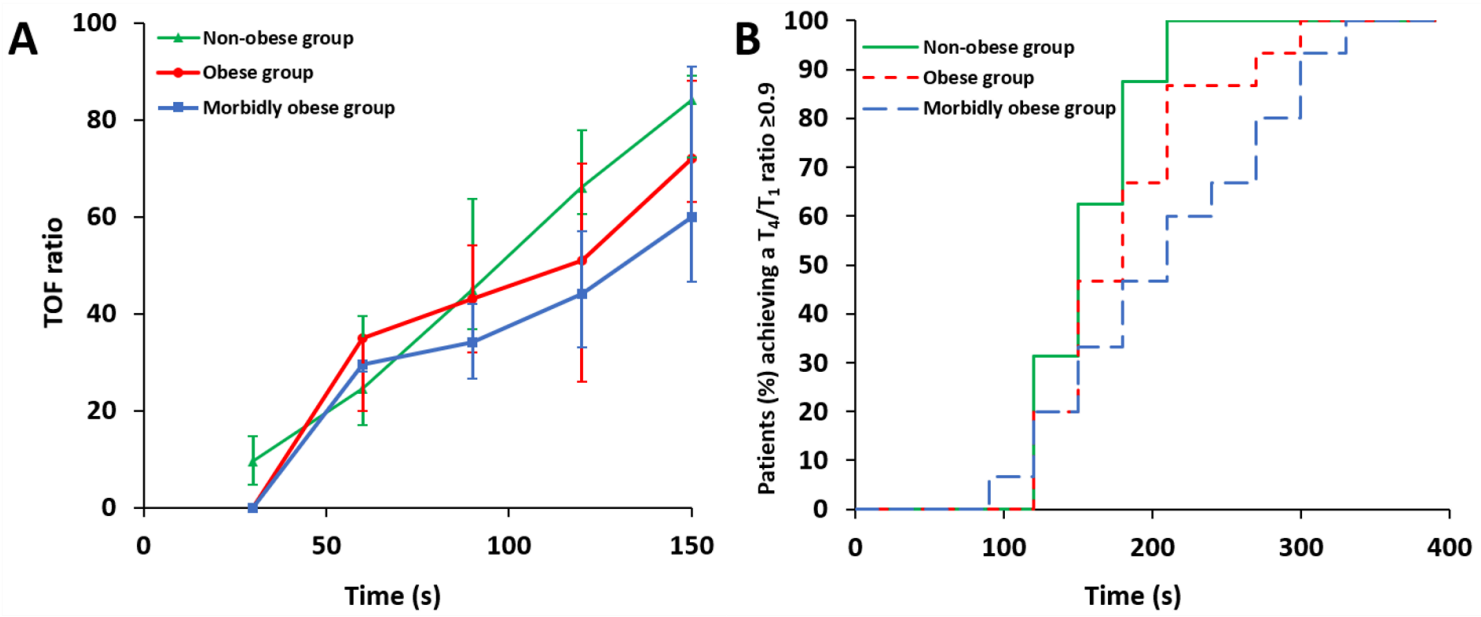


Figure 3

Effect of sugammadex on reversal of the neuromuscular relaxant in patients. A: The recovery of TOF ratio after sugammadex injection in each group (*n* = 16). B: Number of patients who reached 0.9 of the TOF ratio in each group after sugammadex injection (*n* = 16)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STROBEchecklistv4combinedPlosMedicine.docx