THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

Dr. Asztalos László

Improving the safety of anesthesia by using sugammadex

Doctoral Advisor:

Dr. Fülesdi Béla, doctor of the Hungarian Academy of Sciences (MTA)

UNIVERSITY OF DEBRECEN

DOCTORAL SCHOOL OF NEUROSCIENCES

Debrecen, 2019

Improving the safety of anesthesia by using sugammadex

by

László Asztalos MD

Supervisor: Béla Fülesdi, MD, PhD, DSc

Doctoral School of Neurosciences, University of Debrecen

Head of the **Examination Committee:** Prof. Miklós Antal, MD, PhD, DSc

Members of the Examination Committee:

Balázs Pál, MD,PhD

Prof. Katalin Darvas, MD, PhD

The Examination takes place at the Library of the Department of Anesthesiology and Intensive Care, Faculty of Medicine, University of Debrecen, 30.09.2019., 11:00

Head of the **Defense Committee**: Prof. Miklós Antal, MD, PhD, DSc

Reviewers: Prof. Lajos Bogár, MD, PhD,DSc

Prof. Zoltán Papp, MD, PhD,DSc

Members of the Defense Committee: Prof. Lajos Bogár, MD, PhD, DSc

Prof. Zoltán Papp, MD, PhD, DSc

Balázs Pál, MD, PhD

Prof. Katalin Darvas, MD, PhD

The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen

30.09.2019., 13:00

1. Introduction

The world came to know the first records about curare, which was used as poison-arrow in South-America, at the end of the 1500s. Studying this alkaloid experimentally, Claude Bernard came to the conclusion that the place of effect is the neuromuscular junction. Since then it became a routinely applied part of muscle relaxation and general anesthesia used during surgical procedures. The use of neuromuscular blocking agents helps perform intratracheal intubation, reducing the risk of postintubation hoarseness and development of airway injuries, as well as it promotes mechanical ventilation and surgical exploration. Surgical procedures do not require muscle relaxation in every case, thus it is important to use these drugs in the appropriate indications, tailored to individual needs. With the appropriate use of neuromuscular blocking agents, the surgical circumstances can be optimized in each type of surgery. However, the role of the depth of neuromuscular blockade (NMB) in this process created by different muscle relaxants is not adequately clarified. Besides the favorable effects, the use of this class of drugs entails numerous risks as well. Such risks include the residual muscle relaxant effect at the end of surgery (postoperative residual neuromuscular blockade), which can cause several complications (airway obstruction, bronchopulmonary aspiration, hypoxia, pharyngeal- or esophageal dysfunction). During the 234.4 million surgical procedures performed worldwide, critical airway complications related to residual muscle relaxant effect develop in nearly half million patients. These complications can lead to an increase in postoperative morbidity and mortality. The incidence of postoperative residual neuromuscular blockade is around 40%, despite the traditional antagonization with anticholinesterase. This high number draws attention to the importance of adequate monitoring of muscle relaxant effect as well as its effective reversal at the end of surgeries. There are basically two options available to reverse neuromuscular blockade. One of them is the reversal with acetylcholinesterase inhibitors, which may be associated with complications of the parasympathetic nervous system and cannot be used in profound neuromuscular blockade. The other option is using the cyclodextrin called sugammadex for antagonization, which can terminate neuromuscular blockade at any scale without side effects.

The introduction of sugammadex made a definitive change in the management of muscle relaxation during general anesthesia; however, the details about its use require continuous research. Several studies were made, as I have reviewed them in the literary summary, but many further questions await answers, necessitating the continuation of both

pharmacological and economic and clinical research. We have performed our examinations joining to this process, the results of which we have published in two studies. Both studies help the adequate use of sugammadex as part of the international literature, thereby contributing to the safety of anesthesia.

2. Objective

- The purpose of our studies was to optimize the use of sugammadex and offset its high purchase price by lowering the dose.
- We wished to demonstrate the safe applicability of the reduced dose of sugammadex so that it could be used as cost-effectively as possible in everyday practice. The initial hypothesis of our studies was that the dose of sugammadex can be lowered from the quantity recommended by the manufacturer without a decrease in efficacy and safe reversal.
- The aim of this assumption is to make the use of sugammadex financially able because its high purchase price prevents its routine use, thus its benefits are unexploited.
- We examined the optimization of the dose of sugammadex used for reversal for two steroid-type muscle relaxants, vecuronium and pipecuronium.
- Our aim was to find a dose that is necessary, but still clinically safe, to reverse the shallow blockade for the intermediate-acting muscle relaxant vecuronium as well as the profound blockade for the long-acting muscle relaxant pipecuronium.

2.1 Study endpoints

The primary endpoint of our study investigating the reversal of the residual effect of vecuronium with sugammadex is the time from administration of the reversal agent to the return of nTOFR to 0.9 in different groups, which shows the efficacy of reversal. Criterion of adequate reversal was achievement of normalized TOF ratio 0.9 in 5 min or less on average.

Incomplete We defined the inefficiency of reversal as the ratio of events where the normalized TOFR value did not return to above 0.9 even within 30 minutes. The secondary endpoint of the study was to determine the incidence of PORNB during the first 60 minutes in the postoperative observation ward. Additional efficacy endpoints included the time intervals necessary from the reversal until T1 90% or until the non-normalized TOFR value returned to 1.0, and the number of patients achieving an nTOFR of 1.0.

The primary endpoint of our study investigating the reversal of the profound neuromuscular blockade following the administration of pipecuronium was the time necessary from administration of the reversal agent to the return of the nTOFR value to 0.9. As additional endpoints, we examined the incidence rates of the residual neuromuscular blockade in the postoperative period and those of the recurrent neuromuscular blockade.

3. Methods

3.1 Patients and methods, study design, patient recruitment

The recruitment of participants into our single-center, randomized, five parallel-arm, double blind, placebo-controlled study investigating the reversal of the residual effect of vecuronium by sugammadex was done during the everyday patient care. We enrolled sixty-five out of seventy patients undergoing elective surgery, who gave their written informed consent to participate in the study. The participants were randomly assigned into one of the five study groups. Thus, the patients received sugammadex at a dose of 0.5; 1.0 or 2.0 mg/kg or neostigmine at 0.05 mg/kg and atropine at 0,015 mg/kg or 0,9% saline (placebo) to reverse the neuromuscular blockade. The inclusion criteria included age from 18 to 65 years, body mass index (BMI) from 18.5 to 25 kg/m^2, American Society of Anesthesiologists (ASA) physical status class I to III, and elective surgery with an expected duration of at least 50 minutes, where a muscle relaxant was necessary for intratracheal intubation, but the type of surgery did not require continuous full relaxation. We aimed for an identical gender ratio throughout the enrollment. Patients with suspected difficult airway, bronchial asthma, chronic obstructive pulmonary disease, neuromuscular disease, suspected malignant hyperthermia, significant hepatic or renal dysfunction, glaucoma, or allergy to any of the drugs used in this study were excluded from participation. Furthermore, pregnant or breastfeeding women or

those participating in another research study within 30 days prior to surgery were not included.

50 patients awaiting abdominal surgery were included into our study investigating the reversal of profound neuromuscular blockade after pipecuronium administration, who signed an Informed Consent Form after being provided with oral and written information. The same patient recruitment method was used as in the previous study. The inclusion criteria only differed in that the expected time of the surgical procedure under general anesthesia and intratracheal intubation had to be at least 60 minutes long. The other inclusion as well as the exclusion criteria were fully identical in the two studies.

3.2 Execution of the studies: randomization, preparing the patients, neuromuscular monitoring, reversal of muscle relaxation, postoperative observation

In our study investigating the reversal of the residual effect of vecuronium with sugammadex, randomization was done in a 1:1 ratio to acquire patient groups with identical size. The statistician of the study created the randomization sequence with the help of an online program (www.randomizer.org). Sixty-five participants were enrolled into one of the five reversal groups; participants in individual medication groups therefore received sugammadex at a dose of 0.5; 1.0 or 2.0 mg/kg, neostigmine at 0.05 mg/kg and atropine at 0,015 mg/kg or 0.9% saline (placebo), respectively. An assigned anesthesiologist not participating in the study prepared the drug to be administered according to the randomization code. The anesthesiologist performing the narcosis could not know, which group a given patient was enrolled to because the size and color of the syringes were identical.

During our study on the reversal of pipecuronium effect, we divided the patients into 2 groups after randomization. At the end of the surgery, one group received sugammadex at 2 mg/kg, while the other group received 4 mg/kg before extubation of the trachea. We used block-randomization technique to ensure equal number of patients in the two groups. We wrote the numbers 2 and 4 on 25 cards each, then mixed these cards and put them into an envelope. At the end of the surgery, a third assigned anesthesiologist not participating in the evaluation of study results drew a card from the envelope, and prepared sugammadex at the respective dose in an unmarked syringe. The numbers 2 and 4 indicated agents at a dose of 2 mg/kg and 4 mg/kg, respectively. The drug was then injected as instructed by the

anesthesiologist responsible for the patient. Neither the patient nor the anesthesiologist responsible for the patient nor the anesthesiologist assistant did not know which dose of sugammadex from which randomization group was administered.

The patients received premedication with 7,5 mg midazolam orally 60 minutes before the start of anesthesia, then we placed an intravenous cannula in a forearm vein in the operating theatre and monitoring of vital parameters was started. Induction of anesthesia was achieved by intravenous propofol (1.5-2.0 mg/kg) and fentanyl at 2,0 μg/kg, we used the inhalational anesthetic sevoflurane in an oxygen-air mixture of 1.5-1.8 vol% for maintenance, which was supplemented with intravenous fentanyl as needed. Patients were ventilated manually with a face mask until intratracheal intubation. We kept the oxygen saturation above 96%, and we ensured normocapnia and maintained the esophageal temperature above 36°C, for which we used the Bair-Hugger® (Arizant Healthcare Inc, Eden Prairie, MN) forced-air warming system.

The TOF-Watch-SX® (Organon Teknika B.V., Boxtel, Holland) acceleromyograph was used for neuromuscular monitoring. Following stimulation of the ulnar nerve, we registered contractions in the adductor pollicis muscle. The piezoelectric crystal of the acceleromyograph was attached to the distal phalanx of the thumb. The preload of the thumb as well as its return to its original position was ensured by an adapter. During our examination, we immobilized the forearm and the fingers. We placed superficial electrodes on the skin above the ulnar nerve, proximal to the wrist. We performed train-of-four stimulation for 3 minutes every 15 seconds, then we invigorated the function of the synapse with a tetanic stimulation for 5 seconds at a frequency of 50 Hz. This was followed by an automatic calibration (CAL-2) after two minutes, with a goal to determine the supramaximal current intensity and calibrate the device. During TOF stimulation, we used supramaximal square wave stimulation for 0.2 seconds at a frequency of 2 Hz until signal stability was reached. In the absence of stable signal, re-calibration was done. The recorded data was stored on a computer using the TOF-Watch SX software version 2.2 INT (Organon Ireland Ltd. Dublin, Ireland). Skin temperature was measured on the forearm near the wrist and maintained above 32°C.

While performing our study investigating the reversal of the residual effect of vecuronium with sugammadex, IV vecuronium at 0.1 mg/kg (2 x ED95) was injected once neuromuscular data was stable, and intratracheal intubation was performed after the response to TOF stimulation disappeared. If muscle relaxation was necessary from a surgical aspect,

vecuronium at 0.015 to 0.02 mg/kg was administered again when 1 or 2 muscle responses appeared to TOF stimulation. The TOF stimulation was automatically delivered by the equipment every 15 seconds.

During our study investigating the reversal of profound neuromuscular blockade after pipecuronium administration, each patient received IV pipecuronium at 0.08 mg/kg (approximately 1.8 x ED95) once neuromuscular data was stable. When there was no registrable response to acceleromyographic stimulation, the trachea was intubated. Throughout the surgery, we made TOF measurements every 15 seconds and if the TOFC value reached 1, additional pipecuronium at 0.01-0.02 mg/kg was administered, thereby maintaining the continuous presence of profound blockade. (TOFC 0 and PTC $\leq$2). At the end of surgery, we measured PTC (50Hz tetanic stimulation for 5 seconds followed by 12 single stimuli) every 3 minutes, thereby detecting the early signs of termination of profound neuromuscular blockade. Once the measured PTC value reached 1 or 2, we continued the study with TOF measurements.

The reversal of vecuronium block proceeded as follows: when the fourth twitch in response to TOF stimulation reappeared on three consecutive TOF measurements (a threshold of TOFC4), the assigned anesthesiologist injected the reversal agent, which had previously been prepared by the independent anesthesiologist. The reversal agents used during the study were administered in syringes with identical color and volume, and the anesthesiologist responsible for narcosis did not know the contents of the syringes. The changes in TOF ratio (T4/T1) and T1 amplitude (the first muscle response to TOF stimulation) were followed online and recorded for later analysis. Once the TOFR value reached at least 1.0 (and remained unchanged for 3 minutes), the use of sevoflurane was discontinued and patients were extubated after regaining consciousness. If the TOF ratio did not return to 0.9 within 30 minutes after administration of the unknown reversal agent, we assessed it as failed reversal and „rescue medication" was given (sugammadex at 2 mg/kg) to the patient. During this time, the patient remained intubated. Reversal was considered as adequate if attainment of the normalized TOF ratio (nTOFR) of 0.9 required up to 5 minutes after administration of the unknown reversal agent. (During normalization, we divide the returned TOF value by the baseline TOF measured before vecuronium use). For the pipecuronium-induced neuromuscular blockade, sugammadex was injected after a waiting period of 3 minutes following the last PTC measurement. During this time the neuromuscular transmission stabilized, making our measurement results more precise. Then, the use of inhalational

sevoflurane was stopped and the patient extubated, while TOF measurements were made for later analysis. The block was considered as fully reversed for TOF values ≥1.0. In the case of residual block (a TOFR value of ≤0.9 for more than 5 minutes), neostigmine at 0.05 mg/kg with concurrent atropine at 0.015mg/kg was administered.

After extubation, all patients were transferred to the postoperative monitoring room. We did not carry out nerve stimulation during patient transfer, the device was in standby mode while trying to ensure the original condition of the adapter and hand. In the monitoring room, a third anaesthesiologist observed and examined the patients, who also did not know the randomization group of the actual patient. In the first 60 minutes of the postoperative period, vital parameters (blood pressure, pulse rate, respiratory rate, Glasgow Coma Scale, oxygen saturation) of the patients and the clinical signs of muscle weakness were examined every 20 minutes, and acceleromyographic TOF measurements were performed with the device without recalibration. The first measurement took place upon entering the monitoring room, and then every 20 minutes for a total of 4 times. For each measurement, 3 consecutive nerve stimulation were performed, with a 15 second interval between measurements. Later, the mean of the measurements was taken into account. Computer recording and storage of the results, like in the intraoperative period, was done with the TOF-Watch-SX software 2.2 INT (Organon Ireland Ltd. Dublin, Ireland). Postoperative residual neuromuscular blockade was established for normalized TOFR values of ≤0.9%. During examination of the clinical signs of muscle weakness, patients had to perform simple commands for testing muscle function (such as lifting hands and legs, coughing, tongue depressor clenching, hand grip strength, swallowing or moving mimic muscles) that were scored on a scale from 1 to 5 in a table. The last three points in the table were completed based on subjective complaints of patients. Here we were curious about weakness, double vision or breathing difficulty. The data was entered in an electronic table for later analysis. After the first 60 minutes of the postoperative period, patients were observed for an additional 24 hours to detect possible late complications.

3.3 Data management, statistical analysis

In the power analysis of our study investigating the reversal of vecuronium block, we assumed that the recovery time of the normalized TOFR of 0.9 was 600 seconds (SD 200

seconds) during neostigmine antagonism. We assumed that sugammadex at 0.5 mg/kg would reduce this time to 300 seconds. Setting the value of Type I error (α) to 0.05, 10 patients per group were required to achieve a statistical power of 0.8. Accounting for losses to follow-up, a total of 65 patients (13 persons per group) were included in the study.

The primary endpoint of our study was the time from the administration of the unknown reversal agent to the nTOFR of 0.9, which indicated the efficacy of reversal. Reversal was unsuccessful if the nTOF ratio did not return to above 0.9 even in 30 minutes. The secondary endpoint of the study was to assess the incidence of PORNB in the first 60 minutes in the postoperative observation ward. Additional efficacy endpoints included the times needed from reversal until recovery to T1 90% and a non-normalized TOFR of 1.0, and the number of patients reaching an nTOFR of 1.0.

To assess the primary efficiency endpoint, i.e. to determine the time needed from administration of the reversal agent to achieving a normalized TOFR of 0.9, we applied one-way analysis of variance (ANOVA). To determine whether the variables showed a normal distribution, we used the Shapiro-Wilk statistical test. The homogeneity of the variances was checked by Levene's test within each reversal group. Data showing non-normal distributions were transformed to normal distribution by Box–Cox transformation. Variables showing unequal variances even after transformation were equalized by Welch's F-test. In each group, post-hoc analysis of the differences was performed using Tukey's HSD test. If it was possible to do so based on parametric test estimates, we also used the ANOVA statistical method for the analysis of basic variables (patient data, perioperative variables). Otherwise, we used the non-parametric Kruskal–Wallis test for between-groups comparisons. To determine the incidence of unsuccessful reversals constituting the primary endpoint of the study, and determine the secondary endpoint defined as the incidence of recurrent paralyses, we used χ^2 statistical tests. When the χ^2 test was not applicable, we analyzed the associations using Cramer's V statistical method. Given the two components of the primary efficacy endpoint, we chose a significance level of $\alpha = 0.025$ (half the conventional value of 0.05) when assessing the efficacy endpoints. In the statistical analysis of the basic variables, we used a significance level of $\alpha = 0.05$. All statistical calculations were performed using PAST 3.0.79 [(Øyvind Hammer, Sweden), R (version 3.2.2; http://www.r-project.org; accessed: August 14, 2015)].

In our study investigating the reversal of pipecuronium block, the sample size was determined by statistical power analysis. We assumed the reversal time for the sugammadex

dose of 2 mg/kg to be 3 minutes, i.e. twice the time required to recover from a moderate block.[16] At a significance level (α) of 0.025, a power (ß) of 0.9, a noninferiority range (d) defined as 1 minute (see below), and an SD (standard deviation) of 1 minute, 22 participants were required to confirm that sugammadex at 2 mg/kg has non-inferior efficacy vs. 4 mg/kg in the reversal of pipecuronium-induced profound neuromuscular blockade. We enrolled 25 patients on the assumption that some patients may drop out during the study. The sample size was determined using Sealed envelope TM software (Sealed Envelope Ltd, Clerkenwell, London, United Kingdom).

The primary endpoint was the same as described for our study investigating antagonism of vecuronium-induced block. An additional endpoint was the incidence of residual or recurrent neuromuscular blockade occurring in the postoperative period.

To decide whether the two different sugammadex doses have any clinical relevance, we defined noninferiority ranges (delta) based on recommendations by Piaggio. We used data from our previous study in the calculations. In this study, we compared sugammadex at 4 mg/kg with the effect of placebo. In the group of patients receiving sugammadex at a dose of 4 mg/kg, the time required to achieve a normalized TOFR of 0.9 was 1.6 ± 0.5 min (mean ± standard deviation [SD]; 95% confidence interval [CI], 1.22–1.89). This time was observed to be 11.6 ± 5.5 minutes (95% CI, 7.3–15.9) in patients receiving neostigmine rescue medication after placebo administration. The time difference between the two treatments was 10 minutes. In our present study, we defined the limits of the noninferiority range assuming that the time required to reach a normalized TOFR of 0.9 would be less than one minute longer than that experienced in our previous study. This time increase (1 minute) is 10% of the 10-minute time difference between treatments described in our previous study. This difference of 10% is sensitive enough to detect a difference in clinical efficacy between the two doses of sugammadex. In the international literature, some authors find differences of up to 25-50% to be acceptable. Based on these, the noninferiority limit of the primary endpoint was defined as 1 minute.

Our null hypothesis was that the difference in recovery times between the two groups receiving different doses would not exceed the upper limit of the non-inferiority range. In order to test our hypothesis, we first determined the mean±SD values and 95% confidence

intervals of the variables in both groups. We then calculated the treatment difference defined as the difference between the means of the new therapy and the active control. We presented these values as means and the 95% confidence interval of the difference mentioned above. We plotted the treatment difference and their respective 95% Cis, indicating the non-inferiority range as recommended by Piaggio et al. Finally, we calculated the one-sided p-values required for the noninferiority t-test for both the primary and secondary endpoints, as recommended by Mascha & Sessler. With this procedure, we thus tested our null hypothesis that the new treatment is inferior to the active control by at least the length of the non-inferiority range. We could also test our alternative hypothesis that the new treatment has non-inferior efficacy to the active control by more than the non-inferiority range. We calculated standardized differences in demographic variables between the two groups using the "stddiff" statistical program of the R package. For statistical analysis, we used Past 3.07 software (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

4. Results

Reversal of the residual effect of vecuronium with sugammadex upon recovery of the train-of-four response to train-of-four stimulation: a prospective, blinded, randomized controlled, dose-effect study

Sixty-five out of seventy patients meeting the eligibility criteria agreed to participate. A patient included in the sugammadex 1.0 mg/kg group was excluded due to technical reasons (broken-down acceleromyograph during testing), so we analysed the data on the basis of 64 cases. There was no significant difference among the 5 patient groups for gender, age, BMI, control TOF ratio, control T1%, ASA physical status, and duration of surgery (Table 1). In addition, there was no statistical difference among the groups for the dose of vecuronium administered to patients and end-expiration sevoflurane concentration used during reversal. Also, there was no significant difference between individual reversal groups for the time elapsed between the administration of the last dose of vecuronium and the appearance of TOFC4 block. (Table 2)

Table 1. Comparison of baseline characteristics, duration of surgery, and control acceleromyographic values

Variable*	Sugammadex 0.5 mg/kg	Sugammadex 1.0 mg/kg	Sugammadex 2.0 mg/kg	Neostigmine 0.05 mg/kg	Placebo 0.9% Saline	P value
Sex (male/female)	7/6	6/7	7/6	6/7	5/8	0,93†
Age, yr	47±11.6	41±10.1	48±12.9	43±12.4	48±13.5	0.43‡
BMI (kg/m$^{2)}$	22.9 (21.5-24.1)	21.6 (20.1-28.8)	24.6 (21.6-25.1)	24.5 (21.1-24.9)	24.4 (23.2-24.9)	0.17§
Duration of surgery, min	75 (50-113)	45 (38-73)	80 (45-95)	60 (52.5-75)	60 (55-105)	0.34§
Control TOF ratio	1.07 (1.05-1.12)	1.10 (1.04-1.15)	1.07 (1.01-1.11)	1.07 (1.04-1.12)	1.06 (1.03-1.09)	0.77§
Control T1%	96±3.8	99±5.0	98±5.6	96±6.8	100±4.3	0.29‡
ASA class (I/II/III)	3/10/0	5/8/0	4/9/0	6/7/0	4/9/0	0.77†

*Means ± SDs are given when data met the assumptions of parametric statistical tests; otherwise, medians (interquartile ranges) are given. N = 13 in each group. †Data are from chi square test. ‡Data are from one-way ANOVA. §Data are from Kruskal–Wallis ANOVA. ASA = American Society of Anesthesiologists; BMI = body mass index; TOF = train-of-four.

Table 2. Comparison of the study groups at antagonism

Variable*	Sugammadex 0.5 mg/kg	Sugammadex 1.0 mg/kg	Sugammadex 2.0 mg/kg	Neostigmine 0.05 mg/kg	Placebo 0.9% Saline	P value
Total vecuronium dose, mg/kg	0.1 (0.10-0.12)	0.1 (0.10-0.10)	0.1 (0.10-0.11)	0.1 (0.10-0.11)	0.1 (0.10-0.11)	0.44†
Sevoflurane concentration, vol%	1.5(1.3-1.9)	1.8 (0.9-2.1)	1.6 (1.1-2.0)	1.8 (1.4-1.9)	1.7 (1.4-1.8)	0.99†
Time from last vecuronium dose to antagonism, min	53±26	68±33	49±14	50±19	54±23	0.25‡
Normalized TOF ratio	0.10 (0.07-0.11) [11]	0.09 (0.07-0.11) [11]	0.10 (0.10-0.14) [12]	0.09 (0.08-0.13) [12]	0.09 (0.07-0.11) [12]	0.76†
Normalized T1%	32±11	31±13	33±10	34±13	31±9	0.94‡

*Means ± SDs are given when data met the assumptions of parametric statistical tests; otherwise, medians (interquartile ranges) are given. Sample size is 13, except where indicated in brackets. †Data are from Kruskal–Wallis ANOVA. ‡Data are from one-way ANOVA. TOF = train-of-four.

Primary endpoint

The mean time from neostigmine administration to the appearance of a normalized TOFR of 0.9 was 11.3 minutes, which is significantly longer than for reversal with sugammadex at 1.0 mg/kg (mean of 4.4 min) or 2.0 mg/kg (mean of 2.6 min) (Table 3, Tukey HSD test for comparisons, $p < 0.05$). In contrast, the difference between neostigmine and sugammadex at 0.5 mg/kg (mean of 6.8 min) is not statistically significant ($p > 0.05$) (Table 3). However, the variances of time required to achieve a normalized TOF ratio of 0.9 were

significantly higher in the neostigmine group (mean of 94.1 min) than in the 0.5mg/kg sugammadex group (mean of 16.6 min) (F=5,671, p=0,023). There were also significant differences between patients receiving sugammadex in the time to reach an nTOFR of 0.9. For the reversal with sugammadex at 1.0 or 2.0 mg/kg, these times (mean of 4.4 min and 2.6 min) were significantly shorter than in the 0.5 mg/kg sugammadex group (mean of 6.8 min). (Table 3; one-way ANOVA for the three sugammadex groups $F_{2,31}$=12.450, p=0.0001; Tukey HSD test, p<0.05 for both comparisons). Calculating the mean differences between the pairs of patient groups confirmed these results (Table 4) and showed further significant difference for the 1.0 and 2.0 mg/kg sugammadex group (Tukey HSD test, p = 0.047). Among patients receiving sugammadex at 0.5 mg/kg, failed reversal occurred in 4 cases. This figure was 3 in the neostigmine group and 13 in the placebo group. For patient groups antagonized with sugammadex doses of 1.0 and 2.0 mg/kg, there was no failure of reversal of the neuromuscular blockade (Table 3). For incomplete reversals, the comparison of placebo with the other four drug groups combined showed significant difference (Fisher's test, p < 0.0001), while the difference between the 0.5 mg/kg sugammadex and the neostigmine groups was not significant (Fisher's test p = 0.157). The odds ratio calculation also confirmed the difference between placebo and any of the other four drug groups (Table 4). All patients with unsuccessful antagonization received rescue sugammadex medication at a dose of 2.0 mg/kg, after which the nTOFR always returned to above 0.9. These patients were not taken into account upon the examination of recovery times but were considered for PORNB.

Table 3. Primary outcome of the study

Variable*	Sugammadex 0.5 mg/kg [13]	Sugammadex 1.0 mg/kg [12]	Sugammadex 2.0 mg/kg [13]	Neostigmine 0.05 mg/kg [13]	Placebo 0.9% Saline [13]	P value
Incomplete recovery, n	4	0	0	3	13	< 0.0001†
Time to normalized TOF ratio 0.9, min	6.8 ± 4.1 [9]ab	4.4 ± 2.3 [12]bc	2.6 ± 1.6 [13]c	11.3 ± 9.7 [10]a	incomplete recovery	< 0.0001‡
Time to T1 90%, min)	4.5 ± 3.1 [10]	3.0 ± 2.2 [10]	3.6 ± 4.5 [9]	2.9 ± 1.6 [6]	15.3 ± 6.7 [2]	0.21‡
Time to non normalized TOF ratio of 1.0, min	8.4 ± 5.8 [8]ab	4.5 ± 2.3 [12]bc	5.1 ± 6.2 [13][c]	12.8 ± 9.1 [10][a]	incomplete recovery	< 0.0001‡

*Means ± SDs are given for time variables. Group means not sharing superscript letters differ significantly (Tukey HSD test, P < 0.05). Sample sizes are given in brackets. †Data from Cramer's V. ‡Data from one-way ANOVA. HSD = honest significant difference; TOF = train-of-four.

Table 4. Estimates of the mean differences (and their 95% CIs) in the time from injection of the study drug to normalized TOF Ratio of 0.9 between pairs of study groups and odds ratios for the number of failed reversals at 30 min and the number of patients with PORNB between pairs of study groups

Variable*	Study group	Sugammadex 1.0 mg/kg	Sugammadex 2.0 mg/kg	Neostigmine 0.05 mg/kg	Placebo 0.9% Saline
Time to normalized TOF ratio of 0.9	Sugammadex 0.5 mg/kg	–2.5 (–8.6-3.6)	–4.2 (-10.2-1.8)†	4.4 (–1.9-10.8)	-
	Sugammadex 1.0 mg/kg	-	–1.7 (–7.3-3.8)‡	6.9 (1.0-12.8)‡	-
	Sugammadex 2.0 mg/kg	-	-	8.6 (2.8-14.4)§	-
No. of incomplete reversals at 30 min	Sugammadex 0.5 mg/kg	11.84 (0.57-247.85)	12.79 (0.61-266.67)	1.48 (0.26-8.50)	0.018 (0.00-0.37)†
	Sugammadex 1.0 mg/kg	-	1.08 (0.02-58.66)	0.12 (0.01 – 2.60)	0.002 (0.00-0.08)†
	Sugammadex 2.0 mg/kg	-	-	0.11 (0.01 – 2.40)	0.001 (0.00-0.07)†
	Neostigmine 0.05 mg/kg	-	-	-	0.012 (0.00-0.27)†
No. of patients with recurrent block	Sugammadex 0.5 mg/kg	0.67 (0.11-3.93)	1.67 (0.23-12.35)	4.00 (0.36-45.10	1.833 (0.25-13.47)
	Sugammadex 1.0 mg/kg	-	2.50 (0.36-17.3)	6.00 (0.56-63.99)	2.750 (0.40-18.88)
	Sugammadex 2.0 mg/kg	-	-	2.40 (0.19-30.52)	1.100 (0.13-9.34)
	Neostigmine 0.05 mg/kg	-	-	-	0.458 (0.04-5.79)

As an example, the time to normalized TOF ratio of 0.9 was, on average, 2.5 min shorter in the sugammadex 1.0 mg/kg group than in the sugammadex 0.5 mg/kg group.

*Estimates (95% CIs) of the mean differences between study groups are given for time to normalized TOF ratio of 0.9, and odds ratios (95% CIs) are given for number of failed reversals and number of patients with reparalysis. Tukey honest significant difference test was used for P values. ‡$P < 0.05$. †$P < 0.01$. §$P < 0.001$.

PORNB = postoperative recurrent neuromuscular block; TOF = train-of-four.

Secondary endpoint

Twelve patients had postoperative recurrent NMB: 3 patients in the sugammadex 0.5 mg/kg group, 4 in the sugammadex 1.0 mg/kg group, 2 in the sugammadex 2.0 mg/kg group, 1 in the neostigmine group, and 2 in the placebo group (Table 5). These ratios do not show significant differences between groups (χ^2=2.708, df=4, p=0.608). Similarly, odds ratios for recurrent paralysis did not differ significantly between paired comparisons of drug groups (Table 3). In the 18 cases where recurrent paralysis occurred, we also tested the variability of the three consecutive TOF measurements done every 20 minutes in the postoperative period. The mean coefficient of variation was 6.0% (interquartile range of 5.1%) and the geometric mean of the coefficient of variance as a percentage was 5.2. TOF measurements of the postoperative period were considered to be accurate if the fluctuation between TOF measurements was not more than the double of 5.2. Of the 12 patients with postoperative recurrent paralysis, four were asymptomatic (normalized TOFR of 0.85; 0.87; 0.86; and 0.89, respectively). Eight patients, however, complained of muscle weakness (TOFR of 0.85; 0.86; 0.83; 0.85; 0.86; 0.86; 0.74; and 0.72, respectively), which was associated with weakened cough in 7 cases and swallowing difficulty in 4 cases. Additional 4 patients were unable to lift their head and hold it for 5 seconds. The residual block was sustained for 40 minutes for one case and for 20 minutes for the other cases. The lowest TOF ratios were measured at 60 minutes for the 2.0 mg/kg sugammadex and placebo groups (TOFR of 0.72 and TOFR of 0.74). These patients complained of muscle weakness: weakened cough, swallowing difficulty, positive head lift test, and eye movement difficulty. They were discharged from the postoperative observation ward only 20-30 minutes after becoming asymptomatic.

Table 5. Secondary outcome of the study: incidence of postoperative reparalysis during the first 60 min in the recovery room

Variable	Measure	Sugammadex 0.5 mg/kg	Sugammadex 1.0 mg/kg	Sugammadex 2.0 mg/kg	Neostigmine 0.05 mg/kg	Placebo 0.9% Saline
Time from extubation to first TOF meas-urement, min*	Median (IQR)	23.2(19.8-28.2)	24.5(21,0-27.2) [12]	23.3(16.0-30.8)	24.9(18.8-35.9)	21.9(16.5-26.8)
Normalized TOF ratios at 0 min	Mean±SD	1.01±0.09	0.96±0.09	1.01±0.08	1.05±0.09	1.01±0.05
	95% CI	0.96-1.06	0.91-1.01	0.97-1,06	1.00-1.10	0.98-1.03
	Median (IQR)	0.99(0.85-1.27)	0.95(0.83-1.11)	1.02(0.85-1.19)	1.04(0.95-1.33)	1.00(0.96-1.10)
Normalized TOF ratios at 20 min	Mean±SD	1.04±0.15	1.01±0.09	1.01±0.05	1.04±0.10	1.00±0.06
	95%CI	0.96-1.12	0.96-1.06	0.98-1.04	0.98-1.09	0.96-1.03
	Median (IQR)	1.03(0.84-1.42)	1.01(0.85-1.15)	1.02(0.92-1.10)	1.01(0.86-1.28)	1.01(0.89-1.11)
Normalized TOF ratios at 40 min	Mean±SD	0.99±0.08	0.98±0.07	1.01±0.06	1.04±0.07	1.03±0.08
	95%CI	0.95-1.04	0.94-1.02	0.98-1.04	1.00-1.08	0.98-1.07
	Median (IQR)	1.01(0.86-1.14)	1.97(0.87-1.09)	1.02(0.92-1.08)	1.04(0.96-1.17)	1.02(0.86-1.16)
Normalized TOF ratios at 60 min	Mean±SD	1.04±0.13	0.99±0.08	1.00±0.13	1.03±0.07	1.04±0.12
	95%CI	0.97-1.12	0.95-1.04	0.93-1.08	0.99-1.06	0.97-1.11
	Median (IQR)	0.99(0.91-1.32)	1.00(0.86-1.13)	0.99(0.72-1.26)	1.03(0.91-1.12)	1.05(0.74-1.31)
Recurrent block	Yes/No	3/9	4/8	2/10	1/12	2/11

Medians (interquartile ranges) are given for time between the last TOF measurement in the operating room and the first TOF measurement in the recovery room (time 0 min). Means ± SDs and medians (range) of normalized TOF ratios at four points in time in the recovery room are given. The number of patients with and (without) postoperative recurrent neuromuscular block in the study groups is shown. *Kruskal–Wallis H = 2.611, P = 0.625. IQR = interquartile range; TOF = train-of-four.

Additional endpoints

The number of patients achieving an nTOFR of 1.0 was 2, 4, 5, 2, and 0 in the sugammadex 0.5; 1.0; 2.0 mg/kg, neostigmine and placebo groups, respectively. The times required to achieve a non-normalized TOFR of 1.0 did not differ significantly from those required to achieve an nTOFR of 0.9. The times required to reach T1 90% did not differ for the different patient groups (Table 3).

Reversal of profound neuromuscular blockade after pipecuronium administration with moderate and standard dose sugammadex: a randomized, double blind, non-inferiority study

The study ended when the number of participants in both groups reached the predefined number of cases. There was no drop-out from any group. Patient demographics and the characteristics of anaesthesia are shown in Tables 6. and 7.

Table 6. Baseline characteristics of the patients

Variable‡	Sugammadex 2 mg/kg (N=25)	Sugammadex 4 mg/kg (N=25)	Standardized Difference
Sex (M/F)	11/14 [44%, 56%]	13/12 [52%, 48%]	0.16
ASA class (I/II/III)	5/20/0 [20%, 80%, 0%]	12/12/1 [48%, 48%, 4%]	0.73
Age (year)	46.3 ± 11.44	42.5 ± 13.39	0.31
BMI (kg/m^2	24.3 (21.6-25.1)	22.7 (20.3-24.7)	0.50
Body mass (kg)	69.1 ± 11.04	66.2 ± 11.64	0.25
Surgery duration (min)	65 (50-85)	55 (42.5-62.5)	0.32
Control TOFR	1.08 (1.02-1.08)	1.05 (1.02-1.08)	0.10
Control T1 %	100.9 ± 6.94	97.8 ± 4.09	0.53
Type of surgery, (number of cases)			
Laparoscopic cholecystectomy	10	13	
Laparoscopic adrenalectomy	2	1	
Laparoscopic appendectomy	0	1	
Laparoscopic bowel resection	3	0	
Transabdominal preperitoneal hernia repair	5	6	
Laparotomic bowel resection	1	1	
Hartmann reconstruction	1	2	
Liver-, pancreas resection	2	1	
Nutritive ileostomy	1	0	

Abbreviations: ASA, American Society of Anesthesiologists; F, female; M, male; T1%, height of first twitch of TOF; TOF, train of four. a

Means ± standard deviations are given when data meet the assumptions of parametric statistical tests; otherwise, medians (interquartile ranges) are given. N = 25 in each group.

Table 7. Variables of anesthetic treatment

Variable ‡	Sugammadex 2 mg/kg (N=25)	Sugammadex 4 mg/kg (N=25)	Mean difference [95% CI]	P value
Intubation dose of pipecuronium (mg)	5.36 (4.96-6.30)	5.20 (4.4-6.00)	0.24 [-0.28, 0.75]	0.36 #
Onset time (min)	2.5±0.83	2.6±0.82	0,1 [-0.37, 0.57]	0.68 ##
Total dose of pipecuronium (mg)	6.50 (5.78-7.90)	6.00 (4.96-7.00)	0.45 [-0.53, 1.42]	0.15 #
No. of pipecuronium increments (N)	1.44±1.04	1.04±1.14	0.4 [-0.22, 1.02]	0.09 ##
From first pipecuronium to antagonism (min)	83.47±41.07	67.55±37.39	15.92 [-6.41, 38.26]	0.16 ##
From last pipecuronium to antagonism (min)	28.60±19.14	34.60±20.83	6.01 [-5.37, 17.38]	0.29 ##
Sevoflurane concentration at antagonism (vol%)	1.59±0.33	1.68±0.48	0.10 [-0.14, 0.33]	0.41 #

Abbreviation: CI, confidence interval. aMeans ± standard deviations are given when data meet the assumptions of parametric statistical tests; otherwise, medians (interquartile ranges) are given. bMann-Whitney U test.cStudent t test.

Primary endpoint

In the active control group receiving sugammadex at 4 mg/kg, the time from drug administration to achieving a normalized TOF of 0.9 was 1.42 ± 0.63 min (95% CI:1.17-1.67, n = 25), while this time for patients receiving new treatment was 1.73 ± 1.03 min (95% CI 1.33-2.13, n = 25). The upper limit of the 95% CI for the new treatment was within the non-inferiority range. The mean time difference between the two groups for reaching the primary endpoint was 0.31 (95% CI: -0.18-0.80) min, this time difference (95% CI) is below the pre-calculated upper non-inferiority limit (1 min). (The t-test required for non-inferiority testing was significant (t=-2.860, df=48, P=0.003), so we rejected the null hypothesis and determined non-inferiority. The time required to achieve a normalized TOF of 0.9 was under two minutes in 64% of patients in the patient group receiving 2 mg/kg of sugammadex and in 76% in the patient group antagonized with 4 mg/kg of sugammadex. In the patient group receiving 2 mg/kg of sugammadex, the rate of recovery of muscle strength within 3 minutes was 80%,

whereas in the 4 mg/kg group, this was 100%. For each patient receiving 2 mg/kg of sugammadex, the time required to reach a normalized TOF of 0.9 was within 5 minutes.

Additional endpoint

No recurrent and residual neuromuscular blockade occurred in the acute postoperative period (Table 8).

Table 8. Postoperative normalized TOF ratios during the first 60 minutes in the recovery room

Variable[a]	Measure	Sugammadex 2 mg/kg (N=25)	Sugammadex 4 mg/kg (N=25)	Mean Difference (95% CI)	P value
Normalized	Mean ± SD	1.04±0.07	1.04 ± 0.08	000 (-0.04, 0.05)	0.911
TOFR at 0 min	95% CI	1.01-1.07	1.01-1.07		
	Median	1.04	1.02		
	Range	0.90-1.20	0.89-1.19		
Normalized	Mean ± SD	1.04 ± 0.07	1.08 ± 0.15	0.04 (-0.02, 0.11)	0.202
TOFR at 20 min	95% CI	1.01-1.06	1.02-1.14		
	Median	1.03	1.03		
	range	0.88-1.21	0.89-1.61		
Normalized	Mean ± SD	1.04± 0.10	1.04 ± 0.11	0,00 (-0.05, 0.06)	0.856
TOFR at 40 min	95% CI	1.00-1.08	1.00-1.08		
	Median	1.03	1.01		
	range	0.91-1.25	0.90-1. 36		
Normalized	Mean ± SD	1.04 ± 0.10	1.04±0.09	0.00 (-0.05, 0.05)	0.962
TOFR at 60 min	95% CI	1.00-1.08	1.01-1.07		
	Median	1.02	1.03		
	range	0.90-1.25	0.89-1.25		

Abbreviations: CI, confidence interval; SD, standard deviation; TOF, train of four. aMeans ± standard deviations and medians (range) of normalized TOF ratios at 4 points in time in the recovery room are given.

Notes

In a 60-year-old male patient, new-onset atrial fibrillation developed at the beginning of surgery, which was treated with 4 g of intravenous magnesium sulphate. At the end of surgery, the patient was successfully antagonized with 2 mg/kg of sugammadex. No direct interaction is known between pipecuronium, the drug used in the study and the drug administered by us.

5 Discussion

The introduction of sugammadex in 2008 has been a milestone in the history of general anaesthesia. By using cyclodextrin, the barriers occurring during antagonism with neostigmine can be overcome, such as the reversal of deep neuromuscular blockade. By its use, side effects caused by acetylcholinesterase inhibitors can be avoided. In addition, with objective neuromuscular monitoring, the development of postoperative residual neuromuscular blockade can also be prevented by using adequate doses against the appropriate muscle relaxant. Thus, by using sugammadex, we can improve the safety of our patients during general anaesthesia. However, cost efficiency is an inevitable factor. Due to its significant cost claims, sugammadex is not part of routine anaesthesia to date in Hungary, but not even in most countries of the European Union. In our second study it was proved that for reversal of a muscle relaxant chosen properly and using appropriate doses of sugammadex, the costs of antagonizing neuromuscular blockade can be reduced.

Little data is available on antagonization of the vecuronium block with sugammadex. It has not been proven whether low-dose sugammadex can adequately reverse a shallow vecuronium-induced block, and we do not have enough information on the frequency of residual muscle relaxant effect in the postoperative period after antagonization. Our first study looked at whether sugammadex at doses of 0.5 mg/kg and 1.0 mg/kg could adequately reverse vecuronium-induced NMB with spontaneous recurrence until TOFC4. The criterion of adequate reversal was to reach an nTOFR of 0.9 within a mean of 5 minutes. The time limit for unsuccessful reversal was determined as 30 minutes. The incidence of recurrent NMB (nTOFR <0.9) was also investigated. With 1.0 and 2.0 mg/kg doses of sugammedex, the reversal of NMB was successful in all patients. For the 13 patients receiving sugammadex therapy at 0.5 mg/kg, reversal within 30 minutes failed in 4 cases. The mean recovery time for the remaining 9 patients was 6.8 minutes, so they did not meet the criterion for adequate reversal. Reversal with neostigmine did not differ significantly for the mean recovery times of the sugammadex 0.5 mg/kg group (10 patients with a mean recovery time of 11.3 minutes and 3 failed reversals). For twelve patients, we experienced a return of the neuromuscular block. These results did not support our hypothesis that, similar to rocuronium-induced NMB with TOFC4 as the reversal threshold, vecuronium-induced blockade can also be properly antagonized by a limited amount of sugammadex. Reversal of the residual neuromuscular block with low-dose sugammadex may be a cause for concern due to the occurrence of

recurrent paralysis, considering that sugammadex at doses of 0.5 mg/kg and 1.0 mg/kg is unable to restore the 'safety margin' of the NMJ, so there is a potential for recurrent neuromuscular block. The results of our study show that sugammadex at a dose of 0.5 mg/kg is unable to reverse the TOFC4-level residual vecuronium-induced neuromuscular block in 30% of patients, and is not more efficacous than neostigmine in the remaining 70%. In addition, we have shown that the rebound phenomenon can be observed even after the reversal of muscle relaxation, which may still occur after sugammadex administration at 2.0 mg/kg.

There are several factors that might explain these results. The complex formation between sugammadex and the muscle relaxant and its degradation to its components depend on the association and dissociation properties of the two molecules. Because the selectivity of sugammadex is higher for rocuronium than for vecuronium [association constant (Ka) 1.79 x 10^7 mol/l and 5.72 x 10^6 mol/l], complex formation is slower for vecuronium. On the other hand, the dissociation constant of vecuronium is 0.17 μM compared to 0.055 μM of rocuronium, therefore a higher relative sugammadex concentration is required to form a complex with vecuronium than with rocuronium. This may explain why sugammadex at 0.5 mg/kg, which is effective in antagonizing the residual rocuronium block, has only limited ability to reverse the residual vecuronium block. Third, it is the ratio of sugammadex/vecuronium concentration, rather than the absolute number of vecuronium molecules in the body, that is the decisive factor for reversal of the vecuronium block. This is why sugammadex was effective at the doses of 1.0 and 2.0 mg/kg and ineffective at a dose of 0.5 mg/kg for antagonization. Furthermore, none of the amounts of sugammadex used in the study were able to prevent NMB recurrence. The incidence of recurrent paralysis was 18.7% and could observed in all drug groups, including the four patients receiving 2.0 mg/kg of sugammadex. A possible explanation for the development of recurrent paralysis is that low-dose sugammadex was sufficient to bind vecuronium molecules in the central compartment but was unable to eliminate the muscle relaxant from the peripheral compartment. In addition, the continuous separation of vecuronium molecules from the complex formed with sugammadex (according to Kd) also favours the development of recurrent block.

The high incidence of recurrent paralysis may raise the possibility of inaccurate acceleromyographic measurements in vigilant patients waking up from anaesthesia. This is because during postoperative monitoring false measurement results can be obtained by movement of the hands of patients. To control for this bias, the anaesthesiologist performing

the postoperative measurements carefully monitored that the arm be prevented from movement, just as he did for the 47 patients in our previous study. In these patients, no depression was observed in TOF values and there were no clinical signs of muscle weakness, so we used their monitoring data as a control in this study. Therefore, the inaccuracy of postoperative acceleromyographic measurements could be excluded.

A less likely explanation for the development of recurrent neuromuscular block is residual sevoflurane effect, and vecuronium was used at too low doses to make its degradation product responsible for the occurrence of recurrent block. No severe postoperative recurrent paralysis occurred in the patients, and the extent of the residual muscle relaxant effect was also mild (0.83<TOFR<0.89). This shows that the extent of the recurrent block was at the border of the 'safety margin'. Clinical signs indicative of recurrent paralysis without complications were observed in eight patients.

Recurrent neuromuscular block occurred in each antagonizing group after reversal of the residual vecuronium block. Therefore, quantitative neuromuscular monitoring is of great importance when low-dose sugammadex is used for vecuronium- or rocuronium-induced antagonism of residual NMB. Moreover, quantitative monitoring of neuromuscular block is proposed to be continued even in the postoperative recovery room to check the effectiveness of reversal with sugammadex. However, one must therefore be familiar with the proper method and pitfalls of TOF monitoring performed on alert patients in the postoperative period. Applying TOF stimulation in alert patients is painful; stimulation by 50 Hz is associated with unacceptable pain levels measured by visual analogue scale, thus lower current strengths are used during monitoring. According to a previous study, as long as all four responses of TOF stimulation are detectable, it is valid to replace 50 Hz stimuli by using 30 Hz stimuli. Preliminary device calibration is essential because without this it can lead to misidentification of residual curarization, which can be worsened further by involuntary hand movements of the alert patient and the absence of a preload hand adapter.

In our second study, we investigated the applicability of the moderate dose of 2 mg/kg of sugammadex for the reversal of pipecuronium-induced profound neuromuscular block. We evaluated whether the normalised TOF ratio of 0,9 could be reached within 5 minutes from a PTC value of 1 or 2 after sugammadex administration. The results confirmed our hypothesis that the standard dose of 4 mg/kg of sugammadex cannot clinically be considered superior to

the moderate dose of 2 mg/kg. The mean time difference between the two groups to reach the primary endpoint was 0.31 minute, which time difference (95% CI) is below the upper limit (1 minute) of the non-inferiority range. Hence, pipecuronium-induced deep neuromuscular blockade can be reversed by using the sugammadex dose of 2 mg/kg, which is half the dose of 4 mg/kg recommended for profound rocuronium and vecuronium-induced blocks. There was no clinically significant difference between the two doses. No recurrent and residual neuromuscular block occurred in the acute postoperative period. This finding might be explained by the very high assocation constant of the pipecuronium-sugammadex complex, ten times higher than for rocuronium as measured by isothermal microcalorimetry (161.5±28.1 vs. 15.1±2 × 106 M−1) (http://www.pmda.go.jp/files/000153538.pdf). The higher the association complex, the easier it is for sugammadex to form complex with the muscle relaxant. Owing to the high affinity of pipecuronium, immediate encapsulation takes place in the plasma leading to a reduction in the number of muscle relaxant molecules in the neuromuscular junction. The speed of this process is influenced by the binding ratio of sugammadex and pipecuronium. For safe reversal, there is a need for excess sugammadex so that all muscle relaxant molecules can be bound to the antagonist agent. Since pipecuronium is practically unable to dissociate from the complex, thus, like in our previous study, no recurrent neuromuscular block occurred in postoperative period either.

The recommended standard dose of sugammadex is 4 mg/kg for the reversal of rocuronium and vecuronium-induced profound block. In adult patients, this means the use of at least 2 (two) 200 mg vials, making the routine use of the drug too costly. However, the exact dose of sugammadex has not been known in deep pipecuronium-induced block yet. Knowing the pharmacological properties of sugammadex, we assumed that a smaller dose is enough for the reversal of deep pipecuronium-induced block than for rocuronium or vecuronium-induced block. Thus, relevant economic savings are possible, which make sugammadex available. In our study, we compared the efficacy of the standard dose of 4 mg/kg of sugammadex with the moderate dose of 2 mg/kg in the reversal of pipecuronium-induced deep neuromuscular block. We confirmed that deep pipecuronium-induced block can be terminated with a sugammadex dose of 2 mg/kg as efficiently as after administration of the 4 mg/kg dose. The lower dose is safe because no recurarization occurred in any of the cases.

Intermediate-acting muscle relaxants were developed in the hope that the recovery time would be accurately predictable and calculable and fewer postoperative complications should be considered. However, these expectations were not met since recurrent and residual

neuromuscular block occurred in most patients even during the use of these agents, just as severe respiratory failure and other respiratory complications did. Thus, we might conclude that the shortened duration of action of non-depolarizing muscle relaxants decreased the risk of late postoperative complications by a far less extent than expected. The key solution to the problem is to increase the efficacy and safety of antagonization, which has practically been solved since the introduction of sugammadex in 2008. The single unsolved problem with the drug is financial in nature. Implementing deep NMB may be beneficial during numerous procedures (eg. laparotomy, microlaryngoscopy, open eye surgery). Immobility of the patients is indispensable during these interventions, which can be easily achieved by implementing deep neuromuscular block. However, to achieve such deep levels of relaxation, especially for longer procedures, possible repeated administration of intermediate-acting muscle relaxants may be required, which in turn leads to relaxant accumulation and higher costs of anaesthesia. Pipecuronium bromide is a longer-acting and more potent muscle relaxant than recuronium bromide. As a result, one could maintain deep neuromuscular blockade with up to a single intubation dose of pipecuronium for the whole duration of the procedure, depending on the length of surgery. Given all of the above and the more beneficial purchase price of pipecuronium bromide, we can state that the costs of muscle relaxation can be diminished extensively.

The application of deep neuromuscular block makes its antagonism, which is adequately effective and safe, indispensable. Since the introduction of sugammadex, although the reversal of rocuronium or vecuronium-induced deep neuromuscular block fulfilling the above mentioned requirements is possible but widespread availability of this method is hampered by the high price of sugammadex. According to a report from Ledowski et al. in 2012, non-negligable excess costs are imposed on healthcare institutions by the use of sugammadex. Based on their study conducted in Australia where the routine use of sugammadex was introduced, after review of data from a one-month period in 2011, a 743% increase in aminosteroid muscle relaxant – sugammadex utilization and a 48% decrease in neostigmine and glycopyrollate utilization was observed compared to April 2010. Considering muscle relaxant and antagonist costs, this accounted for 127 instead of 42 Australian dollars per each case.

In our second study, we aimed to implement an alternative solution to the current rocuronium-sugammedex paradigm that could preserve the safety and efficacy of antagonism while decreasing costs. A promising solution is the use of pipecuronium instead of

rocuronium to induce deep NMB (but even for surgical procedures lasting 1-1.5 hours and not requiring deep block, only relaxation) because the induced muscle relaxation is effectively antagonized by even half of the standard dose of sugammadex, thereby resulting in remarkable cost reduction since a relatively cheaper muscle relaxant is antagonized by a lower dose of sugammadex. This chemical compound successfully antagonizes all phases of rocuronium-induced neuromuscular block, at a dose of 2 mg/kg - 16 mg/kg, depending on the depth of NMB. This means the opening of two vials per patient on average in case of profound block and for normal body weight (50-100 kg). By using pipecuronium, under the same conditions, half the dose, i.e. one vial of sugammadex is sufficient for safe antagonism, resulting in substantial cost reduction. Although the relatively high concentration ratio of sugammadex-pipecuronium would enable further reduction of the sugammadex dose (1 mg/kg) used for reversal but its use would not be associated with economic benefits. The reason for that is that sugammadex is currently available with a pack size of 200 mg. Even with the use of doses of 1 mg/kg or 2 mg/kg, one vial should be opened, which could not be used later.

Nevertheless, not only the costs of reversal can be reduced with the use of sugammadex. Cost-efficiency can also be improved by the decreased time spent in the postoperative recovery room. Of the complications related to residual muscle relaxant effect, the treatment of postoperative respiratory failure and pneumonia impose the biggest financial burden on healthcare service providers. Hospitalization costs can be reduced by avoiding these complications. The effectiveness of surgical patient care is further improved by the fact that the combination of sugammadex and aminostreoid muscle relaxant shortens the turnover time in the operating rooms. Hence, more patients will get a chance to have surgery within a day. The fact that patients can get back to work and occupy their social positions earlier by the avoidance of postoperative complications using sugammadex, is associated with social benefits.

A common element of both of our studies is to be able to safely reverse neuromuscular block at the end of surgical procedures, without the presence of either residual block or recurarization. Both the residual block and NMB recurrence (recurarization) may be associated with postoperative complications such as hypoxia, weakness, aspiration of gastric content or respiratory failure. Prevention, and timely detection of these complications might improve patient safety and decrease mortality rates.

Eleveld and Duvaldestin proved in their study that low-dose sugammadex is

inappropriate for antagonizing moderate and deep rocuronium or vecuronium-induced neuromuscular block. Since limited number of studies are available in the international literature investigating the reversal of residual neuromuscular block with low doses of sugammadex, the purpose of our first study was therefore to study the safety of this sugammadex dose range. About pipecuronium, our research group was the first to report that sugammadex is very efficacious for the safe reversal of superficial and deep neuromuscular blocks, even in low doses.

In conclusion, it is important during the use of aminosteroidal muscle relaxants to use the lowest, but still efficacious, dose of sugammadex during reversal. On the other hand, using low doses of sugammadex also has economic utility since one can reduce the costs of necessary reversal. Unfortunately, sugammadex is provided by the manufacturer only in one pack size, so the use of the lower dose is limited by the fact that a vial with a greater active ingredient content must be opened even for using lower doses from sugammadex.

6 Conclusions

Postoperative residual neuromuscular block (PRNB) may lead to severe complications, therefore it is important to recognize and antagonize it at the end of surgery. In our study, we analyzed the efficacy of sugammadex in reversing two different neuromuscular blocking agents, vecuronium and pipecuronium. In our first study we have drawn attention to the danger of using small doses of sugammadex for reversal residual vecuronium blockade. In our second study, using a long-acting neuromuscular blocking agent pipecuronium we found that deep neuromuscular block is common at the end of surgery, however it can be safely antagonized by sugammadex. In our first study we antagonized TOFC 4 vecuronium block with different doses of sugammadex. We proved, that low dose sugammadex is insufficient to reverse of TOFC 4 residual vecuronium block. We found that after antagonizing TOFC 4 vecuronium blockade with 1.0 or 2.0 mg/kg sugammadex, incomplete reversal did not occur. After reversal, we experienced recurrent neuromuscular blockade in all treatment groups (sugammadex 0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg, neostigmine, placebo). This observation underline the importance of continouing neuromuscular monitoring in the postoperative period.

In our second study, we didn't find any difference between the efficacy of 4 mg/kg and 2 mg/kg sugammadex doses, after reversal of deep pipecuronium blockade. After reversal of deep pipecuronium blockade the time to achieve normalized TOF ratio of 0.9 was < 3 minutes for 80% of the cases in the 2 mg/kg sugammadex group and for 100% of the cases in the 4 mg/kg sugammadex group. The time to achieve the normalized TOF ratio 0.9 was < 5 minutes in all of the patients of the 2 mg/kg sugammadex group. We proved the safe reversal of deep pipecuronium blockade with 2 or 4 mg/kg sugammadex, since recurrent or residual block did not occur during the early postoperative period. Based on the high affinity of sugammadex to pipecuronium, lower sugammadex dose can be used for reversal of deep pipecuronium blockade, and thus the cost of reversal can be reduced to the half.

7 Own results, new observations

- Low dose sugammadex is insufficient to reverse of TOFC 4 residual vecuronium block.
- After reversal of residual vecuronium blockade with sugammadex, we experienced recurrent neuromuscular blockade in all treatment groups.
- After antagonism of vecuronium induced residual neuromuscular blockade with sugammadex, verify the reversal, continouing neuromuscular monitoring in the postoperative period is outstanding.
- After reversal of deep pipecuronium blockade, we didn't find any difference between the efficacy of 4 mg/kg and 2 mg/kg sugammadex doses.
- After reversal of deep pipecuronium blockade recurrent or residual block did not occur during the early postoperative period.
- Thereby reversal of pipecuronium induced deep neuromuscular blockade by sugammadex the cost of reversal can be reduced to the half.

UNIVERSITY of DEBRECEN

UNIVERSITY AND NATIONAL LIBRAY
UNIVERSITY OF DEBRECEN
H-4002 Egyetem tér 1, Debrecen
Phone: +3652/410-443, email: publikaciok@lib.unideb.hu

Registry number: DEENK/128/2019.PL
Subject: PhD Publikációs Lista

Candidate: László Asztalos
Neptun ID: FY52NN
Doctoral School: Doctoral School of Neurosciences

List of publications related to the dissertation

1. Tassonyi, E., **Asztalos, L.**, Szabó-Maák, Z., Nemes, R., Pongrácz, A., Lengyel, S., Fülesdi, B.: Reversal of Deep Pipecuronium-Induced Neuromuscular Block With Moderate Versus Standard Dose of Sugammadex: a Randomized, Double-Blind, Noninferiority Trial. *Anesth. Analg. 127* (6), 1344-1350, 2018.
   DOI: http://dx.doi.org/10.1213/ANE.0000000000003719
   IF: 3.463 (2017)
2. **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. *Anesthesiology. 127* (3), 441-449, 2017.
   DOI: http://dx.doi.org/10.1097/ALN.0000000000001744
   IF: 6.523

List of other publications

3. Fülesdi, B., **Asztalos, L.**, Tassonyi, E.: Deep Neuromuscular Block Facilitates Laparoscopic Surgery- or Probably Does Not? *Turk. J. Anaesthesiol. Reanim. 2018* (46), 73-74, 2018.
   DOI: http://dx.doi.org/10.5152/TJAR.2018.220318
4. Fülesdi, B., **Asztalos, L.**, Tassonyi, E.: Does Deep Neuromuscular Block Facilitate Laparoscopic Surgery? The Picture is Not Clear. *Turk. J. Anaesthesiol. Reanim. 46* (2), 86-87, 2018.
   DOI: http://dx.doi.org/10.5152/TJAR.2018.060418

UNIVERSITY AND NATIONAL LIBRAY
UNIVERSITY OF DEBRECEN
H-4002 Egyetem tér 1, Debrecen
Phone: +3652/410-443, email: publikaciok@lib.unideb.hu

5. Nemes, R., Fülesdi, B., Pongrácz, A., **Asztalos, L.**, Szabó-Maák, Z., Lengyel, S., Tassonyi, E.: Impact of reversal strategies on the incidence of postoperative residual paralysis after rocuronium relaxation without neuromuscular monitoring: a partially randomised placebo controlled trial.
Eur. J. Anaesth. 34 (9), 609-616, 2017.
DOI: http://dx.doi.org/10.1097/EJA.0000000000000585
IF: 3.958

6. Tassonyi, E., Pongrácz, A., Nemes, R., **Asztalos, L.**, Lengyel, S., Fülesdi, B.: Reversal of Pipecuronium-Induced Moderate Neuromuscular Block with Sugammadex in the Presence of a Sevoflurane Anesthetic.
Anesth. Analg. 121 (2), 373-380, 2015.
DOI: http://dx.doi.org/10.1213/ANE.0000000000000766
IF: 3.827

Total IF of journals (all publications): 17,771
Total IF of journals (publications related to the dissertation): 9,986

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

28 March, 2019