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Reversal of vecuronium-induced neuromuscular blockade with low-dose sugammadex at train-of-four count of four: A randomized controlled trial

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ABSTRACT

Background: Rocuronium-induced neuromuscular block that spontaneously recovered to a train-of-four count of four can be reversed with sugammadex 0.5 or 1.0 mg/kg. We investigated if these doses of sugammadex can also reverse vecuronium at a similar level of block.

Methods: Sixty-five patients were randomized and sixty-four were analyzed in this controlled, superiority study. Participants received general anesthesia with propofol, sevoflurane, fentanyl, and vecuronium. Measurement of neuromuscular function was performed with acceleromyography (TOF-Watch-SX®). Once the block recovered spontaneously to four twitches in response to train-of-four (TOF) stimulation patients were randomized to receive sugammadex 0.5, 1.0, 2.0 mg/kg, neostigmine 0.05 mg/kg or placebo. Time from study drug injection to normalized TOF ratio 0.9 and the incidence of incomplete reversal within 30 min were the primary outcome variables. Secondary outcome was the incidence of re-paralysis (normalized TOF ratio < 0.9).

Results: Sugammadex, in doses of 1.0 and 2.0 mg/kg reversed a threshold TOF count of four to normalized TOF ratio ≥0.9 in all patients in 4.4 ± 2.3 min (mean±SD) and 2.6 ± 1.6 min, respectively. Sugammadex 0.5 mg/kg reversed the block in 6.8 ± 4.1 min in 70 % of patients ($p<0.0001$ vs. 1.0 and 2.0 mg/kg), whereas neostigmine produced reversal in 11.3 ± 9.7 min in 77% of patients ($p>0.05$ vs. sugammadex 0.5 mg/kg). The overall frequency of re-paralysis was 18.7% but this incidence varied from group to group.

Conclusions: Sugammadex 1.0 mg/kg unlike 0.5 mg/kg properly reversed a threshold TOF count of four vecuronium-induced block, but did not prevent re-paralysis.

Like rocuronium, vecuronium is an aminosteroid neuromuscular blocking agent with intermediate duration of action[1]. Sugammadex is a modified ϒ-cyclodextrin compound [2] that reverses the neuromuscular blockade produced by rocuronium[3], vecuronium[4 5] and pipecuronium[6] by encapsulating them, making them unavailable to interact with the nicotinic acetylcholine receptors at the neuromuscular junction. The encapsulation of steroidal relaxants by sugammadex is a one-to-one molecular interaction depending on the affinity of sugammadex for the relaxant[2], on the depth of neuromuscular block at the time of antagonism and on the dose of sugammadex.[7] The affinity of the neuromuscular blocking agent for sugammadex is numerically described by the association constant (*Ka).* The higher the *Ka* the greater the affinity. The *Ka* is 3.1 times higher for rocuronium than for vecuronium (1.79 x 10^7 mol/L and 5.72 x 10^6 mol/L, respectively) [8], whereas the dissociation constant (*Kd*) which is the inverse of the association constant, is 3.1 times higher for vecuronium than for rocuronium (0.17 and 0.055 μM, respectively).[8] Several investigators compared the antagonism with sugammadex of moderate [train-of-four (TOF) count of two][4 9] and deep (post tetanic count 1 to 2) vecuronium- and rocuronium-induced neuromuscular block. [10 11 12] Significant dose-response relationships were demonstrated for mean recovery times to TOF ratio 0.9 with sugammadex 0.5, 1.0, 2.0, 4.0 and 8.0 mg/kg showing slower recovery from vecuronium- (35 min vs. 1.7 min) than from rocuronium-induced neuromuscular block (16 min vs. 1.1 min). [9 10] Also, recurrence of acceleromyographic neuromuscular block (TOF ratio < 0.9) was reported to occur in some patients that received low doses of sugammadex for the reversal of moderate or deep neuromuscular block. [9 10 12] However, the comparative literature on this topic is scant. For example, we do not know whether low dose sugammadex would properly reverse a shallow vecuronium-induced neuromuscular block and whether it would prevent a recurrent block. It has been demonstrated that a threshold TOF count of four rocuronium-induced neuromuscular block can be reversed with sugammadex 1.0 mg/kg within 2.1 min and sugammadex 0.5 mg/kg reversed such neuromuscular block in 4.1 min on average.[13] These data, however, may not be valid for vecuronium. Since the neuromuscular potency of vecuronium is six times greater than that of rocuronium (ED_{95}: 0.05 and 0.30 mg/kg, respectively) [1] and their molecular weight is similar (637 and 610 Dalton, respectively, HTTP://WWW.SCBT.COM/DATASHEET-205880.HTML), fewer vecuronium than rocuronium molecules produce similar degrees of neuromuscular block. To encapsulate 1.0 mg vecuronium 3.4 mg of sugammadex is necessary, and to encapsulate the intubating dose (e.g. 7 mg) 2.4 mg sugammadex is sufficient. Theoretically a sugammadex dose as low as 0.5

mg/kg is enough to encapsulate all vecuronium molecules present in the body at any time after the administration of vecuronium 0.10 mg/kg. Although the affinity of vecuronium for sugammadex is lower than that of rocuronium, we hypothesized that the above described factors may partially compensate the lower affinity of vecuronium and thus low doses of sugammadex would adequately reverse a threshold TOF count of four vecuronium induced neuromuscular block.

METHODS

Trial design and participants

This single-center, randomized, controlled, five parallel-arm, superiority trial was approved by the local ethics committee at the University of Debrecen, Hungary and by the National Institute of Pharmaceutics, Budapest, Hungary: OGYI/3194-8/2014. The study is classified under EUDRACT number 2013-004666-34.

The investigations and data collections were carried out at the University Hospital of Debrecen, Hungary, between April 2015 and May 2016. The study followed the CONSORT 2010 recommendations for randomized controlled trials (www.consort-statement.org).

Seventy patients undergoing routine elective surgery were assessed for eligibility and sixty five were enrolled in this study (Fig.1.). The study staff recruited the participants at the University Hospital of Debrecen, Hungary. Entrants gave written, informed consent to participate. They were randomly assigned to one of the 5 study groups to receive sugammadex 0.5, 1.0, 2.0 mg/kg or neostigmine 0.05 mg/kg and atropine 0.015 mg/kg or 0.9% saline (placebo) (Fig 1). Inclusion criteria were age of 18 to 65 years, body mass index 18.5 to 25 kg/m^2, American Society of Anesthesiologists (ASA) physical status I to III, male/female 1:1, scheduled for elective surgery with an expected duration of at least 50 min necessitating muscle relaxant administration for intubation of the trachea, but not always full relaxation for surgery. Exclusion criteria were suspected difficult airway, bronchial asthma, chronic obstructive pulmonary disease, neuromuscular disease, suspected malignant hyperthermia, significant hepatic or renal dysfunction, glaucoma, allergy to the drugs used in this study, and taking medication known to alter the effect of neuromuscular blocking agents. Patients who participated in another study within 30 days were not included, nor were pregnant or breastfeeding women.

Interventions and neuromuscular monitoring

Patients were given 7.5 mg midazolam orally 60 min before induction of anesthesia. In the operating room, an IV cannula was inserted in a forearm vein and vital signs monitoring was started. The patients then received prophylactic antibiotic in the form of cefazoline (2 g), cefotaxime (2.0 g) or metronidazole (500 mg) depending on the type of surgery. Anesthesia was induced with IV propofol (1.5 to 2.0 mg/kg) and fentanyl (2.0 μg/kg) and maintained with inhaled sevoflurane (1.5 to 1.8 vol%) in air-oxygen mixture supplemented with IV fentanyl according to clinical need. Patients' lungs were manually ventilated with oxygen using a face mask until intubation of the trachea. Oxygen saturation was maintained above 96%, normocapnia was ensured, esophageal temperature was maintained above 36°C using forced air warming system (Bair-Hugger® Arizant Healthcare Inc, Eden Prairie, MN). Neuromuscular monitoring was carried out using TOF-Watch-SX® acceleromyograph (Organon Teknika B.V., Boxtel, Holland). The adductor pollicis muscle contractions in response to ulnar nerve stimulation were recorded. The piezoelectric probe of the acceleromyograph was attached to the tip of the thumb. A hand adapter ensured preload of the thumb while making sure that it continued to return to its original position. The forearm and the fingers were immobilized and surface skin electrodes were placed over the ulnar nerve proximal to the wrist. A TOF mode of stimulation was started and repeated every 15 seconds for 3 minutes followed by a 5-second tetanic train of 50 Hz to stabilize the signal. Two minutes later automatic calibration was carried out (CAL-2 to set out supramaximal current intensity and to calibrate the device). TOF stimulation was recommenced delivering supramaximal square wave stimuli of 0.2 millisecond duration at 2 Hz frequency until the signal was stable. If the signal was not stable, the calibration was repeated. Data were recorded and stored on a computer using TOF-Watch-SX software version 2.2 INT (Organon Ireland Ltd. Dublin, Ireland). Skin temperature was measured at the forearm near the wrist and maintained above 32°C. Once the neuromuscular recording was stable vecuronium 0.10 mg/kg (2 x ED_{95}) was injected IV, and the trachea was intubated when the muscle response to TOF stimulation disappeared. If surgical relaxation was necessary, vecuronium 0.015 to 0.02 mg/kg was administered when 1 to 2 twitches to TOF stimulation returned. The TOF stimulation was automatically delivered at every 15-seconds interval.

Reversal of a threshold TOF count of four block

When four twitches in response to TOF stimulation reappeared at three consecutive TOF measurements (a threshold TOF count of four), a designated anesthesiologist injected the study drug upon the request of the attending anesthesiologist responsible for the patient and for the study, which was blinded to the injected study drug. The evolution of TOF ratio (T_4/T_1) and T_1 amplitude (the first of 4 twitches to TOF stimulation) was followed online every15 seconds and was also recorded for later analysis. Once the displayed TOF ratio reached at least 1.0 (unchanged during 3 min), inhaled sevoflurane was discontinued and the trachea was extubated when the patients emerged from anesthesia. If normalized TOF ratio 0.9 was not reached within 30 min after the study drug injection (time was agreed upon a priori to wait for recovery), incomplete reversal was considered and rescue reversal was given (rescue sugammadex 2.0 mg/kg). During this time period the patient's trachea remained intubated. Adequate reversal was defined as average time of ≤ 5 min from the start of the study drug injection to normalized TOF ratio 0.9.

P**ostoperative assessment of neuromuscular block**

After extubation of the trachea, patients were transferred to the recovery room. During the transport the nerve stimulator was set on standby mode and the forearm and hand adapter's positioning was secured, and oxygen was administered by face mask. In the recovery room vital signs monitoring was continued and oxygen was delivered via a nasal cannula. A second designated anesthesiologist recommenced the acceleromyography without recalibration of the device (time zero). The measurements were repeated every 20 min for 60 minutes. At each point in time 3 consecutive TOF stimuli were delivered at 15-second intervals and their average value was considered. Postoperative recurrent neuromuscular block was defined as reappearance of normalized TOF ratios less than 0.9. Patients were surveyed for muscle weakness, force of coughing, ease to swallow and critical respiratory or circulatory events and would be immediately treated had such complications occurred. Supplementary oxygen administration, balloon-mask ventilation, equipment for intubation of the trachea and rescue sugammadex was available. After discharge from the recovery room, patients were observed by the study team for 24 hours to detect late adverse events.

Outcome measures

Normalized TOF ratios of 0.9 were calculated and assessed as efficacy variables. Normalization was carried out by dividing the recorded values at recovery by baseline values before administration of vecuronium. [14]

Primary outcome measures of the study were: (i) the time from the start of the injection of the study drug to normalized TOF ratio of 0.9 characterized the effectiveness of reversal and (ii) the incidence of no recovery to normalized TOF ratio 0.9 within 30 min characterized the incomplete reversal.

Secondary outcome measure of the study was the incidence of postoperative recurrent neuromuscular block in the recovery room during the first 60 min.

Additional outcome measures were the times from study drug injection to recovery of T_1 90%, to non normalized TOF ratio 1.0 and the number of patients reaching normalized TOF ratio 1.0

Sample size

Calculation of sample size was carried out assuming that the usual time for recovery is 600 s with an SD of 200 s in patients treated with neostigmine and that sugammadex 0.5 mg/kg decreases the time of recovery to 300 s. Using a Type I error rate (α) of 0.05 10 subjects in the treatment groups would be needed to reach a power of 0.8. As we assumed that dropouts might occur, we included 13 patients in each group, bringing the total to 65 patients.

Randomization and blinding

The nature of randomization was 1:1 to obtain equal-sized study groups. The study statistician generated the randomization sequence using a web based online program (www. randomizer.org.). The study staff enrolled participants. A designated anesthesiologist possessed the randomization code who assigned participants to intervention. She prepared the study drug and injected it at the request of the attending anesthesiologist. The size and color

of the syringes were similar to each other. Participants, the attending anesthesiologist and the anesthesiologist who performed the postoperative acceleromyographic measurements were blinded after assignment to interventions.

Statistical analysis

To analyze the primary outcome of time from the start of injection of the study drug to normalized TOF ratio of 0.9, we used one-way analysis of variance (ANOVA). We examined the assumptions of ANOVA using the Shapiro-Wilk W-test for the control of normal distribution of variables and the Levene-test to check the homogeneity of variances among the study groups. Because the assumptions of normality or homoscedasticity were not met by the data, we applied the Box-Cox transformation for evaluating the primary outcome variable. When variances differed even after transformation, we used the Welch F test for unequal variances. Post-hoc testing of differences among group means was based on Tukey's HSD test. We also used ANOVA to analyze baseline variables (patient data and perioperative variables) when the assumptions of parametric tests were met by the data. Otherwise, we used the non-parametric Kruskal-Wallis ANOVA to compare groups. For comparing proportions, including the primary outcome measure of the incidence of incomplete reversals and the secondary outcome measure of the incidence of re-paralysis, we used the χ^2 statistic. When the assumptions of the χ^2 statistic were not met, we applied Cramer's V statistic of association. Because there were two components of the primary endpoint, we used $\alpha = 0.025$ (or half of the conventional α level of 0.05) to infer significance in analyses of outcome variables. We used $\alpha = 0.05$ as a significance level in tests of baseline variables. All statistical calculations were implemented in PAST 3.0.7[9] or in R (version 3.2.2 R Development Team 2015).[15]

RESULTS

Seventy patients were eligible, 65 agreed to participate in the trial. All enrolled patients were assigned to 1 of the 5 study groups. (Fig. 1). One patient in the sugammadex 1.0 mg/kg group was excluded from the study due to technical failure (broken acceleromyographic device) thus the data from 64 cases were analyzed. The trial ended as anticipated, after the 24-hour-long observation period following the tracheal extubation of the last patient.

There were no differences in sex, age, body mass index, control TOF ratio, control T_1 (%), ASA physical status score or the duration of surgery among the five study groups (Table 1). There were no differences among groups in the dose of vecuronium and in the end-tidal sevoflurane concentrations at antagonism. There were likewise no differences among groups in the time intervals from last vecuronium injection to a threshold TOF count of four blocks (Table 2).

Primary outcome

Reversal with neostigmine took 11.3 min, significantly longer than reversal with sugammadex 1.0 mg/kg (4.4 min) or 2.0 mg/kg (2.6 min) (Table 3, Tukey HSD test for both comparisons, $p < 0.05$), whereas the difference between neostigmine and 0.5 mg/kg sugammadex (6.8 min) was not statistically significant ($p > 0.05$) (Table 3). However, the variance in time to TOF ratio of 0.9 was significantly larger in the neostigmine group (94.1) than in the 0.5 mg/kg sugammadex group (16.6) ($F = 5.671$, $p = 0.023$). Within the sugammadex groups, there were significant differences in the times to normalized TOF ratio 0.9 because these times were shorter in the groups receiving sugammadex 1.0 or 2.0 mg/kg (4.4 min and 2.6 min, respectively) than in the sugammadex 0.5 mg/kg group (6.8 min) (Table 3; one-way ANOVA for the three sugammadex groups, $F_{2,31} = 12.450$, $p = 0.0001$, Tukey HSD tests, $p < 0.05$ for both comparisons). Calculations of the mean differences between pairs of study groups (Table 4) confirmed these results, and additionally showed a significant difference between the sugammadex 1.0 mg/kg and 2.0 mg/kg groups (Tukey HSD test, $p = 0.047$).

The number of incomplete reversals was 4 in the sugammadex 0.5 mg/kg group, 3 in the neostigmine group, 13 in the placebo group, and 0 in the sugammadex 1.0 and 2.0 mg/kg groups (Table 3). The difference in incomplete reversals between the placebo and the four treatment groups combined was significant (Fisher's exact probability < 0.0001), whereas the difference between the sugammadex 0.5 mg/kg group and the neostigmine group was not

significant (Fisher's exact p = 0.157). Calculations of odds ratios also confirmed the differences between the placebo and each of the four treatment groups (Table 4). All patients with incomplete reversal received rescue sugammadex 2.0 mg/kg and recovered to normalized TOF ratio 0.9 thereafter. These patients were not considered for the analysis of reversal times but were included in the assessment of the postoperative recurrent neuromuscular block.

Secondary outcome

Postoperative recurrent neuromuscular block occurred in 12 patients: 3 were 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 proportions did not differ significantly among the groups (χ^2 =2.708, df = 4, p = 0.608). Similarly, odds ratios pertaining to the occurrence of re-paralysis did not differ in either of the pairwise comparisons of study groups (Table 4). The within-patient variation between the three separated TOF measurements was analyzed in each of the 18 re-paralysis. The median coefficient of variation was 6.0% (IQR: 5.1%), while the geometric mean of the percentual coefficient of variation was 5.2. Precision of TOF measurement was deemed satisfactory if the discrepancy between repeated observations was within 2 times 5.2 [14] (see additional web material 1.). Of the 12 patients with postoperative recurrent neuromuscular block four were asymptomatic (normalized TOF ratios 0.85, 0.87, 0.86, 0.89). Eight patients with TOF ratios 0.85, 0.86, 0.83, 0.85, 0.86, 0.86, 0.74 and 0.72 complained about muscle weakness, which was associated with weakened coughing in 7, with positive head lift test in 4 and with difficulty swallowing in 4 cases. The duration of recurrent block was 40 min in one subject and 20 min in the others. The lowest TOF ratios were measured at 60 min, one in the sugammadex 2.0 mg/kg group (normalized TOF ratio 0.72) and one in the placebo group (normalized TOF ratio 0.74) after rescue sugammadex of 2.0 mg/kg. Both patients complained about muscle weakness, they had weakened coughing, difficulty swallowing, positive head lift test and difficulty in eye movement. Discharge of these patients from the recovery room was delayed by 20 to 30 min until they became asymptomatic.

Additional outcome:

The number of patients reaching normalized TOF ratio 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 to reach non normalized TOF ratio 1.0 did not differ significantly from the times to reach

normalized TOF ratio 0.9. There was no difference among the treatment groups in times to achieve T_1 90% (Table 3).

Harms: No important harms or adverse effects were observed.

DISCUSSION

Summary of Results

The current study investigated whether sugammadex 0.5 and 1.0 mg/kg adequately reverses a vecuronium induced neuromuscular block that spontaneously returned to a threshold TOF count of four. Criterion of adequate reversal was achievement of normalized TOF ratio 0.9 in ≤ 5 min on average. Incomplete reversal was defined as failure to reach normalized TOF ratio 0.9 within 30 min after administration of reversal agent. Also, the incidence of recurrent neuromuscular block (normalized TOF ratios < 0.9) was studied. Sugammadex 1.0 mg/kg adequately reversed the block in each patient, as did the standard dose (2.0 mg/kg). Of the 13 patients that received sugammadex 0.5 mg/kg, 4 produced incomplete reversal. The mean reversal time for the remaining 9 patients was 6.8 min, thus did not fulfill the criterion of adequate reversal. Neostigmine was not significantly different from sugammadex 0.5 mg/kg with a mean reversal time of 11.3 min in 10 patients and with incomplete reversal in 3 cases. Recurrent block was detected in 12 patients. These results do not support our hypothesis that a threshold TOF count of four vecuronium-induced neuromuscular block can adequately be reversed with limited sugammadex doses similarly to a rocuronium induced block. [13]

There are two reasons to use a small-dose of sugammadex for reversal of residual neuromuscular block. The first is an economic one, attempting to decrease the costs required for sugammadex treatment.[13] The second is that too much sugammadex on board would limit the options should re-intubation of the trachea or repeat surgery be needed shortly after the end of the case. [16, 17] However, the concept of reversal of residual neuromuscular block with clinically limited dose range of sugammadex generated concern about re-paralysis, arguing that sugammadex 1.0 mg/kg or 0.5 mg/kg is insufficient to restore the safety margin of the neuromuscular junction thus rebound of the block may happen.[18 19] Actually only few studies have investigated the effect of low dose sugammadex on the reversal of shallow residual neuromuscular bocks.[20] What we know about this topic is that 0.25 mg/kg of sugammadex is able to reverse a rocuronium induced block at a TOF ratio of 0.5 to 0.9 in an average time of

< 2 min [7] and that sugammadex 1.0 or 0.5 mg/kg adequately reversed a threshold TOF count of four rocuronium-induced block under sevoflurane anesthesia.[13] Also moderate (T_2) rocuronium- and vecuronium-induced neuromuscular blocks were successfully reversed under propofol-remifentanil anesthesia.[4]

A multicentre study [9] demonstrated clear dose-response relationship for the reversal of moderate rocuronium- and vecuronium-induced neuromuscular block with sugammadex 0.5, 1.0, 2.0 and 4.0 mg/kg under sevoflurane anesthesia. Recovery times to TOF ratio 0.9 were shorter in the rocuronium than in the vecuronium group, and the difference was the most pronounced at sugammadex 0.5 mg/kg. Recurrence of the block occurred in seven patients due to suboptimal doses of sugammadex, but also after the recommended dose of 2.0 mg/kg in one case. Duvaldestin et al.[10] investigated the reversal of deep vecuronium and rocuronium induced neuromuscular block with increasing doses of sugammadex under sevoflurane maintenance anesthesia. Sugammadex in doses of ≥ 4.0 mg/kg provided rapid reversal of deep rocuronium- and vecuronium-induced neuromuscular block. Neuromuscular monitoring showed recurrence of neuromuscular block in 5 patients, all in the rocuronium group (2 received 0.5 mg/kg and 3 received 1.0 mg/kg sugammadex). Eleveld et al. observed the rebound of neuromuscular block after attempting to reverse a deep rocuronium induced block with sugammadex 0.5 mg/kg.[12] From these studies we know that low dose sugammadex is unsuitable to reverse moderate or deep rocuronium or vecuronium-induced neuromuscular block.

What the present study adds to our knowledge is that sugammadex 0.5 mg/kg cannot reverse a threshold TOF count of four neuromuscular block to normalized TOF ratio 0.9 in 30% of the patients and it is not more effective than neostigmine in the remaining 70%. We confirmed that re-paralysis can occur even after the reversal of such neuromuscular block with sugammadex 2.0 mg/kg. Therefore caution is suggested when using limited clinical doses of sugammadex (≤ 2.0 mg/kg) for antagonism of vecuronium-induced residual block, and the use of quantitative neuromuscular monitoring is highly recommended.

There may be several explanations of these results. Firstly, the complexation of relaxant-sugammadex and its breakdown into constituent molecules depends on the propensity of the two substances to associate and to dissociate.[2] Since sugammadex is more selective for rocuronium than for vecuronium [association constants (Ka) 1.79×10^7 mol/L and 5.72×10^6 mol/L, respectively], [8] the complexation is slower with vecuronium than with rocuronium.

Secondly, as the dissociation constant of vecuronium is 0.17 μM, vs. 0.055 μM for rocuronium,[8] higher relative sugammadex concentrations are required for complex formation with vecuronium than with rocuronium. This may explain why sugammadex 0.5 mg/kg was limited in reversing the residual effect of vecuronium, in contrast to what was previously found with rocuronium.[13] Thirdly, the sugammadex/vecuronium concentration ratio, not the absolute number of vecuronium molecules in the body appears to be the decisive factor for the reversal of vecuronium block. Therefore, sugammadex 1.0 mg/kg and 2.0 mg/kg were effective while 0.5 mg/kg was not. Furthermore, none of the sugammadex doses administered in this study prevented the recurrence of neuromuscular block. The overall frequency of re-paralysis was 18.7% but this incidence varied from group to group. This was an unexpected outcome, which raises the suspicion of artifacts due to displacement of the arm during the measurement of acceleromyographic TOF responses in patients recovering from anesthesia.[21] In order to prevent this bias, special care was taken by the study anesthesiologists to adequately fasten the arm during TOF stimulation, like in our previous study including 47 awake patients that were monitored for residual neuromuscular blockade during 60 min in the recovery room.[22] Since these patients presented neither clinical signs of residual paralysis nor TOF ratio depression, they can be considered as a control group for the current study and thus validating its results. With regard to the mechanism of re-paralysis, low doses of sugammadex may be sufficient for complex formation with the relaxant molecules in the central compartment, but are insufficient for redistribution from the periphery to the plasma. Furthermore, the dissociation of vecuronium from the complex over time (ref. *Kd*) also takes place and increases the possibility of rebounding block.[12]. Although it cannot be excluded with certitude, it is less likely that residual concentrations of sevoflurane enhanced the block in the postoperative period. It is also unlikely that the metabolite of vecuronium caused re-paralysis; the doses were too small for this. No severe postoperative re-paralysis occurred in the patients, and the majority of recurrent blocks were “slight” (normalized TOF ratios 0.83 to 0.89) apparently at the limit of the safety margin.

Clinical signs of re-paralysis were observed in 8 patients without other adverse event. Nevertheless, recurrent neuromuscular block may be associated with postoperative complications such as hypoxia, weakness, pulmonary aspiration of gastric content and respiratory failure. The prevention of these complications may improve patients’ safety and decreases mortality rate.[23]

Limitation of this study

This study was based on acceleromyographic measurements of neuromuscular transmission, which is known to overestimate the recovery. However, we used preload and normalization to improve its accuracy.[14] Had we considered non-normalized TOF ratios for postoperative recurrent neuromuscular block, five recurrent blocks would have been detected. We did not measure the plasma concentrations of sugammadex, vecuronium or 3-desacetylvecuronium, and spirometry was not carried out for the diagnosis of possible respiratory depression. Although the explanation of the result was based on published data, presumptions about the mechanism of reversal and postoperative recurrent neuromuscular block could not be avoided. Due to ethical reasons and tight operating schedules a 30 minutes cut off point in time was a priori included resulting in reduction of sample size in three treatment groups. Although the placebo control was excluded from the comparison of the reversal times, it allowed distinguishing the effect of sugammadex 0.5 mg/kg and neostigmine from spontaneous recovery. Of note, the administration of rescue treatment to placebo patients confirmed the occurrence of postoperative recurrent neuromuscular block after sugammadex 2.0 mg/kg. This issue is clinically relevant and therefore further studies are highly desirable to confirm these results.

In conclusion, this study demonstrated, that sugammadex 0.5 mg/kg is insufficient to reliably guarantee prompt and satisfactory neuromuscular recovery following vecuronium administration at a threshold TOF count of four. Increasing the dose to 1.0 mg/kg adequately reversed this level of block, although recovery took twice as long as has been reported after rocuronium. In addition, recurrent neuromuscular block occurred in each treatment group. Sugammadex 0.5 mg/kg should not be used for the reversal of vecuronium-induced neuromuscular block and the use of quantitative neuromuscular monitoring is highly recommended.

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Text to figure 1. Study flowchart.

The administration of sugammadex, neostigmine and placebo was randomized and double blinded. The administration of vecuronium was open. nTOF 0.9= normalized TOF ratio 0.9. Light gray quadrangles: comparison for recovery times, dark gray quadrangles: excluded from comparison of recovery times, rescue sugammadex= 2 mg/kg.

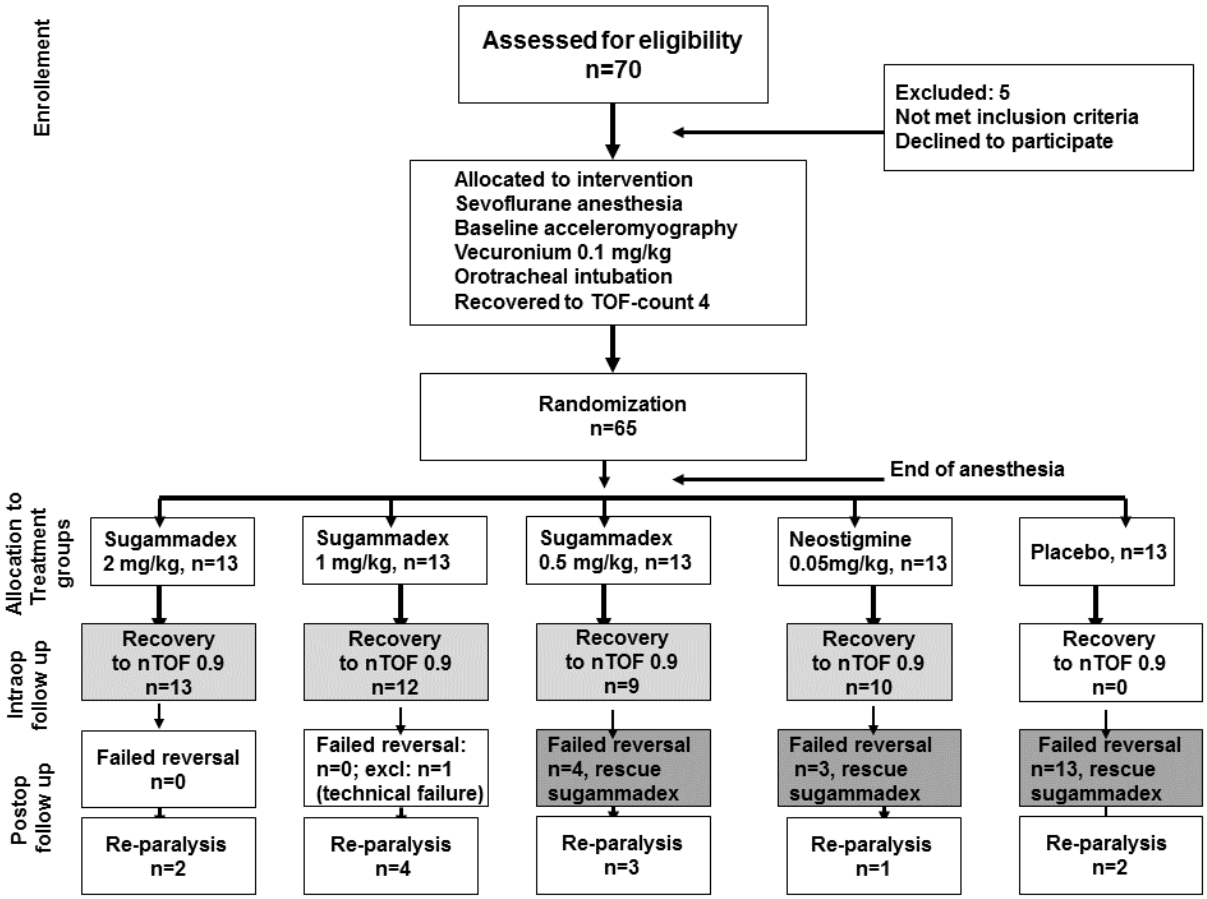

Table 1. Comparison of baseline characteristics, duration of surgery and control acceleromyographic values.

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 (M/F)	7/6	6/7	7/6	6/7	5/8	0.93 #
Age (year)	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 - 23.8)	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 ± standard deviations are given when data met the assumptions of parametric statistical tests, otherwise, medians (interquartile ranges) are given. N = 13 in each group; # χ^2-test, ## one-way ANOVA, ### Kruskal-Wallis ANOVA.

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 ± standard deviations 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; [#] Kruskal-Wallis ANOVA, [##] one-way ANOVA.

Table 3. Primary outcome of the study.

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
Incomplete recovery (N)	4 [13]	0 [12]	0 [13]	3 [13]	13 [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 ± standard deviations are given for time variables. Group means not sharing superscript letters differ significantly (Tukey's HSD test, $p < 0.05$). Sample sizes are given in brackets; [#] Cramer's V, [##] one-way ANOVA.

Table 4. Estimates of the mean differences (and their 95% confidence intervals) 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 post-operative recurrent neuromuscular block (PORNB) between pairs of study groups. For 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.

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)***	–
Number 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)**
Number 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)

‡ Estimates (95% confidence intervals) of the mean differences between study groups are given for Time to normalized TOF ratio of 0.9, and odds ratios (95% confidence intervals) are given for number of failed reversals and number of patients with reparalysis. Tukey HSD test; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 5. Secondary outcome of the study: incidence of postoperative re-paralysis 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 measurement (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 (range)	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 (range)	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 (range)	1.01 (0.86-1.14)	0.97 (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	1.05 (0.74-1.31)
	Median (range)	0.99 (0.91-1.32)	1.00 (0.86-1.13)	0.99 (0.72-1.26)	1.03 (0.91-1.12)	
Recurrent block	Yes /No	3/9	4/8	2/10	1/12	2/11

Medians (interquartile ranges) are given for time between the last train-of-four (TOF) measurement in the operating room and the first TOF measurement in the recovery room (time 0 min). Means ± standard deviations 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) post-operative recurrent neuromuscular block in the study groups. #Kruskal-Wallis H = 2.611, p = 0.625.

ADDITIONAL WEB MATERIAL

Variation of acceleromyographic TOF ratios during measurements in the recovery room.

Twelve patients had recurrent neuromuscular block (normalized average TOF ratio < 0.9) on 18 occasions (bold italic fonts). Three normalized TOF ratios are reported for each patient on each occasion. Each table shows data obtained at different measurement times (0, 20, 40, 60 min). The coefficients of variation of TOF ratios have been calculated for each patient. The median coefficient of variation for the dataset was 6% (IQR: 5.1).

Table 1. Time 0

Patients	Study group	TOFR 1	TOFR 2	TOFR 3	Mean TOFR	Coefficient of variation
34	***sug 0,5 mg /kg***	***0.86***	***0.83***	***0.88***	***0,85***	***0.02***
36	sug 1.0 mg/kg	0.87	0.88	0.88	0,88	0.006
44	***sug 1.0 mg/kg***	***0.86***	***0.86***	***0.78***	***0,83***	***0.05***
62	***sug 1.0 mg/kg***	***0.90***	***0.84***	***0.85***	***0,86***	***0.037***
55	sug 2.0 mg/kg	0.87	0.87	0.87	0,87	0

sug:=sugammadex, TOFR=train-of-four ratio

Table 2. 20 min

Patients	Study group	TOFR 1	TOFR 2	TOFR 3	Mean TOFR	Coefficient of variation
18	placebo	1.0	0.78	0.88	0,88	0.068
37	neostigmine	0.93	0.80	0.85	0,86	0.076
10	sug 0,5 mg /kg	1.21	0.81	0.61	0,87	0.34
34	***sug 0,5 mg /kg***	***0.78***	***0.85***	***0.90***	***0,84***	***0.07***
60	sug 0,5 mg /kg	0.91	0.88	0.88	0,89	0.02
11	sug 1.0 mg/kg	0.88	0.79	0.89	0,85	0.06

sug: sugammadex, TOFR=train-of-four ratio

Table 3. 40 min

Patients	Study group	TOFR 1	TOFR 2	TOFR 3	Mean TOFR	Coefficient of variation
7	***placebo***	***0.82***	***0.88***	***0.87***	***0,85***	***0.06***
34	***sug 0,5 mg /kg***	***0.86***	***0.85***	***0.88***	***0,86***	***0.017***
62	***sug 1.0 mg/kg***	***0.81***	***0.90***	***0.90***	***0,87***	***0.06***

sug: sugammadex, TOFR=train-of-four ratio

Table 4. 60 min

Patients	Study group	TOFR 1	TOFR 2	TOFR 3	Mean TOFR	Coefficient of variation
7	***placebo***	***0.70***	***0.73***	***0.80***	***0,74***	***0.07***
44	***sug 1.0 mg/kg***	***0.96***	***0.85***	***0.78***	***0,86***	***0.105***
62	***sug 1.0 mg/kg***	***0.82***	***0.88***	***0.91***	***0,87***	***0.05***
3	sug 2.0 mg/kg	0.81	0.64	0.71	0,72	0.13

sug: sugammadex, TOFR=train-of-four ratio