

Postoperative impairment of motor function at train-of-four ratio ≥ 0.9 cannot be improved by sugammadex (1 mg kg^{-1})

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Editor's key points

- Recovery of neuromuscular block to a train-of-four ratio ≥ 0.9 is deemed sufficient for extubation.
- At this ratio, many postsynaptic receptors are still occupied by the neuromuscular blocking agent.
- The authors thus studied the effect of sugammadex 1 mg kg^{-1} on muscle function and well-being.
- No effect was found.

Background. A train-of-four ratio (TOFR) ≥ 0.9 measured by quantitative neuromuscular monitoring is accepted as an indication of sufficient neuromuscular recovery for extubation, even though many postsynaptic acetylcholine receptors may still be inhibited. We investigated whether antagonism with sugammadex after spontaneous recovery to TOFR ≥ 0.9 further improves muscle function or subjective well-being.

Methods. Following recovery to TOFR ≥ 0.9 and emergence from anaesthesia, 300 patients randomly received either sugammadex 1.0 mg kg^{-1} or placebo. Fine motor function (Purdue Pegboard Test) and maximal voluntary grip strength were measured before and after surgery (before and after test drug administration). At discharge from the postanesthesia care unit, well-being was assessed with numerical analogue scales and the Quality-of-Recovery Score 40 (QoR-40).

Results. Patients' fine motor function [6 (sd 4) vs 15 (3) pegs (30 s^{-1}), $P < 0.05$] and maximal voluntary grip strength (284 (126) vs 386 (125) N, $P < 0.05$) were significantly lower after anaesthesia compared with the pre-anaesthesia baseline. After sugammadex or placebo, motor function was significantly improved in both groups but did not reach the preoperative level. There was no difference between groups at any time. Global well-being was unaffected (QoR-40: placebo, 174 vs 185; sugammadex, 175 vs 186, $P > 0.05$).

Conclusions. Antagonizing rocuronium at TOF ≥ 0.9 with sugammadex 1.0 mg kg^{-1} did not improve patients' motor function or well-being when compared with placebo. Our data support the view that TOFR ≥ 0.9 measured by electromyography signifies sufficient recovery of neuromuscular function.

Clinical trial registration. The trial is registered at ClinicalTrials.gov (NCT01101139).

Keywords: neuromuscular blocking agent; postoperative residual paralysis; quantitative neuromuscular monitoring; sugammadex

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The use of neuromuscular blocking agents (NMBAs) during anaesthesia is associated with the risk of residual neuromuscular block and respiratory complications.¹ In the early 1970s, Ali and colleagues^{2,3} promoted the development of quantitative neuromuscular monitoring. They introduced the train-of-four ratio (TOFR) as an objective index of adequate recovery from neuromuscular block. In addition, clinical recovery from neuromuscular block was evaluated by the ability to lift the head.³ Based on their findings, recovery to a TOFR of 0.7 was initially recommended before tracheal extubation.³ According to current expert opinion, a TOFR ≥ 0.9 measured by quantitative neuromuscular monitoring indicates sufficient recovery from neuromuscular block.⁴ This threshold was suggested based

on recovery of respiratory function,^{5,6} leading to intense discussion on whether recovery to TOFR = 0.9 is indeed sufficient for extubation.⁷ In this context, other aspects of residual neuromuscular block, such as muscle weakness and discomfort in the postanesthesia care unit (PACU), were gradually ignored, although they have a significant impact on patients' postoperative rehabilitation and may be critical for street readiness.^{8,9}

After absence of any twitch depression detectable by neuromuscular monitoring, approximately 75% of postsynaptic acetylcholine receptors are still occupied by non-depolarizing NMBAs.^{10,11} The magnitude of residual NMBA effects at the neuromuscular junction, however, cannot be quantified by current methods of neuromuscular monitoring.^{10,11} Therefore,

we hypothesized that the remaining block at $\text{TOFR} \geq 0.9$ is the reason for the patients' feeling of muscle weakness and compromised subjective well-being.

This study was designed to examine whether fine motor skills, maximal voluntary contraction force, and patients' well-being can be improved by eliminating rocuronium with a dose of sugammadex 1.0 mg kg^{-1} after spontaneous recovery to $\text{TOFR} \geq 0.9$.

Methods

Patients

The trial was registered at ClinicalTrials.gov (NCT01101139) and approved by the local ethics committee (Ethikkommission der Fakultät für Medizin der Technischen Universität München, Munich, Germany; study coordinator, M.B.). After written informed consent, we enrolled 300 patients (ASA I–III) scheduled for elective low-risk surgical procedures under general anaesthesia. Patients were excluded if they participated in another randomized clinical trial, if their age was < 18 or > 65 yrs, if they had a history of neuromuscular diseases or malignant hyperthermia, if they had significant hepatic or renal dysfunction, if they were allergic to anaesthetics, NMBAs, or sugammadex, if they had a psychiatric disorder, or if they were pregnant or breastfeeding.

Study design

This study was a single-centre, randomized, controlled, double-blinded trial. Following recovery to $\text{TOFR} \geq 0.9$ and emergence from anaesthesia, all patients were randomly assigned to receive either sugammadex or saline in the PACU. The surgical and anaesthesia team, including the postanaesthesia care team, were blinded to the group assignment. Only the study coordinator, who prepared the study medication labelled with the randomization code, was unblinded to group assignment. He was not involved in any testing or care taking of the patients.

Preoperative assessment

After preoperative assessment and written consent, patients performed initial testing of gross and fine motor function and completed a well-being questionnaire. Maximal voluntary muscle strength was measured using hand dynamometry (Jamar Plus+Hand Dynamometer™; Patterson Medical, Sammons Preston, Bolingbrook, IL, USA). Before testing, the study assessor demonstrated the handling of the hand dynamometer and coached patients through the procedure. They were asked to choose a hand and to press the hand dynamometer once, with maximal force (measured in newtons).^{12 13} The Purdue Pegboard was used to test fine motor skills (Purdue Pegboard Test™; Lafayette Instrument Company, Lafayette, IN, USA)¹⁴ and was also demonstrated to each participant before testing. By using the dominant hand, patients placed 3-cm-long pegs in a row on a wooden board; as many and as fast as they could within 30 s. Preoperative well-being was measured by the Quality-of-Recovery Score 40 (QoR-40).^{15 16} This patient-assessed questionnaire evaluates the quality of recovery after surgery and anaesthesia. It encompasses the following five dimensions that have been identified to be clinically

relevant: emotional state, physical comfort, psychological support, physical independence, and pain. As a result of its high validity, reliability, and responsiveness, the questionnaire is a valuable tool to assess well-being in the perioperative period and is recommended for clinical use and research.^{15 16}

Anaesthesia

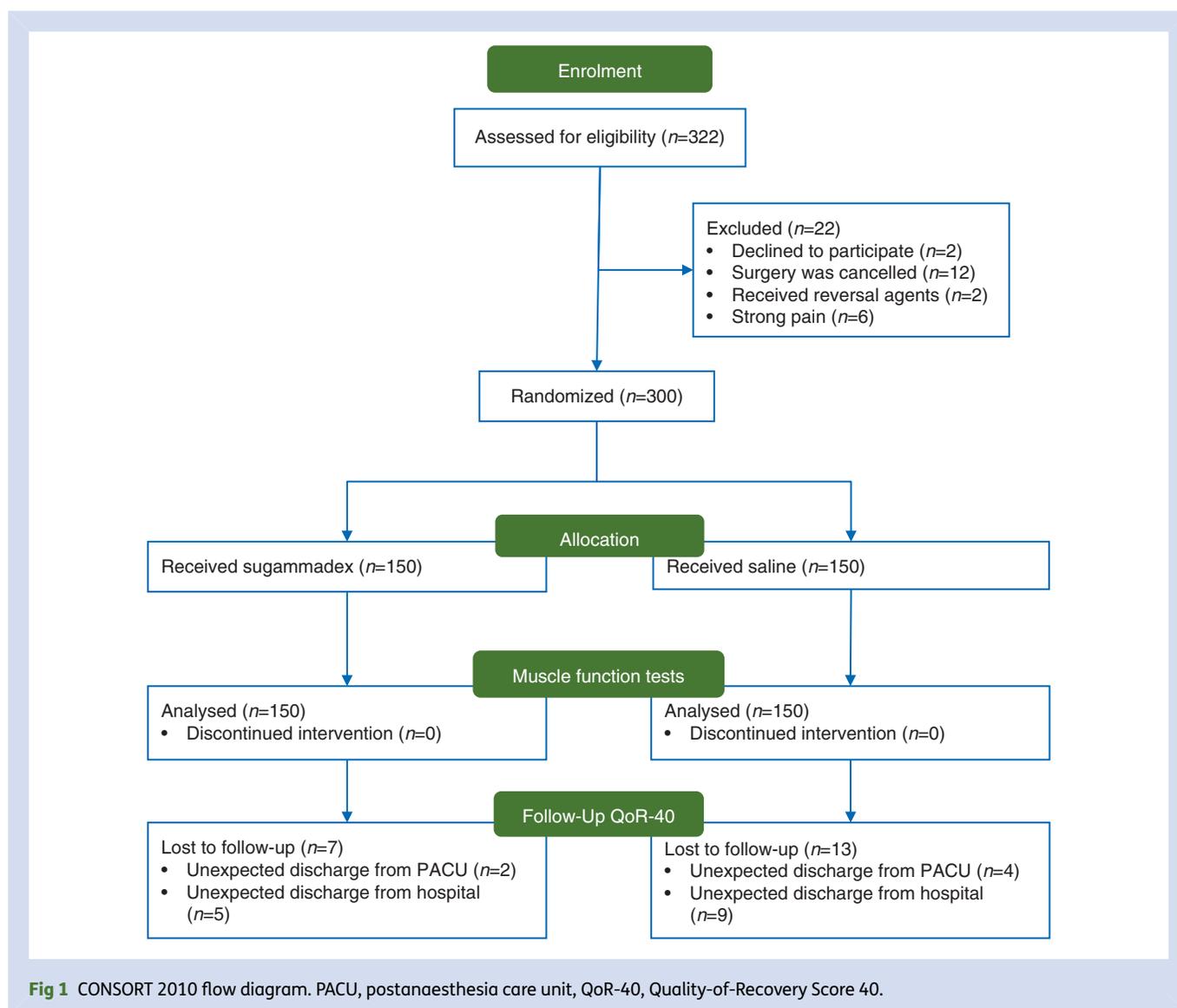
Patients received no premedication. After arrival in the preoperative area, an i.v. cannula was placed in a proximal forearm vein in order to avoid interference with the muscle function tests, and an infusion of Ringer's acetate solution was administered. Standard anaesthesia monitoring, including pulse oximetry, non-invasive blood pressure, and electrocardiography, was established. To prevent postoperative nausea and vomiting, patients were given dexamethasone (8 mg) i.v. After the Entropy™ Module (GE Datex-Ohmeda Entropy™; GE Healthcare, Milwaukee, WI, USA) was set up to monitor depth of hypnosis, anaesthesia was induced with fentanyl ($0.1\text{--}0.2 \text{ } \mu\text{g kg}^{-1}$) and propofol ($2\text{--}3 \text{ mg kg}^{-1}$). After patients became apnoeic, their lungs were ventilated by facemask with 100% oxygen.

Neuromuscular monitoring was performed using evoked electromyography of the adductor pollicis muscle with a NMT module in an S/5 GE Datex Light monitor (GE Datex Medical Instrumentation, Inc., Tewksbury, MA, USA). In brief, the forearm was immobilized, and surface skin electrodes were placed over the ulnar nerve proximal to the wrist. After 3 min of calibration, the ulnar nerve was stimulated with supramaximal train-of-four stimulation at 20 s intervals and the evoked electromyogram of the adductor pollicis muscle recorded. Following the calibration of the neuromuscular monitoring with stable TOFR ($0.97\text{--}1.0$), rocuronium 0.6 mg kg^{-1} was injected i.v., and tracheal intubation was performed at $\text{TOFR}=0$.

After intubation, anaesthesia was maintained with remifentanyl and sevoflurane according to the clinical needs monitored with the Entropy™ Module (GE Datex-Ohmeda Entropy™; GE Healthcare) and the preference of the responsible anaesthetist. Ventilation with 40–50% oxygen in air was controlled to maintain normocapnia (end-tidal carbon dioxide tension $4.6\text{--}6 \text{ kPa}$). During surgery, maintenance doses of rocuronium were given if required to improve mechanical ventilation or surgical conditions. Oropharyngeal temperature was kept $\geq 36^\circ\text{C}$ using a forced air-warming device.

At the end of surgery, neuromuscular function was allowed to recover spontaneously. Paracetamol (Perfalgan™ $1 \text{ g } 100 \text{ ml}^{-1}$; Bristol-Myers Squibb, NY, USA) was administered for preventive analgesia, and Ondansetron-hameln 2 mg/ml (Hameln Pharmaceuticals GMBH, Hameln, Germany) for additional prophylaxis of postoperative nausea and vomiting. Remifentanyl infusion and sevoflurane inhalation were discontinued. At $\text{TOFR} \geq 0.9$, the trachea was extubated and patients were immediately transferred to the PACU.

Only after spontaneous recovery to a $\text{TOFR} \geq 0.9$ and emergence from anaesthesia were patients eligible for randomization in the PACU in order to avoid dropouts because of secondary exclusion criteria (e.g. requirement for an antagonistic agent because of insufficient spontaneous neuromuscular recovery; please see also Fig. 1) and organizational problems.



Postoperative monitoring (in the PACU)

Fifteen (range, 13–17) minutes after reaching TOFR=0.9, a blinded PACU anaesthetist performed the study-related tests in the PACU. Hand dynamometry and Purdue Pegboard Test were carried out with the same hand as for the preoperative testing. After that, patients were asked to rate vigilance, muscular strength, well-being, nausea, feeling cold/shivering, and pain subjectively on numerical analogue scales ranging from 0 to 10.

At the same time, the non-blinded study coordinator randomly assigned the patients to one of the two groups to receive either sugammadex 1.0 mg kg⁻¹ or saline, prepared the respective syringe, and injected it after the blinded anaesthetist had completed the tests. Ten minutes after injection of the investigational drug, the blinded anaesthetist repeated the hand dynamometry, the Purdue Pegboard Test, and the subjective rating regarding vigilance, muscular strength, well-being, nausea, feeling cold/shivering, and pain.

Patients stayed in the PACU for at least 60 min. During that time, they received standard postoperative care. Heart rate,

blood pressure, and oxygen saturation were monitored routinely and documented by the study coordinator before testing, before and 5 min after injection of the study medication, and at discharge from the recovery room. Before being transferred to the ward, patients answered the QoR-40 for the second time. At discharge from the hospital or at postoperative day 3 at the latest, patients were asked to fill out the QoR-40 for the third time.

Throughout the whole study period, the blinded safety assessor, the patients' blinded anaesthetist, and the blinded anaesthetist in the PACU were in charge of monitoring adverse events. The safety assessor evaluated severity and classification of any adverse event and ultimately decided about coding (definitely, probably, or possibly related to the study drug).

Data management and statistical analyses

The research hypothesis was to test whether antagonism of a subclinical, rocuronium-induced neuromuscular block

(TOFR \geq 0.9) with sugammadex 1.0 mg kg⁻¹ improves patients' postoperative muscle function and well-being. The primary end point was the number of pegs placed within 30 s. Secondary end points were grip strength and the patient's subjective well-being after anaesthesia.

Based on our previously performed multicentre study evaluating various clinical tests to detect residual neuromuscular block,¹⁷ we expected an 80% incidence of muscle weakness in untreated patients and 67% in treated patients at TOF \geq 0.9. To demonstrate this difference between two groups by χ^2 test with a significance level $P=0.05$ and a power of 80%, we calculated that 150 patients were necessary per group.

The final analysis included data from all patients who had a general anaesthesia regimen in accordance with the study protocol as indicated in our Methods 'Anaesthesia' section, and who were randomized and received the study drug (i.e. without any protocol violation).

Data were analysed with generalized linear models and non-parametric models as appropriate. Normally distributed data are shown as means and their standard deviation. Non-parametric variables are depicted as boxplots including outliers. For these data, median differences and the 95% confidence intervals (CIs) were calculated. The outcome of the QoR-40 is presented as a table. Calculation of the median differences and comparison by analysis of variance (ANOVA) were also performed with a 95% CI.

For all comparisons, a value of $P=0.05$ was applied. Statistical analysis was performed with IBM SPSS Statistics, version 21 (IBM, Armonk, NY, USA).

Results

Initially, a total of 322 patients gave written informed consent. After exclusion of 22 patients, 150 patients were randomized to each group, received the study medication, and completed the requested testing (Fig. 1). Seven patients of the sugammadex group and 13 of the saline group were discharged from the PACU or the hospital before filling out the last QoR-40 (Fig. 1).

The groups were similar in their characteristics and perioperative data (Table 1). After anaesthesia and surgery, gross and fine motor function was significantly impaired in both groups compared with preoperative values (Fig. 2A and B). After injection of the study medications (placebo or sugammadex), postoperative motor function was significantly improved in both groups, but did not reach the preoperative level. Neither the decrease nor the time-related increase of the measured variables differed between groups (Fig. 2A and B).

Rating of vigilance, muscular strength, nausea, shivering/feeling cold, subjective well-being, and pain revealed no significant differences over time or between groups (Fig. 3). The quality of recovery did not differ in any dimension at any time between groups (Table 2). In the PACU, vital parameters were consistently sufficient before and after intervention (Table 1). No patient in this study had an adverse event or a severe adverse event throughout the study period.

Table 1 Patients' characteristics and perioperative data. Values are given as mean (sd) or number (percentage)

	Placebo (n=150)	Sugammadex 1.0 mg kg ⁻¹ (n=150)
Patient characteristics		
Age (yrs)	43 (13)	42 (13)
Body height (cm)	173 (10)	173 (10)
Body weight (kg)	74 (17)	74 (16)
Sex female	81 (54%)	87 (58%)
Sex male	69 (46%)	63 (42%)
ASA I	110 (73%)	108 (72%)
ASA II	39 (26%)	40 (27%)
ASA III	1 (1%)	2 (1%)
Perioperative data for surgery and anaesthesia		
Surgical procedures		
Minor low abdominal	46 (30%)	36 (24%)
Peripheral vascular/ orthopaedic	70 (47%)	87 (58%)
Breast	34 (23%)	27 (18%)
Duration of surgery (min)	84 (42)	81 (44)
Duration of anaesthesia (min)	131 (44)	131 (52)
Vital parameters in the postanesthesia care unit		
Peripheral oxygen saturation (%)		
Before intervention	96 (3)	97 (3)
After intervention	97 (3)	97 (3)
Heart rate (beats min ⁻¹)		
Before intervention	84 (14)	83 (14)
After intervention	79 (13)	78 (13)
Mean arterial blood pressure (mm Hg)		
Before intervention	102 (15)	102 (13)
After intervention	103 (14)	102 (14)

Discussion

In this study, fine and gross motor function were significantly impaired after emergence from general anaesthesia at a TOFR \geq 0.9. Antagonism of a subclinical neuromuscular block with sugammadex 1.0 mg kg⁻¹ did not improve fine motor skills, maximal voluntary force contraction, or well-being.

Recently, Murphy and colleagues¹⁸ compared signs and symptoms of subjective muscle weakness in patients with and without residual neuromuscular block based on the threshold of TOFR=0.9. Patients with TOFR<0.9 had a higher incidence and a greater severity of symptoms of muscle weakness than patients with TOFR \geq 0.9. This proven difference between a recovery above or below a TOFR of 0.9, however, still does not imply that a TOFR \geq 0.9 is the final clinically detectable level of adequate recovery.¹⁸

The reason for investigating the benefit of neuromuscular recovery to a TOFR \geq 0.9 is that NMBAs must occupy roughly 75% of the acetylcholine receptors in healthy individuals before any signs of muscle weakness occur.^{10 11} This is also

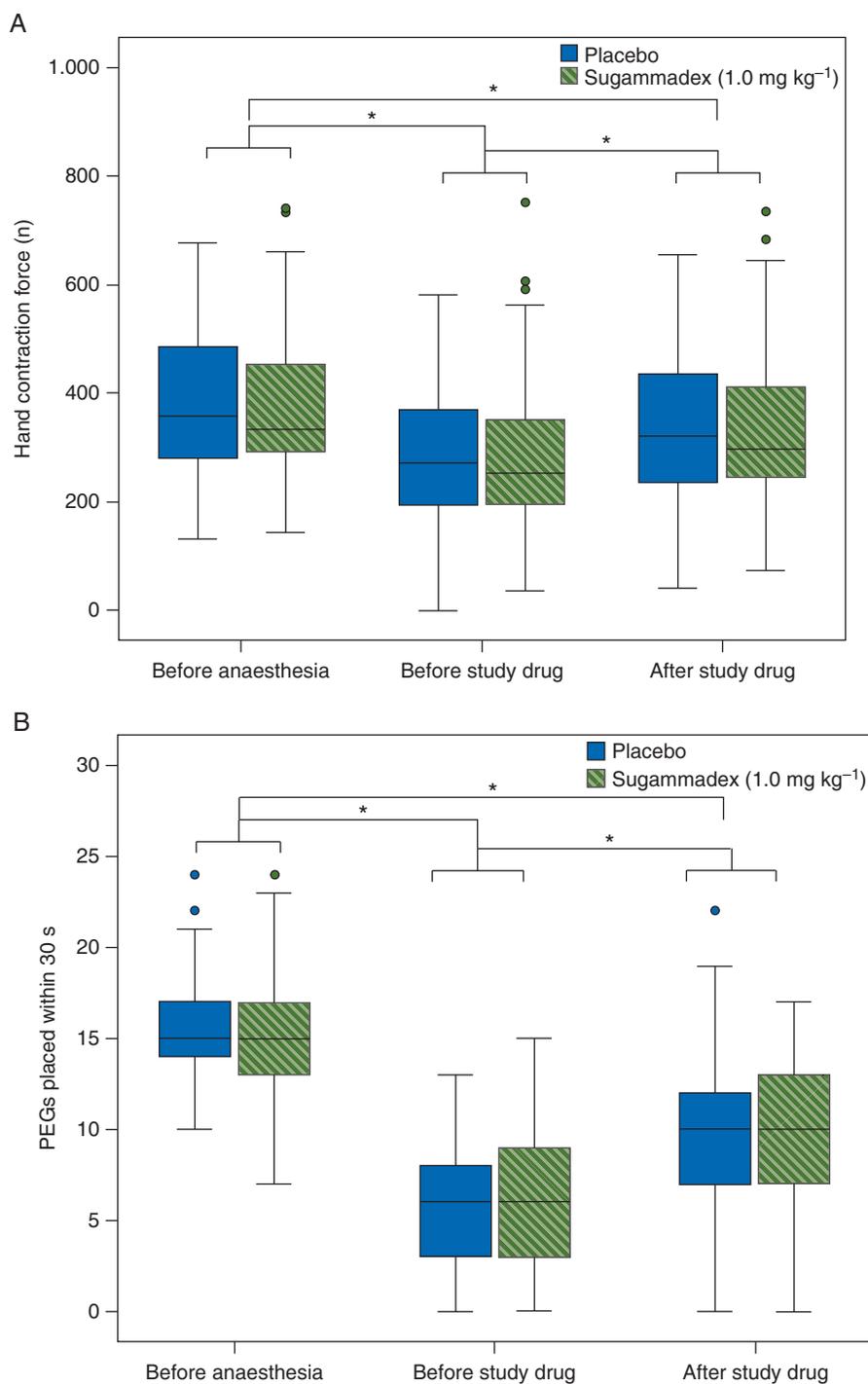


Fig 2 Motor function. Preoperative maximal voluntary force motor skills were evaluated with hand dynamometry and fine motor skills with the Purdue Pegboard Test (before anaesthesia) and before and after application of the study medication in the postanaesthesia care unit. Values are presented as box-and-whisker plots. The first and the third quartile define the length of the box. The median is represented as the line dividing the box. The whiskers represent the highest and the lowest value within the 1.5 times interquartile range, respectively. Values outside the interquartile range are outliers, which are shown as circles. (A) Gross motor function tested with the hand dynamometer. Analysis of variance revealed a significant decrease of gross motor function after anaesthesia compared with preoperative values ($P < 0.05$). After injection of the study drug, gross motor function recovered significantly in both groups, but did not reach the preoperative level. There were no significant differences between treatment groups. (B) Fine motor function tested with the peg board. Analysis of variance revealed a significant impairment of fine motor function after anaesthesia compared with preoperative values ($P < 0.05$). After injection of the study drug, fine motor function improved significantly in both groups, but did not reach the preoperative level. There were no significant differences between treatment groups.

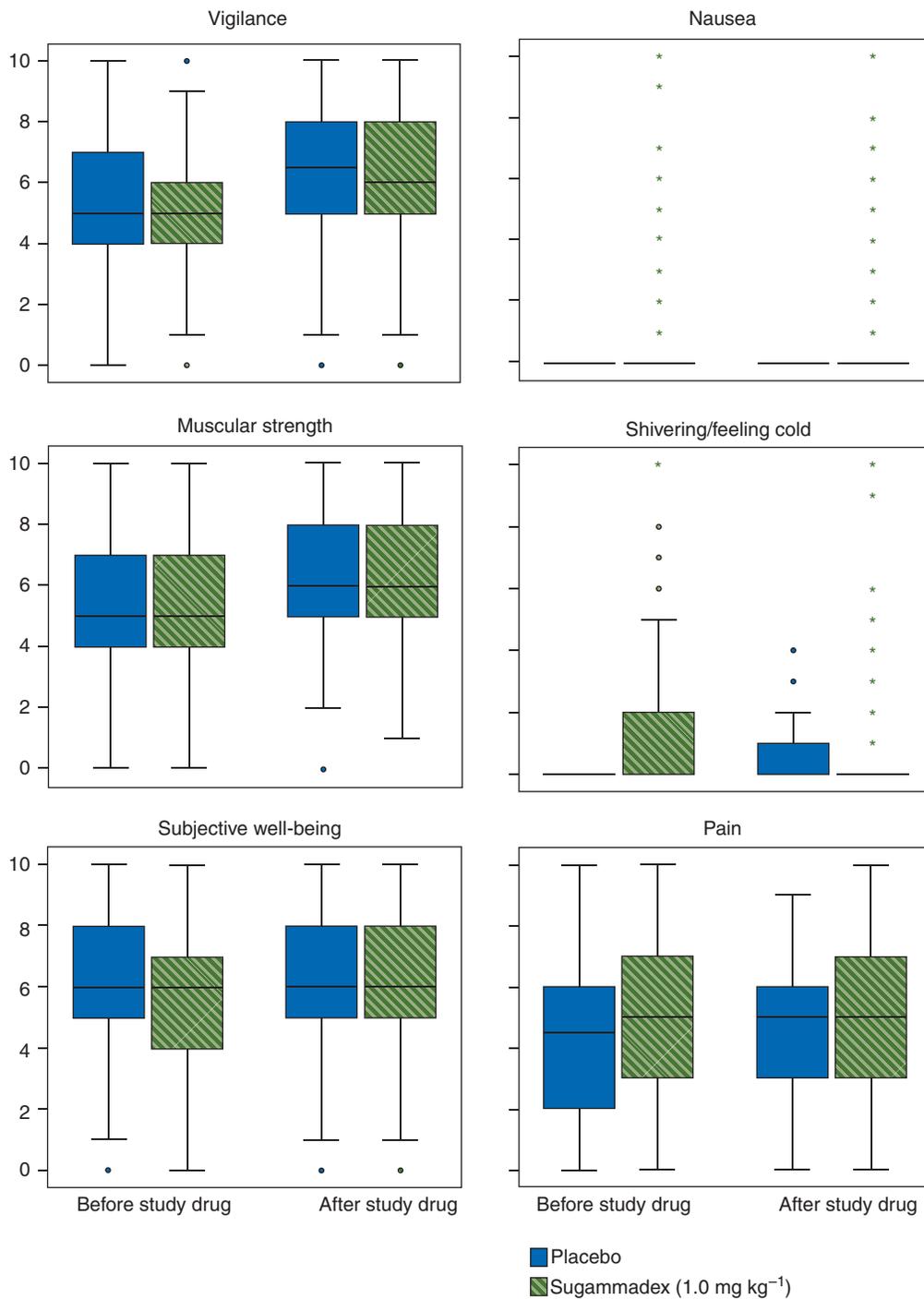


Fig 3 Numerical analogue scales. In the postanesthesia care unit, all patients rated their vigilance, muscular strength, well-being, nausea, feeling cold/shivering, and pain on numerical analogue scales from 0 to 10 before and after application of the study medication. Analysis of variance did not reveal any significant differences in rating of vigilance, muscular strength, nausea, shivering/feeling cold, pain, and well-being over time or between groups.

referred to as the ‘margin of safety’ of the neuromuscular transmission.^{10 11} Unfortunately, the margin of safety differs between skeletal muscle groups, which results in different responsiveness of individual muscles to NMBAs.

Pharyngeal muscles, for example, are very vulnerable to even minimal effects of NMBAs and recover slowly, whereas the diaphragm is more resistant and often the first muscle to recover.^{19–22} Therefore, complete recovery of one specific

Table 2 Quality-of-Recovery Score 40. CI, confidence interval; PACU, postanaesthesia care unit.

	Placebo		Sugammadex (1.0 mg kg ⁻¹)		Placebo vs sugammadex	
	Number	Median (ranges)	Number	Median (ranges)	Median difference (95% CI)	P-value
Emotional state						
Preoperative	150	42 (20–45)	150	42 (21–45)	0 (–1 to 1)	0.819
Discharge from the PACU	146	41 (23–45)	148	41 (25–45)	0 (–1 to 1)	0.988
Postoperative day 1–3	137	43 (25–45)	143	42 (23–45)	0 (0 to 1)	0.245
Physical comfort						
Preoperative	150	52 (24–70)	150	53 (25–55)	0 (–1 to 1)	0.652
Discharge from the PACU	146	53 (32–60)	145	54 (34–60)	0 (–2 to 2)	0.763
Postoperative day 1–3	138	52 (28–55)	143	52 (31–55)	0 (–1 to 1)	0.831
Psychological support						
Preoperative	150	35 (21–35)	149	35 (17–35)	0 (0–0)	0.603
Discharge from the PACU	146	34 (11–35)	147	33 (15–35)	0 (0–0)	0.711
Postoperative day 1–3	138	35 (23–35)	143	35 (19–35)	0 (0–0)	0.041
Physical independence						
Preoperative	150	25 (12–25)	150	25 (6–25)	0 (0–0)	0.590
Discharge from the PACU	145	20 (6–25)	148	19 (7–25)	1 (–1–3)	0.116
Postoperative day 1–3	137	23 (11–25)	143	21 (11–25)	0 (0–1)	0.125
Pain						
Preoperative	150	33 (15–35)	150	33 (7–35)	0 (–1–1)	0.890
Discharge from the PACU	147	30 (20–35)	149	30 (14–35)	0 (–1–1)	0.582
Postoperative day 1–3	138	33 (14–35)	143	31 (18–35)	0 (0–2)	0.151
Global score						
Preoperative	150	185 (121–195)	149	186 (109–195)	0 (–4–3)	0.883
Discharge from the PACU	145	174 (120–200)	144	175 (115–200)	1 (–5–7)	0.573
Postoperative day 1–3	136	189 (115–200)	143	185 (120–200)	2 (–2–6)	0.202

muscle group does not prove complete recovery of all other muscles.

To address this variability in the physiological responsiveness of small and bigger muscles in the present study, we used two muscle function tests, representing maximal voluntary force (hand dynamometry),²³ but also fine motor skills (Purdue Pegboard Test).²⁴ In addition, the QoR-40 questionnaire and other subjective information were obtained to receive an integrated picture of patients' subjective muscle recovery. We did not address pharyngeal muscle function because of the large body of knowledge about these muscles.^{5 25 26}

Gross motor function was tested with hand dynamometry, an objective tool that provides reliable assessment of muscle strength in various neuromuscular diseases and critically ill patients.^{27–29} A deficit in handgrip force is considered as a parameter of functional impairment.²⁷ In our patient cohort, 15 min after extubation at a TOFR \geq 0.9, gross motor function was decreased by 27% and, a further 10 min later, by 12% compared with baseline values. These values are consistent with those found by Alkhazrajy²³ and Kopman.⁹ Alkhazrajy examined patients 1 h after general anaesthesia. The 'no relaxant group' showed a decrease of handgrip strength of 16%. Kopman investigated healthy awake volunteers, whose grip force was tested during infusion of mivacurium. At a TOFR \approx 0.7, there was a decrease of 43%, and at a TOFR \approx 0.9,

a decrease of 17% compared with baseline values. Importantly, in our study, antagonism with sugammadex 1.0 mg kg⁻¹ at TOF \geq 0.9 did not improve maximal voluntary force compared with placebo.

We tested fine motor skills with the Purdue Pegboard Test, which challenges patients' hand function and eye fixation. This test is well established in medical research and employs tasks that resemble activities of daily living.²⁴ A high retest reliability was demonstrated in different study populations varying in age, gender, and health status.³⁰ Fine motor skills are still impaired, even when neuromuscular recovery has reached TOFR \geq 0.9.⁹ Eye muscles, for example, are very sensitive to muscle relaxation, which can lead to diplopia and visual disturbances at TOF \approx 0.9.⁹ We found a significant reduction of fine motor skills 15 min after extubation by 61%, and 10 min later, still by 35% compared with preoperative baseline values in both groups.

Both qualities of muscle function were decreased immediately after anaesthesia, demonstrating the sufficient sensitivity of the tests. Although injection of placebo and sugammadex 1.0 mg kg⁻¹ improved postoperative fine and gross motor function, muscle function did not reach preoperative baseline values. If compared with placebo, encapsulating the remaining rocuronium after spontaneous recovery to TOFR \geq 0.9 with sugammadex 1.0 mg kg⁻¹ did not show a superior effect.

Accordingly, we conclude that the decrease in fine motor skills and maximal voluntary muscle force 15 min after emergence from anaesthesia and after spontaneous recovery to TOFR ≥ 0.9 is more likely to be related to the drugs used for general anaesthesia (e.g. anaesthetic agents, analgesics) than to any residual effect of rocuronium.

The dimensions of the QoR-40 are of clinical interest, as poor quality of recovery in the first days after surgery is related to postoperative complications, longer hospital stay, and impaired quality of life at 3 months after surgery.^{15 31 32} Our results on quality of early postoperative recovery evaluated with the QoR-40 were similar to previously reported data,^{15 31 32} where pain and physical independence were mainly affected shortly after surgery, but recovered on postoperative day 1–3. Importantly, the time course of questionnaire items did not differ with respect to treatment with sugammadex. In addition, patients' rating of vigilance, muscular strength, subjective well-being, nausea, shivering/feeling cold, and pain on numerical analogue scales also revealed no differences between treatment groups.

Our data were generated using electromyography. However, in clinical and experimental settings, acceleromyography is widely used for neuromuscular monitoring. Acceleromyography, however, overestimates neuromuscular recovery. Recommendations to wait for recovery of TOFR ≥ 1.0 using acceleromyography,³³ therefore, are not contradictory to our results.

A challenge of this study was to define the required dose of sugammadex to antagonize a subclinical neuromuscular block at a TOFR ≥ 0.9 . For rocuronium, sugammadex doses ranging from 2 mg kg⁻¹ for antagonism after reappearance of T2,^{34–36} 4 mg kg⁻¹ for antagonism of post tetanic count 1–2,^{37–39} and 16 mg kg⁻¹ for immediate antagonism after injection of 1.2 mg kg⁻¹ rocuronium⁴⁰ are recommended. A TOFR ≥ 0.9 indicates a more advanced neuromuscular recovery; accordingly, less sugammadex should be required in this trial. We decided to use sugammadex 1 mg kg⁻¹ to prove our hypothesis because of the following considerations. Previously, a dose of sugammadex 0.22 mg kg⁻¹ was shown to antagonize a TOFR ≥ 0.5 within 2 min.⁴¹ For complete antagonism, a sugammadex to rocuronium dose ratio of 3.6:1 was required;⁴² therefore, a sugammadex dose of 1.0 mg kg⁻¹ equates to a dose four-fold higher than necessary to antagonize rocuronium at a TOFR = 0.5. At a TOFR ≥ 0.9 , this dose ensures that all remaining rocuronium molecules are encapsulated and that the acetylcholine receptors are vacant. It is important to note that the dose of sugammadex that we used (1.0 mg kg⁻¹) cannot be put in context with any dose recommendation for antagonism of a residual neuromuscular block.

Our study has limitations. We did not evaluate the consequences of sugammadex antagonism at TOFR ≥ 0.9 in patients given drugs known to interfere with acetylcholine receptors, such as calcium channel blockers, antibiotics, or magnesium. As a result of their properties of interacting with the acetylcholine receptors, such drugs may lead to reoccurrence of neuromuscular block even when the TOFR has recovered ≥ 0.9 .^{43 44} Our patients' ability to perform volitional muscle function tests was impaired as a consequence of anaesthesia and surgery. It is possible that the resolution to identify minimal

effects of lingering neuromuscular blocking agents was decreased by the effects of anaesthetics on consciousness.

In summary, our data show that fine motor skills and maximal voluntary contraction force are compromised after surgery and anaesthesia. Antagonizing rocuronium after TOFR ≥ 0.9 with sugammadex 1.0 mg kg⁻¹ does not improve fine motor function, maximal voluntary force, or well-being of patients. Our data support the view that TOFR ≥ 0.9 measured by electromyography indicates sufficient recovery from neuromuscular block.

Authors' contributions

E.B. and M.B. helped design the study, conduct the study, analyse the data, and write the manuscript. S.J.S. and H.F. helped design the study, analyse the data, and write the manuscript. Y.C.L. helped conduct the study and analyse the data. C.G.F. helped analyse the data and write the manuscript. T.B. helped conduct the study. M.E. helped write the manuscript.

Declaration of interest

E.B., Y.C.L. and T.B.: none declared. S.S. holds stocks of the following companies in the health-care sector in small amounts: Bayer AG, Siemens AG, GE Healthcare, Merck & Co. Inc., Rhoen-Klinikum AG, and Fresenius SE; however, these holdings do not influence any decisions regarding the study. C.G.F. has received honoraria and a travel grant from MSD Sharpe & Dohme. M.E.: funded research, Merck & Co. Inc., ResMed, Massimo. H.F. has received honoraria and travel grants from the following companies: MSD Sharp & Dohme, Essex, Baxter, Care Fusion, and GE Healthcare. M.B. has received honoraria and travel grants from MSD Sharp & Dohme and GlaxoSmithKline.

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