

RESPIRATION AND THE AIRWAY

Rapid sequence induction and intubation with rocuronium–sugammadex compared with succinylcholine: a randomized trial

M. K. Sørensen^{1*}, C. Bretlau², M. R. Gätke², A. M. Sørensen¹ and L. S. Rasmussen¹

¹ Department of Anaesthesia, Centre of Head and Orthopaedics, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark

² Department of Anaesthesiology, Copenhagen University Hospital, Herlev Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark

* Corresponding author. E-mail: martin@kryspin.dk

Editor's key points

- Succinylcholine is recommended for rapid sequence induction because of its quick onset and offset of actions.
- The offset of action of succinylcholine was compared with that of the rocuronium–sugammadex sequence.
- Sixty-one patients were studied in a randomized and blinded manner.
- Importantly, the rocuronium–sugammadex sequence had significantly quicker offset of neuromuscular blocking agent effect compared with succinylcholine.

Background. An unanticipated difficult airway may arise during rapid sequence induction and intubation (RSII). The aim of the trial was to assess how rapidly spontaneous ventilation could be re-established after RSII. We hypothesized that the time period from tracheal intubation to spontaneous ventilation would be shorter with rocuronium–sugammadex than with succinylcholine.

Methods. This randomized and patient- and observer-blinded trial was approved by the regional Ethics Committee and the Danish Medicines Agency. We included elective surgical patients undergoing general anaesthesia for RSII using alfentanil ($10 \mu\text{g kg}^{-1}$), propofol (2 mg kg^{-1}), and either succinylcholine (1 mg kg^{-1}) or rocuronium (1 mg kg^{-1}). Sugammadex (16 mg kg^{-1}) was given in the rocuronium group after tracheal intubation. The primary endpoint was the time from correct placement of the tracheal tube to spontaneous ventilation, defined as a respiratory rate of more than 8 bpm and a tidal volume of at least 3 ml kg^{-1} for 30 s.

Results. We included 61 patients; of whom, 55 were evaluated for the primary endpoint. The median time from tracheal intubation to spontaneous ventilation was 406 s with succinylcholine and 216 s with rocuronium–sugammadex ($P = 0.002$). The median time from tracheal intubation to 90% recovery of the first twitch in train-of-four (T_1 90%) was 518 s with succinylcholine and 168 s with rocuronium–sugammadex ($P < 0.0001$). Intubation conditions and time to tracheal intubation were not significantly different.

Conclusions. RSII with rocuronium followed by reversal with sugammadex allowed earlier re-establishment of spontaneous ventilation than with succinylcholine.

Keywords: anaesthesia, intravenous; intubation, intratracheal; neuromuscular block

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Rapid sequence induction and intubation (RSII) is performed when there is an increased risk of pulmonary aspiration of gastric contents. RSII consists of the following: optimal positioning of the patient, pre-oxygenation, injection of an opioid and a hypnotic i.v., injection of a fast-acting neuromuscular blocking agent (NMBA), cricoid pressure, and tracheal intubation.^{1–3}

Succinylcholine has been for a long time the NMBA of choice for RSII, because of quick onset along with excellent intubation conditions.⁴ However, it has been desirable to identify an alternative to succinylcholine because of its side-effects and the risk of delayed recovery of neuromuscular function. Spontaneous recovery of a succinylcholine-induced

neuromuscular block may take too long to avoid desaturation in a 'cannot intubate, cannot ventilate' situation. In some patients, the hydrolysis of succinylcholine may be severely impaired as a result of genetic or acquired low cholinesterase activity.^{5, 6}

As an alternative to succinylcholine, the non-depolarizing NMBA rocuronium can be used for RSII.⁷ The onset time of rocuronium 1 mg kg^{-1} is around 60 s.⁷ Its duration of action is, however, 122 (33) min [from injection to recovery of first twitch of train-of-four (TOF) to 75% of baseline] for a single bolus dose of 0.9 mg kg^{-1} .⁸ A new antagonist, sugammadex, binds the rocuronium molecules in a 1:1 ratio⁹ without having an effect on the plasma cholinesterase

or on any receptor system in the human body.^{10–14} Even profound neuromuscular block with rocuronium can be quickly antagonized with sugammadex.¹⁵

The aim of this trial was to assess the time from verified correct tracheal tube placement after RSII until regular and spontaneous ventilation was re-established. In addition, we assessed the intubation conditions and the duration of action of NMBA using acceleromyography. We hypothesized that the time from correct tracheal tube placement to spontaneous ventilation would be shorter with rocuronium followed by sugammadex, than with succinylcholine.

Methods

The Danish Medicines Agency and the Regional Ethics Committee approved the trial, which adhered to the standards of the International Conference on Harmonization Good Clinical Practice. The trial (NCT00953550) was registered at ClinicalTrials.gov before inclusion of the first patient. Written informed consent was obtained from all patients participating in this two-centre trial.

The patients were eligible if they were between 18 and 60 yr of age and undergoing RSII. We excluded patients with known allergic reactions to propofol, alfentanil, succinylcholine, rocuronium, or sugammadex, patients undergoing emergency surgery (operation scheduled <24 h), a BMI of above 35 kg m⁻², severe renal disease defined by S-creatinine >0.200 mmol litre⁻¹, New York Heart Association Functional Classification above II, a Canadian Cardiovascular Society Functional Classification of Angina above II, potassium >5.0 mmol litre⁻¹, untreated glaucoma, neuromuscular disease, a known disposition for malignant hyperthermia, female patients of child-bearing potential, and breastfeeding women.

Trial protocol

Patients were randomized 1:1 according to a computer-generated list (GraphPad QuickCalcs, GraphPad Software®, Inc., La Jolla, CA, USA). A total of 65 sealed and opaque envelopes were prepared for the trial by staff with no other involvement in it. The Regional Ethics Committee approved inclusion until 55 assessable patients for the primary endpoint (time to re-establishment of spontaneous ventilation) were collected, with a maximum of 65 included patients. Thus, enrolment was planned to be stopped when reaching 55 patients where the primary endpoint was assessed. The intervention allocation list was securely stored without access for the investigators, along with an allocation key.

The patients were randomized to receive either succinylcholine (1 mg kg⁻¹) or rocuronium (1 mg kg⁻¹) followed by sugammadex (16 mg kg⁻¹). The investigation was timed in a logged software program TOF-Watch® SX Monitor (Version 2.5 INT 2007, Organon, The Netherlands) from the start of pre-oxygenation.

The patients were monitored with a three-lead ECG, non-invasive arterial pressure measurement, and pulse oximetry. Hypnotic depth was assessed using BIS VISTA®

(Aspect Medical Systems, Inc., Norwood, MA, USA). Neuromuscular monitoring was performed with acceleromyography using the TOF-Watch SX® (MSD, Glostrup, Denmark) connected to a computer in accordance with 'Good Clinical Research Practice in Pharmacodynamic Studies of Neuromuscular Blocking Agents II'.¹⁶ The study arm was immobilized and the skin was cleansed before two paediatric electrodes (Cleartrode™, Conmed, Utica, NY, USA) were placed 3–6 cm apart over the ulnar nerve near the wrist. With Hand Adaptor® (MSD), a small preload was placed on the thumb for monitoring acceleration. After induction of anaesthesia, supramaximal stimulation was ensured using an automated calibration (CAL2). Every 15 s, a TOF pattern was delivered. The neuromuscular monitoring was performed until recovery of twitch responses in TOF had reached a plateau that was maintained for at least 2 min. A re-calibration was performed after ensuring that the first twitch (T_1) in TOF had reached the plateau. The plateau was defined as: little or no further increase in T_1 -amplitude. The re-calibration was followed by TOF stimulation of at least three measurements with <5% variation in T_1 values. Measurements were discarded if they did not acquire this stable plateau. We also discarded measurements that did not reach <95% depression in T_1 after injection of succinylcholine. The palmar skin temperature was kept above 32°C and the central temperature was kept above 35°C.

The RSII procedure was conducted as described below (Fig. 1). After pre-oxygenation, alfentanil (10 µg kg⁻¹) and propofol (2 mg kg⁻¹) were given. Thereafter, propofol infusion was started. This was followed by calibration of TOF-Watch® SX and TOF nerve stimulation. Either succinylcholine (1 mg kg⁻¹) or rocuronium (1 mg kg⁻¹) was then given, followed by cricoid pressure and tracheal intubation. Upon verification of correct tracheal tube placement, sugammadex (16 mg kg⁻¹) was given to patients in the rocuronium group. Correct tracheal tube placement was confirmed by auscultation of the chest and epigastrium, visualization of thoracic movement, and the appearance of a typical capnography waveform.

Hypnotic level was kept in bispectral index (BIS) target range of 4.5–5.5 with a propofol infusion, starting at 3 mg kg⁻¹ h⁻¹. Additional small bolus doses of propofol were given as required to maintain BIS within the target range. End-tidal P_{CO_2} was targeted to just below 7.0 kPa with gentle ventilation at low frequency to avoid excessive hypercapnia and also desaturation.

The patient and the investigator evaluating the primary endpoint were blinded to the investigated drug. The investigator (in all cases, an anaesthesiology consultant) was blinded by only being allowed to enter the operating theatre after correct placement of the tracheal tube had been verified. The personnel doing the statistical evaluation were blinded to the allocation by being presented the allocation list without the key. After statistical evaluation, an abstract and a conclusion were written in two copies, one for each allocation possibility. After completion of the abstracts, the allocation key was revealed. The staff in the

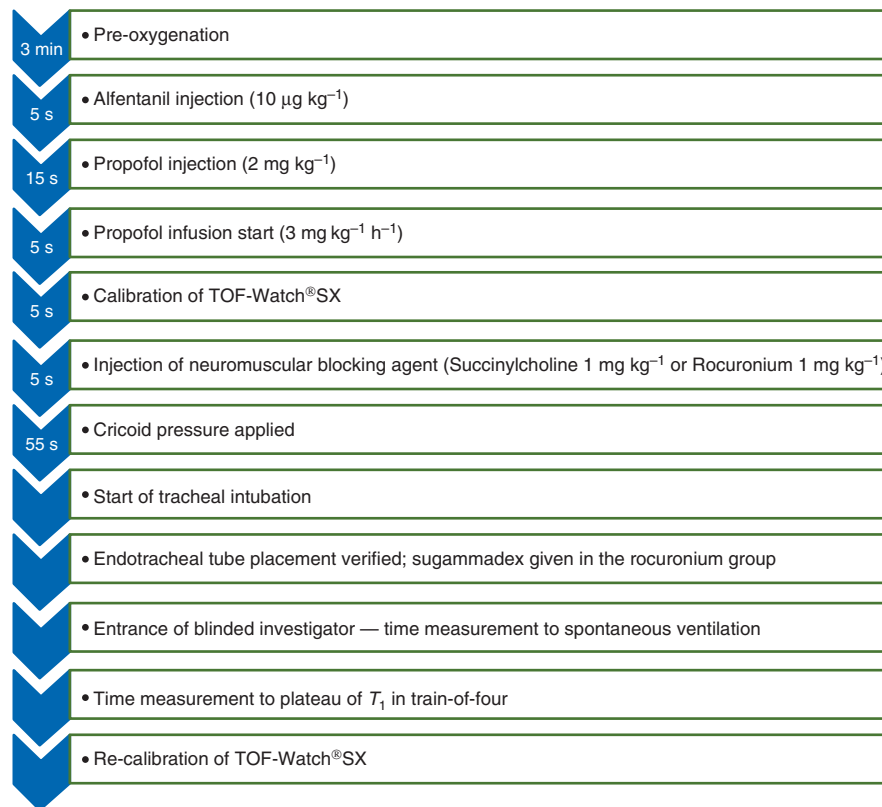


Fig 1 Flow diagram of RSII.

operating theatre could not be blinded. Neuromuscular data from 17 patients randomized to the succinylcholine group had their butyrylcholinesterase genotype analysed along with the enzyme activity for another study.¹⁷

The primary outcome variable was the time from correct placement of the tracheal tube (confirmed by auscultation after intubation) until re-establishment of spontaneous ventilation, defined as a respiratory rate of 8 bpm, a tidal volume above 3 ml kg^{-1} , and an arterial oxygen saturation of above 90%, for 30 s. Tidal volume was measured using the built-in spirometer in the anaesthetic machine.

Secondary outcomes were duration of action of NMBA measured with TOF-Watch SX[®] from start of injection of the NMBA to recovery of T_1 in TOF to above 90% (T_1 90%) and from tracheal intubation to recovery of T_1 to 90%. The T_1 90% value was calculated as 90% of the T_1 -max value, which was the second of three consecutive T_1 values in the TOF, after T_1 had reached a plateau. The T_1 -max value evaluation was done independently by two investigators; in the case of discrepancy, a third investigator judged what observation to report or whether the measurement should be discarded. Intubation difficulty scale (IDS)¹⁸ and intubation conditions¹⁶ were also assessed. Adverse events were reported by a non-blinded investigator, and the possibility of awareness was evaluated after operation after discharge from the postoperative care unit and again within 24 h after surgery by a modified

Brice interview for all randomized patients^{19 20} along with an assessment of generalized muscle ache.

Statistical analysis

The sample size calculation was based on a pilot protocol with 10 included patients. The data from the pilot indicated that a presumed standard deviation of 80 s would be realistic for return of spontaneous ventilation. A difference of 60 s in time to spontaneous ventilation was considered to be clinically relevant. Based on this, we calculated a sample size of 55 patients for the primary endpoint, assuming a power of 0.80 at the 5% significance level.

Patient characteristic data and continuous variables were presented as median values (inter-quartile range). The primary endpoint and other continuous variables were compared using the Mann-Whitney rank-sum test. Proportions were compared using a χ^2 test or Fisher's exact test. $P < 0.05$ was considered statistically significant. We made an 'intention to treat' analysis on all randomized patients who received an intervention using SAS[®] statistical software version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Between September 2009 and January 2011, we enrolled 61 patients at two centres (Fig. 2). A total of 55 patients were

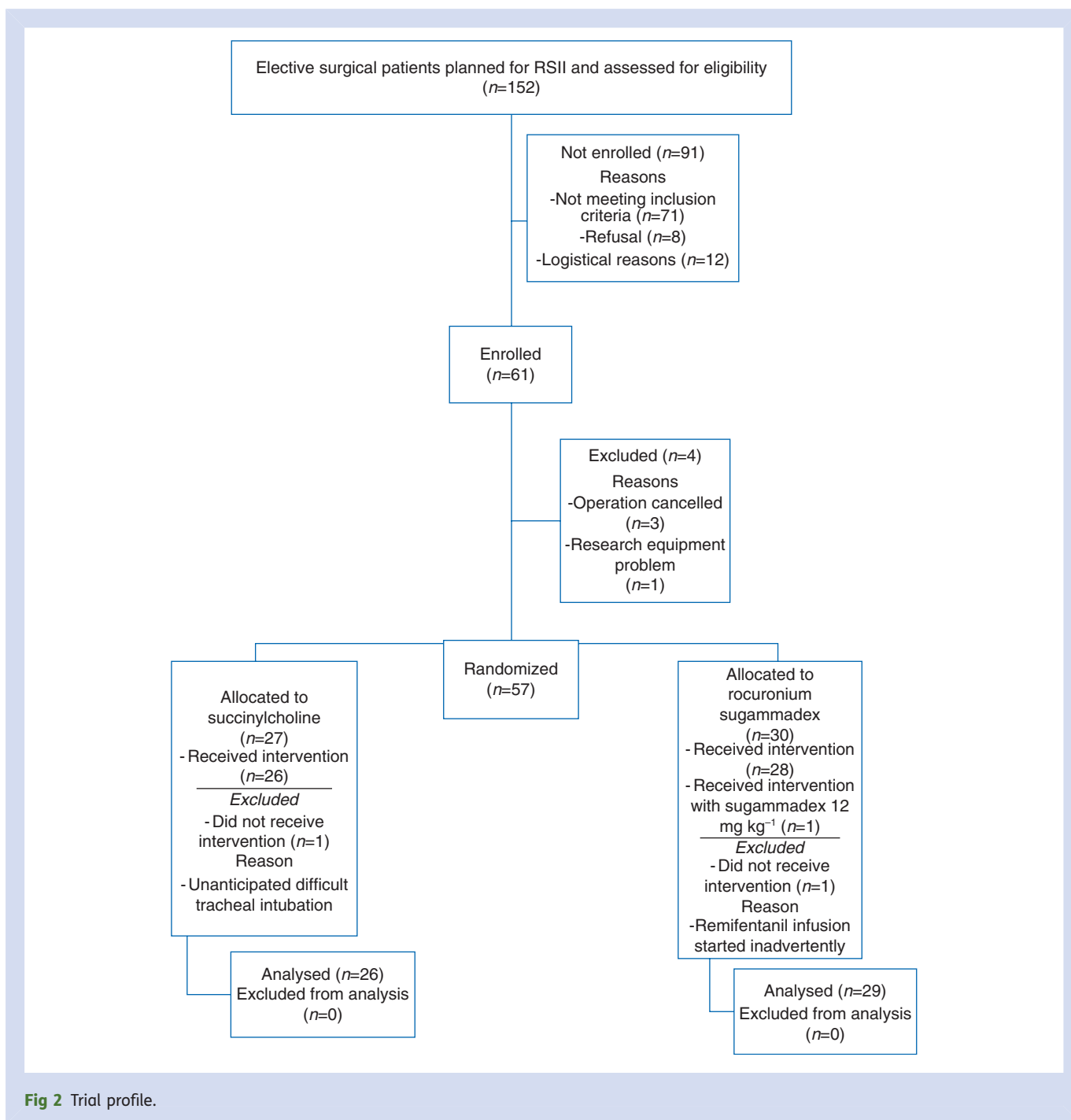


Fig 2 Trial profile.

evaluated in the ‘intention to treat’ analysis. Patient characteristic data are given in Table 1. All patients had an increased risk of aspiration. Two patients were excluded after randomization because of a protocol violation: one due to an unanticipated difficult airway, which resulted in the use of a NMBA out of protocol to re-paralyse the patient, and in the other, a remifentanyl infusion was started inadvertently.

The median time from intubation to spontaneous ventilation was 406 s with succinylcholine and 216 s with rocuronium-sugammadex ($P=0.002$, Table 2). The median time

from tracheal intubation to T_1 90% was 518 s with succinylcholine and 168 s with rocuronium-sugammadex ($P<0.0001$, Table 2). The median time from injection of NMBA to recovery of T_1 90% was 719 s with succinylcholine and 282 s with rocuronium-sugammadex ($P<0.0001$, Table 2). Eleven patients were not included in the analysis of acceleromyography measurements due to a calibration error (Table 2). Intubation conditions and time to tracheal intubation were not significantly different.

In the succinylcholine group, we observed: desaturation to 80% ($n=1$), bronchospasm ($n=1$), severe generalized

Table 1 Characteristics for elective surgical patients given either succinylcholine or rocuronium–sugammadex for RSII. Values are median (inter-quartile range). ASA PS class, American Society of Anesthesiologists physical status class; BMI, body mass index

	Patients given succinylcholine (n=26)	Patients given rocuronium and sugammadex (n=29)
Age (yr)	49 (46–53)	53 (48–56)
Gender (male/female)	6/20	11/18
Weight (kg)	76 (68–80)	79 (72–85)
BMI (kg m ⁻²)	26.8 (23.7–28.9)	25.5 (24.1–27.7)
ASA PS class		
I	5 (19%)	9 (31%)
II	19 (73%)	18 (62%)
III	2 (8%)	2 (7%)
Mallampati score		
1	15 (57%)	18 (62%)
2	9 (35%)	9 (31%)
3	2 (8%)	2 (7%)
Neck movement		
≤90°	0 (0%)	0 (0%)
>90°	26 (100%)	29 (100%)
Ability to prognath		
Yes	26 (100%)	27 (93%)
No	0 (0%)	2 (7%)
Indication for RSII		
Gastrooesophageal reflux disease	20 (76%)	21 (73%)
Hiatus hernia	1 (4%)	7 (24%)
Nausea or vomiting within 24 h of surgery	3 (12%)	0 (0%)
Previous gastric bypass	1 (4%)	1 (3%)
Oesophageal diverticulum	1 (4%)	0 (0%)
Type of surgery		
Abdominal	2 (8%)	2 (7%)
Breast	3 (12%)	2 (7%)
Ear–nose–throat	4 (15%)	3 (10%)
Gynaecological	7 (27%)	4 (14%)
Orthopaedic	4 (15%)	6 (21%)
Plastic	4 (15%)	8 (27%)
Urological	2 (8%)	4 (14%)
Co-morbidity		
Hypertension	8 (31%)	3 (10%)
Other cardiovascular disease	1 (4%)	2 (7%)
Pulmonary disease	3 (12%)	3 (10%)
Excessive alcohol consumption, >48 g per day	0 (0%)	2 (7%)
Other	2 (8%)	4 (14%)

muscle ache ($n=2$), and unanticipated difficult tracheal intubation, defined by an IDS value above 5 ($n=3$; one patient excluded after randomization). Adverse events of importance during induction in the rocuronium–sugammadex group were: urticaria in the surgical zone after chlorhexidine application ($n=1$) and tachycardia to above 100 bpm ($n=3$). Recall was not suspected in any of the patients within 24 h after operation. No patient has contacted an investigator describing memories or events suggestive of awareness during induction or intraoperatively.

Discussion

We found that spontaneous ventilation was re-established significantly earlier using rocuronium–sugammadex instead of succinylcholine for rapid sequence induction. The difference in the median values was around 3 min, and an even greater difference was found in the recovery of neuromuscular function. The trial was conducted on two well-matched groups of patients undergoing RSII, which was performed in a standardized regimen. The primary endpoint was evaluated by a blinded investigator and the tidal volume of 3 ml kg⁻¹

Table 2 Tracheal intubation conditions, time to reappearance of a spontaneous ventilation, and recovery of neuromuscular function in surgical patients randomized to either succinylcholine or rocuronium–sugammadex for RSI. Values are median (inter-quartile range), n =number of patients. The T_1 -max value was the second value of three consecutive T_1 values in the TOF, after T_1 had reached a plateau with little or no further increase in its amplitude. The T_1 90% value was calculated as 90% of the T_1 -max value

	Succinylcholine (1 mg kg ⁻¹) (n=26)	Rocuronium (1 mg kg ⁻¹) Sugammadex (16 mg kg ⁻¹) (n=29)	P-value
Time from start of procedure to tracheal intubation (s)	330 (313–351)	324 (312–343)	0.45
Intubation conditions			0.13
Excellent	20 (76%)	27 (93%)	
Good	6 (24%)	2 (7%)	
Poor	0 (0%)	0 (0%)	
Intubation difficulty score			0.23
≤5	24 (92%)	28 (100%)	
>5	2 (8%)	0 (0%)	
Time from tracheal intubation to spontaneous ventilation (s)	406 (313–507)	216 (132–425)	0.002
Time from tracheal intubation to T_1 90% (s)	518 (451–671) (n=17)	168 (122–201) (n=27)	<0.0001
Time from injection of NMBA to T_1 90% (s)	719 (575–787) (n=17)	282 (242–319) (n=27)	<0.0001

and respiratory rate of 8 bpm kept for 30 s must be considered conservative when concluding the presence of spontaneous ventilation after RSI. We studied patients with increased risk of aspiration and we assessed recovery of spontaneous ventilation, which we consider as a more clinically important endpoint than evaluating recovery of neuromuscular function alone.¹⁵

We included only elective patients. This was done for practical and research ethical reasons since it would be difficult to strictly standardize the anaesthetic procedure in emergency patients who could have compromised haemodynamic status and fluid deficits necessitating a reduction in the propofol and alfentanil doses. Patients with significant heart disease were excluded, and a reduction in the induction dosages would be needed in some of these patients as well. Our findings are not applicable in obese patients, because the intubation dose of rocuronium should not be 1 mg kg⁻¹ according to total body weight.²¹ RSI in elderly patients would have to be based on different doses as propofol especially needs to be given in a reduced dose.^{22 23} A propofol infusion was given after intubation to avoid awareness. This may have prolonged the time to spontaneous ventilation, but we do not suspect that it has caused a difference between the two groups. The tracheal tube kept the airway open, and even little diaphragmatic movement can create airflow in this situation because the diaphragm is relatively resistant to NMBAs.²⁴ This limitation is known to us, but due to ethical considerations, it would not have been possible to leave these research patients in apnoea and *not* to intubate the trachea because of the risk of aspiration. Another limitation of the study was that onset of spontaneous ventilation could be influenced by even gentle ventilation as this may lower the respiratory drive. The observer was effectively blinded, but onset of spontaneous ventilation was the primary endpoint. Still, we consider this approach

appropriate in this clinical trial to avoid desaturation and excessive hypercapnia. In a study aimed at investigating reversal of profound neuromuscular block, when comparing succinylcholine 1.0 mg kg⁻¹ with rocuronium 1.2 mg kg⁻¹ and sugammadex 16 mg kg⁻¹, Lee and colleagues¹⁵ demonstrated a recovery to T_1 90% in 10.9 min (mean value) from the start of injection of succinylcholine. This is in accordance with our finding of 12.0 min (median value). The automated calibration (CAL2) of the TOF-Watch® SX was not successful in all patients in our study due to a narrow time frame in which it had to succeed between onset of the hypnotic and of NMBA. If calibration was obstructed or the equipment was defective, this was not known until the algorithm of the procedure was running. We compensated for these errors by re-calibrating the equipment after full recovery of the neuromuscular block in all patients. This was done to verify that the true plateau in the T_1 values was in fact reached.

In the rocuronium group, intubation conditions tended to be better and a lower IDS was observed. This tendency is in contradiction with the conclusion of a systematic Cochrane review reporting succinylcholine to be superior to rocuronium (all doses) in creating optimal intubation conditions.⁴ The reason for this discrepancy could be that we used 1 mg kg⁻¹ rocuronium and that the timing of NMBA administration in our study favours rocuronium as the intubation attempt was done as late as 60 s after the drug had been given. The choice of using 1 mg kg⁻¹ rocuronium was based on the recommendation by the Scandinavian Society of Anaesthesiology and Intensive Care Medicine² and it reflects our practice. All patients received 2 mg kg⁻¹ propofol, which most likely improved intubation conditions when compared with a smaller dose or a different hypnotic. An advantage of using rocuronium is the fact that intubation conditions will be favourable until reversal with sugammadex is initiated.

The most serious adverse effects of succinylcholine are bradycardia, asystole, elevation of the plasma potassium concentration, and malignant hyperthermia.²⁵ Other adverse effects include muscle ache. Sugammadex has a low incidence of adverse effects and the profile of the adverse events has so far not been serious.^{26 27}

Unassisted spontaneous ventilation in patients administered succinylcholine may not occur sufficiently soon after failed intubation to avoid desaturation.⁵ The genotype of the butyrylcholinesterase is known to be of importance for the ability to metabolize succinylcholine.⁶ This might explain the variability in time to recover from succinylcholine-induced block. Recent studies have shown that succinylcholine was associated with a more rapid desaturation than rocuronium during RSII.^{28 29} Patients with a BMI of 25–30 kg m⁻² had a 46 s difference in time to desaturation to 92% between succinylcholine and rocuronium.²⁸ A study in patients with an average BMI of ~24 kg m⁻² showed similar results.²⁹ The reason is probably the skeletal muscle fasciculation that increases oxygen consumption induced by the depolarizing effect of succinylcholine,³⁰ whereas rocuronium does not have this effect. Thus, RSII using rocuronium seems to be associated with later onset of desaturation and better intubation conditions due to the prolonged duration of action. Desaturation to 95% has been reported ~7 min after injection of rocuronium 1 mg kg⁻¹ in patients carefully pre-oxygenated²⁷ and sugammadex should therefore be expected to allow re-establishment of spontaneous ventilation before profound hypoxemia occurs. In our study, however, sugammadex was given much sooner than in a real clinical situation where several tracheal intubation attempts will usually be done before a decision to wake the patient. Our study did not include this delay, but it is difficult to see how a research protocol could reflect an emergency situation in a more realistic way.

The price of an escape bolus of sugammadex (16 mg kg⁻¹) for a 75 kg patient with intense neuromuscular block is approximately €760 in Denmark. It is an expensive drug, but an escape dose of sugammadex is needed in only very few patients. If the possible complications of prolonged apnoea in a high-risk patient during induction can be avoided, then the cost of the drug is not important.³¹ Unanticipated prolonged apnoea will make most anaesthesiologists to begin forced bag-valve ventilation at some point to avoid desaturation, although this increases the risk of aspiration considerably, especially in patients already categorized as being at high risk of aspiration.

The safety of RSII can probably be enhanced when using rocuronium if sugammadex is available as an escape drug. We recommend a strict RSII protocol, where the escape sugammadex dose is calculated, the drug is readily available in the operating theatre, although not drawn up, and syringes are prepared for emergency draw up, before initiation of RSII.³² In conclusion, RSII with rocuronium followed by sugammadex allowed earlier re-establishment of spontaneous ventilation than with succinylcholine.

Declaration of interest

None declared.

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