Earlier and lower dose administration of sugammadex
A randomised placebo-controlled trial

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BACKGROUND Sugammadex allows for rapid reversal of muscle relaxation after the use of rocuronium or vecuronium. The lowest recommended dose is 2 mg kg\(^{-1}\) intravenously when there are two twitches during the train-of-four stimulation.

OBJECTIVE To study the efficacy and risks of a lower dose of sugammadex administered earlier.

DESIGN Monocentric randomised controlled double-blind study.

SETTING Academic hospital.

PATIENTS Eighty patients were enrolled and randomised in 8 groups of 10 patients, 56 were finally evaluated.

INTERVENTIONS Patients were distributed in two clusters constituting four groups each. In the first cluster, injections were administered after the return of one twitch with the train-of-four (TOF1). In the second cluster, injections were delivered after the return of two twitches with the TOF (TOF2). We created four groups in each cluster for different dosages: placebo, 0.5, 1 or 2 mg kg\(^{-1}\).

MAIN OUTCOME MEASURES Time between the injection of sugammadex and full recovery (TOF ratio > 0.9) that is expressed in minutes.

RESULTS Fifty-six successive patients were assessed between February and August 2018. The difference to TOF greater than 0.9 was not statistically significant between groups with the same dose administered at different times (\(F\) value = 0.001, \(P\) value = 0.975). There was a significant difference between groups with a different dosage administered at the same time (\(F\) ratio = 28.34; \(P\) value < 0.0001). Concerning the time to TOF greater than 0.9 from the time point of TOF1, the timing of the dosages were statistically significant using log rank test (\(P\) < 0.0001). No patient presented a re paralysis.

CONCLUSION No difference between injecting sugammadex at TOF1 or TOF2 was found regarding time to full recovery. Difference regarding sugammadex quantity was found and compatible with other studies.


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Introduction

The introduction of neuromuscular blocking agents (NMBA) in the 1940s was a big step in anaesthesia to improve safety during orotracheal intubation.\(^1\)

Recently, antagonist molecules have been discovered that actively cancel out NMBA effects. Neostigmine was the first drug to be used as a NMBA reversal agent. In 2008, Schering-Plough Corporate \(^3\) launched on the market sugammadex (Bridion \(^8\)) as a rocuronium and vecuronium-binding drug. The current manufacturer, Merck Sharp and Dohme \(^\text{®}\) (MSD), recommends three dosages depending on the depth of the neuromuscular blockade needed: 16 mg kg\(^{-1}\) if there is a complete and deep muscle relaxation, 4 mg kg\(^{-1}\) if the patient presents a complete but not deep muscle relaxation and 2 mg kg\(^{-1}\) for end of muscle relaxation.\(^2\)

However, economic problems have appeared and operating room occupancy time has become an important issue, as well as the cost of surgery. The price of a
200 mg vial of sugammadex is about 70 euros in Europe and is not reimbursed by government health systems in most countries. It is of paramount importance to optimise the operating room occupancy time as much as possible with the lowest possible cost for the patient.3,4

Regarding these components at the end of surgery, three situations may arise: patient totally paralysed, partially paralysed patient or patient totally unparalysed (decurared). The anaesthetist in charge can provide four answers: immediate injection of a high dose of sugammadex, wait for partial reversal before injecting sugammadex, wait for spontaneous reversal or wake up the patient.

The objective of this study is to optimise rocuronium or vecuronium reversal using sugammadex while keeping in mind the economic constraint: what is the minimal dose to inject and when to inject it?

Materials and methods

Design

We conducted a randomised, double-blind, parallel group study of placebo with three different sugammadex-dosing schemes, in an academic hospital in Belgium from February to August 2018.

Patients were distributed in two clusters constituting four groups each. In the first cluster, injections were administered after one twitch was visible with the train-of-four (TOF1). In the second cluster, injections were delivered when two twitches were visible on the train-of-four (TOF2).

We created four groups in each cluster with different dosages: placebo, 0.5, 1 or 2 mg kg\(^{-1}\) of sugammadex.

Ethical approval for this study (Ethical Committee No. P2018/115) was provided by the Ethical Committee of Erasme Hospital, Anderlecht, Belgium (Chairperson Professor J-M BOEYNAEMS) on 29 March 2018. The trial was registered at www.clinicaltrials.gov with the ID: ‘BRIDION_ERASME’, and at EudraCT with the reference 2017-005074-19. All the patients had to consent to free and informed participation in writing.

Population

Patients over 18 years old with a body mass index (BMI) less than 30 mg kg\(^{-2}\), and undergoing ear, nose, and throat elective surgery with an expected duration of surgery of more than 4 h were included.

The exclusion criteria were patients under 18 years old, patients refusing to sign the consent form, patients included in another trial within the last 3 months, pregnant or nursing patients, patients with a history of allergy to sugammadex, patients with known neuromuscular disease, and patients with renal or hepatic impairment.

Endpoints

The primary endpoint was the time between the injection of the sugammadex (at TOF1 or TOF2) and a TOF ratio greater than 90% (TOFR > 0.9).

The secondary endpoints were the recovery time to a TOFR greater than 0.9 after TOF1, the percentage incidence of a TOFR less than 0.7 after total recovery, the time spent in the recovery room after surgery, the occurrence of an episode of oxygen desaturation less than 92% (SpO\(_2\)) in the immediate postoperative period and oxygen administration time in the recovery room.

Drug preparation

Two syringes were prepared for each patient. The former was administered at TOF1 and the latter at TOF2. The syringes contained either sugammadex or 0.9% sodium chloride and were standardised (same type of syringe, same volume of liquid) and, to be sure of the double-blind procedure, a label was added around all the syringes to mask the solution.

Anaesthesia protocol

All the patients benefited from the same anaesthesia protocol according to the hospital guidelines.

Patients were monitored with a Draeger MS40 system and a Dräger Zeus \(^{\text{R}}\) ventilator. Cardiac monitoring was done by a 3-lead system, SpO\(_2\) was registered continuously, and blood pressure was measured every 5 min.

Induction followed a sequence: lidocaine 40 mg, sufentanil 10 \(\mu\)g, propofol 2 mg kg\(^{-1}\), then rocuronium 0.6 mg kg\(^{-1}\), and dexamethasone 8 mg. During the surgery, patients received 5 \(\mu\)g of sufentanil every hour. The TOF scan was tested for reference measurements after propofol infusion and before rocuronium injection. Orotracheal intubation was done after TOF-scan control with TOF count = 0/4 for more than 40 s. After the intubating dose of 0.6 mg kg\(^{-1}\), no further rocuronium was administered, and anaesthesia was maintained with Sevoflurane (Minimum Alveolar Concentration 1.5%) in an air/oxygen mixture (70/30) before and after the sugammadex was administered.

Hardware

TOFScan from IDMED was used. The patient’s arms were placed at a 90° angle from the body, on a hard surface, with the wrist and hand freely visible, so the thumb was not constrained in any way. A reference measurement was performed before the start of the study protocol to test the patient’s impedances and that the set-up was stable with no arm or wrist movement. The measurement was done every 20 s during the entire duration of surgery.

Statistics

Tests

Continuous variables were expressed using the mean ± SD or median [range]. The means were compared with a two-way ANOVA test. Categorical values were expressed using an absolute number and a percentage. All the variables were compared between different groups with
a post hoc Tukey Test. A time to event analysis was undertaken using log rank test and Kaplan–Meier curve. All tests were two-sided and a \( P \) less than 0.05 was considered as statistically significant. All analyses were performed using IBM SPSS 24 for Mac OS X (IBM Corporation, Somers, New York, USA) or R, version 3.4.1 (R Programming).

**Randomisation**
The randomisation was done by a physician not involved in the study using R 3.4.1 (R Programming), with the `blockrand` (\textcopyright{}13; Greg Snow, 2013) package.

**Sample size calculation**
Sample size calculation was based on the study by Sorgenfrei \textit{et al.},\textsuperscript{5} where groups of five patients were sufficient to demonstrate differences in the time from the start of administration of sugammadex or placebo to the recovery of the TOF ratio to 0.9. The number of patients was doubled to take into account the possible loss of patients in the final analysis.

**Results**

**Patient characteristics**
Eighty successive patients were enrolled between February and August 2018. All patients were scheduled for ear, nose and throat surgery with an estimated duration of more than 4 h. Among these, 19 patients were excluded from the final analysis because of low-quality recordings, and 5 because of missing values. Finally, 56 patients were included in the statistical analysis and each group had at least 5 patients.

The 19 patients with poor quality data were excluded as the data set was not consistent, and some of the reported times were not plausible. During the initial inclusion period, one physician did not understand the protocol and noted wrong timings. This physician was excluded from the protocol. In order to avoid analytical bias, we chose to exclude these patients. Figure 1 represents the Consort Flowchart.

The two groups were comparable regarding the following parameters: age, sex, BMI, ASA status (Table 1).

Regarding the pharmacodynamic status, there was no statistically significant difference between the time of rocuronium injection and the onset of the reversal, defined by the first TOF response [TOF1 group: mean \( = 38 \pm 10.8 \text{ min} \), TOF2 group: mean \( = 39.6 \pm 17.1 \text{ min} \); \( P = 0.685 \) using ANOVA test]. All patients had received the exact rocuronium dosage scheduled, that is, \( 0.6 \text{ mg kg}^{-1} \).

**Primary endpoint**
Concerning the timing of injection of sugammadex (TOF recovery to a single twitch or two twitches), the time difference to reversal was not statistically significant between the groups receiving the same dosage (placebo, 0.5, 1 and \( 2 \text{ mg kg}^{-1} \)) (ANOVA test: \( F \) value \( = 0.001, P \) value \( = 0.98 \) at different timings (TOF1 or TOF2).

In contrast, the difference to reversal was statistically significant between the groups receiving different dosage administered at the same timing (ANOVA test: \( F \) ratio \( = 8.14, P < 0.01 \)) and different doses (ANOVA test: \( F \) ratio \( = 15.77, P < 0.01 \)) (Table 2 and Fig. 2b).

Likewise, no patient presented a subsequent partial neuromuscular blockade (TOFR < 0.7) after recovery to TOFR > 0.9.

There was no difference between TOF1 and TOF2 clusters regarding the time spent in the recovery room after surgery [TOF1: mean \( = 114.7 \pm 51.9 \text{ min} \) and TOF2: mean \( = 123.33 \pm 56.17 \text{ min} \), \( P = 0.56 \)].

No patient presented an episode of \( \text{SpO}_2 \) less than 92% desaturation in the immediate postoperative period and oxygen administration time in the recovery room was only because of the service protocol requiring routine oxygen administration within the first few minutes after arrival in the recovery room.

**Discussion**
Our study provides evidence of the efficacy and safety of a widespread practice in operating theatres: early injection of a low dose of sugammadex in order to achieve a rapid recovery for the patient.

The lowest recommended dose is \( 2 \text{ mg kg}^{-1} \) when there are two twitches during the TOF response. We found that injecting sugammadex earlier (at TOF1) provided a reversal as quickly as injection after TOF2, no matter the dose. An earlier injection of sugammadex was as efficacious, with no adverse events. Likewise, using a lower dose of sugammadex (\( 1 \text{ mg kg}^{-1} \)) was as well tolerated and as efficacious as using the recommended dose (\( 2 \text{ mg kg}^{-1} \)). We add robust evidence to the pharmacodynamic literature,\textsuperscript{6} that using an earlier and lower dose of sugammadex can be safely administered to the patient thereby saving time.
Indeed, no difference in the NMBA reversal time according to the time of injection was found. In addition, no case recurrence of neuromuscular block after an initial successful (but transient) reversal was observed in our population, showing that an earlier injection of sugammadex is as well tolerated as a later injection.

Nevertheless, the originality of our study resides in its design. All possible combinations of doses and times were tested on a homogeneous population. This design is both a strength and a weakness.

The use of a placebo group allows us to confirm the pharmacodynamics of rocuronium in our population. The protocol was designed to include patients scheduled for long surgeries (more than 4 h) in order to study the main risk of the decrease in the quantities of products administered, that is, back to partial neuromuscular paralysis.

**Fig. 1** CONSORT flowchart diagram.

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Our observations covered an average of more than 5 h of surgery and 3 h in the recovery room. Despite these very long monitoring times, we did not observe any partial neuromuscular blockade after reversal.

Nevertheless, the adequate analysis (not foreseen in the protocol) was performed, that is, the ANOVA comparison of the two groups (TOF1 and TOF2), by removing patients from the placebo subgroups. Comparing the two clusters with different moment of injection with patients with sugammadex injected (i.e. placebo excepted) does not lead to differences \((P\text{ value }= 0.12)\).

The notion of statistical difference takes on a particular meaning in our study. Differences between some subgroups are statistically significant. Nevertheless, from a clinical point of view, these differences are not important. Differences of a few minutes on a waking procedure that can take up to 15–20 min are not clinically significant.

The chosen population allowed us to analyse consistent data and to avoid possible confounding variables introduced by patients with extreme overweight, major renal insufficiency\(^\text{10}\) or even dialysis. Recent studies suggest a need for dosage prescription modification for these patients.\(^\text{11}\) As the debate within ideal and real weight for dose calculation is not defined, our protocol neglected this issue. For all sugammadex infusion, and especially for these particular patients, it is a legal obligation in most European countries to monitor sugammadex action. The study gives only a partial answer regarding dose reduction.

The difference between minimum and maximum in each subgroup in the times measured reminds us of the need for precise monitoring of the action of the NMBA and their antidotes.\(^\text{13}\) Indeed, based on mean or median values, some patients would be awake, although still partially curarized. Sugammadex develops a rapid and effective action even with very low doses but this must be monitored at every moment of the anaesthesia and awakening period. Its use without monitoring represents a danger that no scientific society recommends.

No cases of anaphylaxis with sugammadex were present in the study population. Although it has been described,\(^\text{14}\) it is very rare. Maybe some of these side-effects will be controlled by the use of new alternatives to sugammadex.\(^\text{15}\) Not only do the risks of sugammadex anaphylaxis need to be put in perspective with neostigmine anaphylaxis and its other side effects\(^\text{16}\) but also with complications of patients waking up with partial neuromuscular paralysis.

In some countries, neostigmine is the first drug used in order to reverse NMBA action during the wake-up period. The use of this medication is not without consequences.\(^\text{17}\) It’s effect of bradycardia is well known and requires the concomitant use of atropine or glycopyrrolate. The use of neostigmine for some patients with cardiac rhythm...
disorders or diseases has risks. As European recommendations do not require an electrocardiogram before surgery, except in special cases, neostigmine use could be hazardous. The use of sugammadex may be a solution for these patients with cardiac risk or undocumented cardiac risk.18

The main limitation of the study is the loss of 24 patients because of the lack of interpretable data. Nineteen patients had inconsistent, incomplete, or unrealistic data, making exclusion of these patients from the analysis necessary. Only one physician was in charge of these 19 patients and was hardly involved in the protocol implementation at the 1-day surgery unit. As no explanation from the physician about the reason of these inconsistent data was given, they were excluded from the final analysis and the physician was excluded from the protocol for the next patients. It seems that the physician did not understand the timings to register and noted them with a delay.

Five patients did not have any data concerning neuromuscular paralysis reversal. This was explained by a rapid blockade reversal, which was not anticipated by the anaesthetist in charge, and therefore, did not check the TOF Watch monitoring for 1 min or less in order to prepare a drug or to prepare the postoperative chart. During that minute, the patient moved from one twitch (or two twitches) at TOF to four twitches at TOF.

At the end of the surgery, the anaesthetist is confronted with two problematic situations because of the need for a rapid awakening. A deep muscle relaxation would require a large quantity of sugammadex to be effective. Waiting for a partial muscle relaxation does not bring any benefit both in terms of dose reduction to be administered, and in terms of speed of awakening. Regarding guidelines, partial muscle relaxation requires large doses of sugammadex, we bring the proof that reduction of doses is possible without loss of effectiveness. However, reap any financial benefit from lower doses would require the manufacturer to produce lower dose ampoules or to ask hospital pharmacies to create syringes containing a lower dose.

**Table 2** Timings regarding injection and dosage, detailed (SI) Sugammadex injection at first twitch in train-of-four or second twitch in train-of-four

<table>
<thead>
<tr>
<th></th>
<th>0 mg kg⁻¹ (placebo)</th>
<th>0.5 mg kg⁻¹</th>
<th>1 mg kg⁻¹</th>
<th>2 mg kg⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time from injection (SI) to TOFR &gt;0.9</strong></td>
<td></td>
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</tr>
<tr>
<td>TOF1</td>
<td>33.9 ± 10.0bcd</td>
<td>6.8 ± 6.2cd</td>
<td>2.5 ± 0.7a</td>
<td>1.8 ± 1.0ab</td>
</tr>
<tr>
<td>TOF2</td>
<td>30.80 ± 16.3bcd</td>
<td>3.7 ± 1.1bcd</td>
<td>1.9 ± 0.4ab</td>
<td>1.3 ± 0.75ab</td>
</tr>
<tr>
<td><strong>Time from TOF1 to TOFR &gt;0.9</strong></td>
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</tr>
<tr>
<td>TOF1</td>
<td>33.9 ± 10.0bcd</td>
<td>6.8 ± 6.2cd</td>
<td>2.5 ± 0.7a</td>
<td>1.8 ± 1.0ab</td>
</tr>
<tr>
<td>TOF2</td>
<td>36 ± 15.4cd</td>
<td>14.0 ± 7.6d</td>
<td>9.7 ± 4.6a</td>
<td>12.5 ± 13.0a</td>
</tr>
</tbody>
</table>

Data are mean ± SD. All timings are expressed in minutes. TOF1, first twitch in train-of-four; TOF2, second twitch in train-of-four. a Different from placebo group. b Different from 0.5 mg kg⁻¹ group. c Different from 1 mg kg⁻¹ group. d Different from same dosage but other timing.

**Fig. 3** Time-to-event analysis curve, with different dosages and different timings of injection. x-axis: time scale (minutes). y-axis: event rate (percentage)
Conclusion
Two main principles in anaesthesia are: ‘the ideal dose of a medicine is the lowest dose that produces the expected effect’ and ‘you can always add medicine to the patient but only she/he can eliminate it’.

Our study answers the two main questions an anaesthetist asks during the recovery phase: should I inject sugammadex at any moment? If so, at what dose? We bring evidence that a lower dose of sugammadex (0.5 and 2 mg kg⁻¹) injected earlier can be safely used if monitored correctly.

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References