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Author: Boon, M.
Title: Deep neuromuscular blockade and neuromuscular reversal: applications and implications
Issue Date: 2018-10-10
Chapter 5

Improved postoperative oxygenation following reversal of moderate neuromuscular block with sugammadex compared to neostigmine

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Adapted from: British Journal of Anaesthesia 2016; 117(3): 410-411.
ABSTRACT

Background
Incomplete recovery of neuromuscular block (NMB) at the end of surgery is one of the leading causes of postoperative adverse events, most importantly hypoxaemia. Adequate reversal of NMB may overcome these complications. This study was designed to compare reversal with neostigmine and sugammadex on postoperative oxygenation during the first 45 minutes postoperatively.

Methods
In this randomized controlled, double-blind trial, 100 patients received propofol/sufentanil/rocuronium anaesthesia and were randomized to NMB reversal at 1-2 twitches in the train of four (TOF) with sugammadex 2 mg.kg\(^{-1}\) or neostigmine 2.5 mg. Extubation was based on clinical signs of adequate muscle strength. Postoperative use of supplemental oxygen was not allowed unless saturation dropped to values below 94%.

Results
Mean (SD) TOF ratio at extubation was 0.74 (0.22) in patients reversed with neostigmine; 70% of these patients had a TOF ratio < 0.9. In contrast, patients reversed with sugammadex had a TOF ratio of 0.99 (0.3) (p < 0.0001 vs. neostigmine); 4% of these patients had a TOF ratio < 0.9. Postoperatively, the lowest oxygen saturation was 96.8 (2.2)% against 93.3 (3.9)% in sugammadex and neostigmine groups, respectively (p < 0.0001). The combination of TOF ratio > 0.90 and oxygen saturation levels ≥ 94% occurred in 90% of patient reversed with sugammadex compared to 16% of patients reversed with neostigmine.

Conclusions
Compared to reversal with neostigmine, reversal of a moderate neuromuscular block with sugammadex resulted in improved muscle function at extubation with less postoperative hypoxaemia in patients not receiving supplemental oxygen.
INTRODUCTION

Neuromuscular blocking agents are routinely used during general anaesthesia to optimize intubation and improve surgical conditions. For example, we recently showed that a deep neuromuscular block (NMB) improves the quality of the surgical field in retroperitoneal laparoscopic surgery. The persistence of some level of NMB (residual relaxation defined by a train-of-four (TOF) ratio < 0.9) is an independent risk factor for postoperative pulmonary complications, with hypoxaemia as most frequent event. We relate the relatively high incidence of residual relaxation following general anaesthesia to the lack of adequate quantitative monitoring (but instead subjective monitoring based on clinical signs of recovery) and the impatience of the anaesthetist (not realizing that reversal with some agents is relatively slow). For example, even when the NMB is reversed with the acetylcholinesterase inhibitor neostigmine residual relaxation is a frequent observation in the PACU, independent of the use of monitoring. We previously showed that more than 30% of patients experience frequent hypoxic events in their 45 min stay in the PACU following isoflurane/fentanyl-based anaesthesia with spontaneous recovery or reversal with neostigmine of a moderate NMB. The link between residual relaxation and hypoxaemia in the PACU is that persistence of even low levels of acetylcholine receptor blockade cause inadequate pulmonary and upper airway muscle function as well as reduced carotid body activity. Consequently, alveolar hypoventilation combined with loss of upper airway patency and a reduced ventilatory response to hypoxaemia facilitates frequent hypoxic events in the PACU.

A relatively new reversal agent is the γ-cyclodextrin sugammadex, which encapsulates rocuronium (and vecuronium) in plasma and consequently causes the diffusion of the NMB agent from the neuromuscular junction. While several studies show that sugammadex causes rapid and complete reversal of moderate and deep NMB, a recent study showed that even following sugammadex reversal residual relaxation (defined by a train-of-four (TOF) ratio < 0.9) occurred in 4% of patients. No data are available on the incidence of hypoxaemia in the PACU following reversal with sugammadex or the association between TOF ratio at extubation following sugammadex reversal and oxygen saturation levels in the PACU.

We conducted a double-blind randomized controlled trial comparing the effect of reversal of a moderate NMB (TOF 1-2 twitches) with sugammadex 2 mg.kg⁻¹ and neostigmine 2.5 mg on oxygen saturation levels in the PACU. The use of supplemental oxygen in the PACU was not allowed unless arterial oxygen saturation dropped to values below 94%. We hypothesize that, compared to neostigmine, reversal with sugammadex is associated with less hypoxaemia in postoperative patients that do not receive supplemental oxygen.
METHODS

The study with acronym Neuropa was conducted between February 2015 and February 2016 at two medical centres in the Netherlands, Leiden University Medical Centre in Leiden and Haga Ziekenhuis in The Hague. Ethics approval of the protocol was obtained from the ethics committees of both institutions; the protocol was registered at clinicaltrials.gov under number NCT02243943. The study was conducted in accordance with Good Clinical Practice and Good Research Practice guidelines. Eligible patients were approached in advance by one of the investigators and received oral and written information about the study. If a patient was willing and able to participate, written informed consent was obtained.

Patients and randomization

Patients were eligible to participate in the study if they fulfilled the following criteria: 18 years or older, ASA class I-III, body mass index <35 kg.m⁻², scheduled for elective surgery with a planned duration of at least 60 minutes and requiring general anaesthesia with the use of muscle relaxants. Exclusion criteria included known or suspected neuromuscular disorder, allergy to muscle relaxants or reversal agents, a (family) history of malignant hyperthermia, (suspected) pregnancy or current breast feeding, contraindications for neostigmine use, planned regional or neuraxial anaesthesia, pulmonary disease and renal insufficiency (glomerular filtration rate < 30 mL.min⁻¹).

All patients were randomized to receive either sugammadex or neostigmine as reversal agent at the end of surgery. Randomization was performed before induction of anaesthesia and the ‘time out’ procedure. Randomization was performed using a computer-generated randomization list (obtained from www.randomization.org). Allocation to treatment was at the end of surgery. The patient and researchers were fully blinded, but the attending anaesthetist was not and he or she administered the drugs at a train-of-four (TOF) count of 1 (T1) or 2 (T2) twitches. Thereafter the anaesthetist was blinded to the TOF count and TOF ratio and his or her decision to extubate the patient was based on clinical grounds.

Anaesthesia and neuromuscular management

Premedication consisted of oral midazolam 3.75 to 7.5 mg and rectal paracetamol 1000 mg one hour before surgery. All patients received total intravenous anaesthesia with sufentanil, propofol and rocuronium and inhaled a 50/50 mixture of oxygen and nitrogen. Monitoring was according to local practice and included electroencephalogram monitoring using the Philips BIS module (Philips, Eindhoven, the Netherlands). Target BIS values in this study were values between 45 and 55. Relaxation was measured using
the TOF cuff device (RGB Medical Devices, SA, Madrid, Spain), which was applied around the left or right upper arm, contralateral to the blood pressure cuff. The TOF cuff was calibrated after induction but before administration of rocuronium. The TOF cuff is equally reliable to acceleromyography and has been used in our previous studies on NMB. In our opinion, the TOF cuff is easier to use in daily practice than the TOF watch and is less prone to error. One hour before the end of surgery, morphine 0.1 mg.kg\(^{-1}\) was given.

The target level of neuromuscular relaxation was T1 or T2 throughout the procedure until reversal. If measurement indicated a TOF of 3 twitches or higher during surgery, an incremental dose of vecuronium 10 mg was administered. At the end of the procedure, neuromuscular block was reversed with sugammadex 2 mg.kg\(^{-1}\) or neostigmine 2.5 mg (combined with atropine), according to randomization. Upon the discretion of the attending anaesthetist additional doses could be given. At reversal, the inhaled oxygen concentration was set at 100%; lung recruitment manoeuvres were not allowed unless deemed necessary by the attending anaesthetist.

Extubation was performed by the attending anaesthetist based on clinical signs as is commonly practiced in both medical centres. These signs include adequate level of spontaneous ventilation, eye opening, hand grip strength, 5s. head lift and tongue protrusion. A blinded research nurse collected TOF data at 1-minute intervals from the time of reversal.

After extubation and transport to the PACU oxygen saturation (SpO\(_2\)) was continuously monitored and recorded at 2-minutes intervals. Supplemental oxygen was only allowed when SpO\(_2\) dropped below 94%. The SpO\(_2\) was collected on the case record form and the lowest value observed in the PACU was used for analysis. Additionally, the following variables were recorded on the case record form at 15-minutes intervals: blood pressure, heart rate, pain (using an 11-point numerical rating scale from 0 to 10) and sedation (using a 5-point scale ranging from 0, normal alertness to 5, not aroused by a painful stimulus). After 45 minutes in the PACU the study ended.

**Sample size and statistics**

We judged that a difference in SpO\(_2\) between treatment groups of at least 2% is clinically relevant. Assuming a SD of 3.0%, a sample size of 49 patients per group would provide at least 90% power to detect the observed difference at \(\alpha = 0.05\).

The primary outcome was the lowest SpO\(_2\) as measured during the first 45 minutes in the PACU. Data analysis was based on an intent-to-treat basis. A significant difference between treatment groups was tested by two-tailed Student \(t\)-test. Secondary outcomes were time to a TOF ratio > 0.9, time from reversal to extubation, postoperative pain level
and sedation scores in the PACU. Student t-tests and Mann Whitney U tests were used as appropriate. The data were analyzed with SPSS (version 22; IBM corporation, Armonk, NY, USA). All data are presented as mean (SD) or mean (95% confidence interval) unless otherwise stated. p-values < 0.05 were considered significant.

RESULTS

Figure 1 shows the flow diagram of the study. A total of 126 patients were contacted of whom 16 refused consent, 4 did not meet inclusion criteria and 6 patients could not enter the study due to logistic reasons (e.g. rescheduling of surgery). One-hundred patients were randomized between the treatment groups. No patients were lost to follow-up and postoperative data of all patients were used in the final analysis.

![Flowchart](image)

**Figure 1.** Study flow chart.

Reversal

Table 1 gives the baseline characteristics and perioperative measurements. No significant differences were present between both groups. In addition, no significant differences in duration of surgery and anaesthetic medication were present. At the end of surgery, relaxation was reversed at a mean TOF count of 1.4 (1.1-1.7) and 1.6 (1.2-1.9) twitches in sugammadex and neostigmine groups respectively (p > 0.05). Patients in
Table 1. Baseline characteristics and perioperative data.

<table>
<thead>
<tr>
<th></th>
<th>Sugammadex N=50</th>
<th>Neostigmine N=50</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASELINE CHARACTERISTICS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years; median, range)</td>
<td>55 (27-72)</td>
<td>55 (19-94)</td>
<td>NS</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>27 (53%)</td>
<td>24 (44%)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79 (75-83)</td>
<td>75 (71-79)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg.m⁻²)</td>
<td>26 (25-27)</td>
<td>25 (24-26)</td>
<td>NS</td>
</tr>
<tr>
<td>ASA (n, %)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>1</td>
<td>18 (35%)</td>
<td>32 (59%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>32 (63%)</td>
<td>22 (41%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 (2%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Preoperative saturation (%)</td>
<td>99 (98-99)</td>
<td>99 (98-99)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>SURGERY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>107 (91-123)</td>
<td>90 (77-105)</td>
<td>NS</td>
</tr>
<tr>
<td>Propofol dose (mg)</td>
<td>1114 (972-1256)</td>
<td>951 (803-1098)</td>
<td>NS</td>
</tr>
<tr>
<td>Sufentanil dose (μg)</td>
<td>52 (45-58)</td>
<td>43 (38-49)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>REVERSAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sugammadex dose (mg)</td>
<td>170 (156-184)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Neostigmine dose (mg)</td>
<td>-</td>
<td>2.5 (2.4-2.6)</td>
<td></td>
</tr>
<tr>
<td>Atropine dose (mg)</td>
<td>-</td>
<td>1.08 (1.03-1.13)</td>
<td></td>
</tr>
<tr>
<td>BIS at reversal</td>
<td>46 (44-49)</td>
<td>44 (42-46)</td>
<td>NS</td>
</tr>
<tr>
<td>TOF count at reversal</td>
<td>1.4 (1.1-1.7)</td>
<td>1.6 (1.2-1.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Time to TOF ratio 0.9 (min)</td>
<td>2.5 (2.1-2.8)</td>
<td>10.0 (7.6-12.3)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>EXTUBATION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOF ratio at extubation</td>
<td>0.99 (0.98-1.00)*</td>
<td>0.74 (0.68-0.80)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>TOF ratio below 0.90 at extubation</td>
<td>-</td>
<td>0.60 (0.55-0.67)**</td>
<td></td>
</tr>
<tr>
<td>Time to extubation from reversal (min)</td>
<td>8.0 (6.9-9.1)</td>
<td>11.7 (9.9-13.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Time to extubation from TOF 0.9 (min)</td>
<td>5.8 (4.7-6.8)</td>
<td>3.8 (2.1-5.4)#</td>
<td>NS</td>
</tr>
<tr>
<td>BIS at extubation</td>
<td>79 (76-82)</td>
<td>77 (74-80)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>POST ANAESTHESIA CARE</strong></td>
<td></td>
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</tr>
<tr>
<td>Lowest Saturation in PACU (%)</td>
<td>96.8 (96.1-97.4)</td>
<td>93.3 (91.9-94.7)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Morphine dose (mg)</td>
<td>11 (10-12)</td>
<td>11 (9-12)</td>
<td>NS</td>
</tr>
<tr>
<td>Pain score (NRS)</td>
<td>3.0 (2.4-3.7)</td>
<td>3.2 (2.4-3.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Sedation score</td>
<td>1.4 (1.2-1.6)</td>
<td>1.4 (1.2-1.6)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean (95% confidence interval) unless otherwise stated; *n= 48; ** n = 35; # n = 20
the neostigmine group received a mean of 2.5 (2.4-2.6) mg of the reversal agent. Eight patients (16%) required one additional neostigmine dose of 1 mg; three others (6%) received a dose of sugammadex after their initial neostigmine dose. Patients in the sugammadex group received 170 (156-184) mg; none received an additional dose of sugammadex or neostigmine.

**Extubation**

In 2 patients, TOF values could not be measured following sugammadex reversal due to patient movement and rapid extubation. Thirty-five patients (70%) treated with neostigmine had a TOF ratio < 0.9 upon extubation against 2 (4%) patients treated with sugammadex (Fig. 2). The TOF ratio at extubation was 0.74 (0.71-0.83; \( n = 50 \)) in the neostigmine group and 0.99 (0.98-1.00; \( n = 48 \)) in sugammadex group (\( p < 0.0001 \)). In the 35 patients reversed with neostigmine that had a TOF ratio < 0.9 their average ratio was 0.60 (0.55-0.67); the two patients reversed with sugammadex that had a ratio < 0.9 had ratios of 0.88 and 0.82. In those subjects that reached a TOF ratio of 0.9 or greater, the time from reversal to a TOF ratio > 0.9 was significantly shorter in the sugammadex group, 2.5 (2.1-2.8; \( n = 48 \)) minutes, compared to the neostigmine group, 10.0 (7.6-12.3; \( n = 15 \)) minutes (\( p < 0.001 \)). The time from reversal to extubation was shorter for sugammadex, 8.0 (6.9-9.1; \( n = 50 \)) minutes, compared to neostigmine, 11.7 (9.9-13.4; \( n = 50 \)) minutes (\( p = 0.01 \)).

![Figure 2. Train-of-four ratio at extubation following reversal with sugammadex or neostigmine.](image)

**Figure 2.** Train-of-four ratio at extubation following reversal with sugammadex or neostigmine.
Post-anaesthesia care

The main outcome, lowest SpO₂ in the 45 minutes following reversal, was 3.5% lower in patients treated with neostigmine compared to patients treated with sugammadex: 93.3 (91.9-94.7)% against 96.8 (96.1-97.4)% (p < 0.0001). Figures 3A and 3B show the distribution of the lowest SpO₂ per group and highlight the difference in SpO₂ distribution for the two treatments. Figure 4 shows the individual lowest saturation values in the PACU in relation to TOF ratio at extubation. In the sugammadex group, 90% of the patients were in the upper right quadrant of the graph (TOF ratio of > 0.9 combined with lowest saturation ≥ 94%), while for neostigmine treated patients just 16% of patients were in the upper-right quadrant.

**Figure 3.** Frequency distribution of the lowest oxygen saturation values measured in the PACU following reversal with sugammadex (A) and neostigmine (B).

**Figure 4.** Lowest saturation values measured in the PACU versus train-of-four ratio's at extubation for sugammadex (A) and neostigmine (B).
In the PACU, no significant differences in sedation and pain scores were observed. No adverse events occurred.

**DISCUSSION**

This double-blind, randomized, controlled trial compared the effect of reversal of a moderate neuromuscular block (NMB) with sugammadex and neostigmine on oxygen saturation levels in postoperative patients. The main results are that NMB reversal with sugammadex resulted in less patients with postoperative hypoxaemia (defined by SpO₂ levels < 94%) compared to neostigmine in patients not receiving supplemental oxygen.

Low SpO₂ levels are not uncommon in the PACU and are related to multiple factors, including residual effects of opioids and anaesthetics, type of surgery, patient characteristics, underlying disease, the use of recruitment manoeuvres and the inhaled oxygen concentration during anaesthesia and recovery. Since these factors were either evenly distributed between the two treatment groups or tightly controlled according to protocol, we hold the intervention (sugammadex versus neostigmine) responsible for the large difference in SpO₂ distribution in the PACU (Figs. 3 and 4). Reversal of the NMB with neostigmine resulted in SpO₂ levels < 94% in 47% of patients compared to 8% of patients after reversal with sugammadex. On average SpO₂ levels (i.e. lowest measured SpO₂) were 3.5% lower after neostigmine (neostigmine 93.3% vs. sugammadex 96.8%). Our data support the growing body of evidence showing that neostigmine reversal is associated with an increased risk of postoperative respiratory complications such as hypoxaemia,¹⁰, ¹⁶-¹⁸ and additionally show the beneficial effect of sugammadex with significantly less risk of postoperative hypoxaemia. These are important results and indicate that the choice of reversal agent has a significant effect on postoperative conditions.

This is the first study that measured residual NMB at extubation in conjunction with postoperative SpO₂ levels in patients that did not receive supplemental oxygen. By initially restricting the use of oxygen in the PACU, the masking effect of supplemental oxygen on the measured SpO₂ levels was absent and hypoxaemia related to hypoventilation either from reduced respiratory drive or from persistent muscle weakness (or hypoxaemia from any other cause) was now readily detected.¹⁹, ²⁰ Consequently, we were able to identify a significant difference in postoperative oxygenation between treatments in a relatively healthy population. The difference between treatments was however relatively small (3.5%) since we administered supplemental oxygen by mask or nasal cannula when SpO₂ dropped below 94%. Evidently, this was done to prevent any harm to the patient. It is highly probable, however, that in a more susceptible population the difference in SpO₂ would have been more pronounced. Such populations include
patients with pulmonary disease, muscle weakness, heart failure, elderly patients and ASA class 3-4 patients.

Neostigmine is commonly used upon spontaneous recovery of muscle relaxation (i.e. $T > 0$). In the current study we administered neostigmine 2.5 mg at T1 or T2. The use of neostigmine at T1 or T2 is not unusual, although in most studies the dose is higher than used by us.\textsuperscript{21, 22} In the two institutions in which the study was performed, neostigmine is generally used at $T > 0$ in doses of 1 to 2.5 mg, irrespective of the patient’s weight and without proper NMB monitoring. Our current data indicate that this practice is associated with slow recovery, residual curarization at extubation (in 70% of patients) and hypoxic events in the PACU (in 47% of patients). In Figure 4, we associate the TOF ratio at extubation with the lowest $\text{SpO}_2$ in the PACU and observed that 90% of patients had a TOF ratio of > 0.9 combined with saturation levels of 94% or above following sugammadex (upper-right quadrant of Fig. 4), compared to 16% after neostigmine reversal. Possibly higher neostigmine doses might have improved either of these outcomes,\textsuperscript{22} however, it is our experience that higher neostigmine doses come at the expense of uncomfortable cholinergic side effects such as nausea, vomiting, abdominal cramps and blurred vision. Given the results of our current study we changed our practice and now routinely reverse a moderate NMB with sugammadex 2 mg.kg\textsuperscript{-1}.

We observed a TOF ratio < 0.9 at extubation in 70% of patients after neostigmine and 4% after sugammadex reversal. The incidence of residual block varies widely among studies, with incidences ranging from 2% to 64%, depending on definition, clinical circumstances, agents used and timing of measurements.\textsuperscript{4} For example, Murphy et al.\textsuperscript{23} and Fortier et al.\textsuperscript{24} observed residual curarization in 63% to 88% of patients at extubation following predominantly neostigmine reversal; in agreement with our study, the anaesthetists were blinded to NMB monitoring. Brueckmann et al.\textsuperscript{10} performed measurements in the PACU and detected TOF ratio values < 0.9 in 43% and 0% following neostigmine and sugammadex treatment, respectively.\textsuperscript{10} We contend that similar values may have occurred in our patients in the PACU. We did not measure TOF ratio’s in the PACU to prevent possible respiratory stimulation from TOF measurements. An important observation was made by Kotake et al. who studied sugammadex reversal and detected an incidence of residual NMB of 4% in a setting where no monitoring was used.\textsuperscript{14} These findings are in agreement with our results and emphasize the importance of neuromuscular monitoring.

In our current study extubation was performed under “blinded” conditions (i.e. the anaesthetist was unaware of the number of twitches and TOF ratio). This practice is very similar to standard of practice in many institutions. The use of monitoring at extubation might have reduced the incidence of residual curarization in both groups and possibly might have improved oxygenation in the PACU. The effect of reversal with neostigmine
versus sugammadex on SpO₂ levels in the PACU in a monitored setting should be assessed in future studies.

In conclusion, we show that the selection of reversal agent controls not only the speed and intensity of recovery of the neuromuscular block, but additionally has a significant effect on postoperative respiratory conditions. Both the TOF ratio at extubation and the oxygen saturation levels in the PACU differ significantly in patients reversed with neostigmine and sugammadex with favorable conditions for both end-points in 90% of patients after sugammadex versus just 16% of patients after neostigmine reversal.
REFERENCES


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