

# Respiratory events with sugammadex vs. neostigmine following laparoscopic sleeve gastrectomy: a prospective pilot study assessing neuromuscular reversal strategies

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## Abstract

Abdominal surgery in obese patients may be associated with pulmonary morbidity, and mortality. Some patients may arrive in the PACU with residual paralysis.

**The purpose of this study** was to find out if there was an association between the type of muscle relaxant reversal agent and the development of postoperative respiratory events in patients undergoing laparoscopic sleeve gastrectomy surgery.

**Methods:** From September 2012 to February 2013, in a prospective randomized pilot study, two different muscle relaxant reversal agents were administered at the end of surgery in 57 patients undergoing laparoscopic sleeve gastrectomy: sugammadex 2 mg/kg (32 patients) vs. neostigmine 2.5 mg (25 patients). We compared the occurrence of early and late respiratory events/complications by the type of reversal agent. Postoperative respiratory rate, oxyhemoglobin saturation (SpO<sub>2</sub>), number of patients with SpO<sub>2</sub> lower than 95% in PACU, the minimum value of SpO<sub>2</sub> in PACU, train-of four counts (TOF) before reversal, unexpected ICU admissions, duration of hospitalization and incidence of reintubation were recorded.

**Results:** SpO<sub>2</sub> in the PACU was significantly lower in the neostigmine group – 95.80 (± 0.014) vs. in sugammadex group – 96.72 (± 0.011) (p < 0.01), despite a lower TOF count measured in the sugammadex group *before* reversal, meaning a deeper level of residual relaxation in this group *before* the administration of the reversal agent (2.53 ± 0.98 vs. 3.48 ± 0.58 p < 0.01). Also, the minimal SpO<sub>2</sub> was significantly lower in the PACU in the neostigmine group: 93% vs. 94% (p = 0.01). Respiratory rates were not different. After the administration of reversal, both groups had TOF counts of 4 with no fade assessed visually. There were no postoperative respiratory events or complications.

**Conclusions:** The use of sugammadex (as compared to neostigmine) as a reversal agent following laparoscopic sleeve gastrectomy surgery was associated with higher postoperative SpO<sub>2</sub> despite the lower TOF count before the administration of reversal agent. Despite the statistical difference in SpO<sub>2</sub>, its clinical importance seems to be minimal. The lack of difference in the other measured variables may stem from the small number of patients studied (pilot).

**Keywords:** muscle relaxants, reversal, sugammadex, neostigmine, respiratory events

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## Introduction

The worldwide increase in the incidence of obesity in the last decades has been associated with metabolic, respiratory and cardiovascular complications [1-5] leading to an increased demand for bariatric surgeries

[6-9]. General anesthesia for these surgeries has been associated with complications including respiratory failure [10-15], need for unplanned intensive care unit, prolonged hospitalization and increased mortality [16]. The need for high doses of neuromuscular blocking agents in these surgeries may cause residual paralysis and consequently critical respiratory events and late complications such as hypoxemia, pneumonia, atelectasis and the need for reintubation [17-21]. Neostigmine is unable to completely reverse deep neuromuscular blockade and may be associated with muscarinic side effects [22-26].

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Sugammadex (Bridion<sup>®</sup> Merk Sharp and Dohme (MSD), Oss, the Netherlands), a gamma-cyclodextrin is a novel agent for reversal of the aminosteroidal (rocuronium, vecuronium and to a lesser degree, pancuronium) non-depolarising neuromuscular blockade [22]. It has been proven to have benefits over neostigmine [23-26].

The objective of this prospective, pilot study was to compare the effects of neostigmine vs. sugammadex on critical respiratory events and late respiratory complications in morbidly obese patients undergoing laparoscopic sleeve gastrectomy surgery.

## Methods

This randomized pilot trial was conducted at The Edith Wolfson Medical Center from September 2012 to February 2013 on patients undergoing elective laparoscopic sleeve gastrectomy under general anesthesia with rocuronium induced neuromuscular blockade. The study was approved by the Institutional Review Board of Wolfson Medical Center, Hollon, Israel. All patients signed a written informed consent form before enrolment in the study. Inclusion criteria were age  $\geq 18$  yrs and ASA classes I-III. Exclusion criteria were neuromuscular disorders, known or expected difficult intubation, renal or liver disease, family history of malignant hyperthermia, pregnancy or breast feeding and allergy to non depolarizing blocking agents, sugammadex, opioids and other anesthetic drugs.

Patients were randomly assigned using computer generated randomization to receive either neostigmine 2.5 mg with atropine sulfate 1 mg or sugammadex 2 mg/kg. Neuromuscular relaxation depth was qualitatively assessed by TOF count from the ulnar nerve. Anesthesia was induced with propofol 2 mg/kg, fentanyl 1  $\mu$ g/kg and rocuronium 0.6 mg/kg to facilitate endotracheal intubation. When gastroesophageal reflux was a concern, rapid sequence induction using succinylcholine 1 mg/kg was employed. For maintenance of anesthesia we used boluses of 50  $\mu$ g fentanyl as deemed necessary, propofol infusion (TIVA) 100-200  $\mu$ g/kg/min and repetitive doses of rocuronium bromide 0.2 mg/kg in order to keep a TOF count of 0 or 1 during the surgical procedure. At the end of surgery, either sugammadex 2 mg/kg total body weight or neostigmine 2.5 mg with atropine sulfate were administered to antagonize the effect of neuromuscular blocking agents. All patients required a TOF count of at least 2 before the administration of the reversal agent. Muscle strength was also assessed on the operating table, before extubation, for clinical signs of residual neuromuscular block (head lift and hold-up for at least five seconds and hand grip). These tests

were not repeated in the PACU and TOF monitoring was not continued during the postoperative follow-up.

In the PACU, heart rate, blood pressure, respiratory rate/min and SpO<sub>2</sub> were recorded at the admission to the PACU and every 10 min thereafter until discharge. Values of SpO<sub>2</sub> and respiratory rate were analyzed during the first PACU hour.

The mean and minimal SpO<sub>2</sub> and number of events with SpO<sub>2</sub> < 95% were also recorded. Hypoventilation (< 10 breath/min) and tachypnea (> 20 breath/min) were also recorded.

Immediate and late respiratory adverse events in the PACU were also recorded including respiratory distress, upper airway obstruction, aspiration, need for reintubation, unplanned admission to the intensive care unit and prolonged hospitalization.

### Data analysis

Analysis of data was carried out using SPSS 9.0 statistical analysis software (SPSS Inc. Chicago, IL, USA). For continuous variables, descriptive statistics were calculated and reported as means  $\pm$  standard deviations. Normality of distribution of continuous variables was assessed using the Kolmogorov-Smirnov test (cut-off at  $p = 0.01$ ). Categorical variables such as treatment group and symptoms were described using frequency distributions and are presented as frequency (%).

The t test for independent samples was used to compare continuous variables between subjects by treatment group. Chi square or Fisher exact tests used to assess associations between treatment group and other categorical variable. All tests were two-sided and considered significant at  $p < 0.05$ .

When making multiple measures, the rate of type I error is increased. Therefore, repeated measures analysis was performed first and only if significant overall difference was detected and if post hoc, pair wise comparisons could be made.

## Results

The data from 57 patients were analyzed. There were 32 patients in the sugammadex group and 25 in the neostigmine group. Table 1 shows the demographic data. Sex, smoking habits, ASA physical status, BMI and duration of hospitalization did not differ statistically. Four patients were intubated following succinylcholine administration, two in each group.

Table 2 shows the TOF count before reversal and respiratory parameters. Sugammadex patients had lower TOF counts before reversal but higher mean and minimal SpO<sub>2</sub>.

A decrease in SpO<sub>2</sub> < 95% was recorded in one patient after sugammadex and three after neostigmine. One neostigmine patient with a COPD background

**Table 1.** Demographic data

Parameter	Neostigmine	Sugammadex	p
Age (years)	45 ± 13	42 ± 13	0.54
Sex – Women %	65	56	0.55
Height – cm	164 ± 14	166 ± 11	0.60
Weight – kg	127 ± 23	120 ± 21	0.24
BMI – kg/m <sup>2</sup>	44 ± 5	42 ± 6	0.30
Days of hospitalization	3.5 ± 1	3.5 ± 0.8	0.70

required reintubation eight hours following surgery (five hours after the last opiate dose), due to CO<sub>2</sub> retention. She was admitted and ventilated for two days in the intensive care unit. The rest of her postoperative course was uneventful. There were no postoperative complications and there was no need for reintubation and unplanned admission to the ICU in either group.

## Discussion

In this prospective randomized, pilot study we sought to determine the incidence of postoperative respiratory events and pulmonary complications in patients undergoing laparoscopic sleeve gastrectomy surgery in relation to the type of muscle relaxant reversal agent. We have found that despite the deeper muscle relaxation before reversal in the sugammadex group, oxyhemoglobin saturation was higher with this reversal agent, supposedly indicating a more effective reversal effect as compared to neostigmine. It has to be noted that despite the statistical difference in SpO<sub>2</sub>, its clinical importance seems to be minimal. There were no postoperative complications and there was no need for unplanned admission to the ICU in either group. The use of such an effective and reliable agent (sugammadex) has special importance during laparoscopic bariatric surgery when high doses of muscle relaxant are required for optimal muscle relaxation [23, 27, 28].

We did not measure the effectiveness of sugammadex in the reversal of deep muscle relaxation as shown in previous studies [29-32] since all our patients

required a TOF count of at least 2 twitches before reversal.

Sugammadex has been shown to provide effective and complete reversal of muscle relaxant agents [33, 34]; therefore, we speculate that the higher oxyhemoglobin saturations in the PACU in patients who received sugammadex may stem from a more effective reversal effect.

Despite the apparently evident advantages of sugammadex regarding its efficacy in reversal of aminosteroidal (i.e., rocuronium) muscle relaxants effects, in a prospective, partially randomized, placebo-controlled trial, Nemes et al. [35] concluded, based on their findings that pharmacological reversal did not prevent postoperative residual paralysis, irrespective of the reversal agent.

In **conclusion**, the use of sugammadex as compared to neostigmine following laparoscopic sleeve gastrectomy surgery was associated with higher postoperative oxyhemoglobin saturation despite deeper muscle relaxation (lower TOF count) before the administration of reversal agent. However, the clinical significance of this difference is questionable. Larger studies are required to elucidate the significance and the mechanism of better oxygenation after sugammadex reversal subsequent to sleeve gastrectomy surgery. The lack of statistical difference in the other variables measured may stem from the small patients' group sizes, since this was a pilot study.

## Conflict of interest

Nothing to declare

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**Table 2.** Train of four count before reversal administration and respiratory parameters recorded in the PACU\*

Parameter	Neostigmine	Sugammadex	p
TOF count before reversal administration	3.5 ± 0.6	2.5 ± 1	< 0.01
Mean SpO <sub>2</sub>	95.8 ± 0.01	96.7 ± 0.14	< 0.01
Minimal SpO <sub>2</sub>	93%	94%	< 0.01
Respiratory rate breath/min	15 ± 3	15 ± 2	0.9
% of patients with respiratory rate < 10/min	4%	0%	0.27
% of patients with abnormal respiratory rate < 10 or > 20/min	8%	0%	0.19

\* Results are presented as means ± SD or percentage

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