

# Residual Curarization and Postoperative Respiratory Complications Following Laparoscopic Sleeve Gastrectomy. The Effect of Reversal Agents: Sugammadex vs. Neostigmine

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## ABSTRACT

**Background:** Incomplete muscle relaxant reversal or re-curarization may be associated with postoperative respiratory complications. In this retrospective study we compared the incidence of postoperative residual curarization and respiratory complications in association with the type of muscle relaxant reversal agent, sugammadex or neostigmine, in patients undergoing laparoscopic sleeve gastrectomy.

**Material and methods:** We reviewed the charts of all patients (179) undergoing laparoscopic sleeve gastrectomy from July 2012 to July 2013 at Wolfson Medical Center. Sugammadex 1.5-2 mg/kg (112 patients) or neostigmine 2.5 mg (67 patients) were used as reversal agents. Results were compared by the type of reversal agent employed. Compared parameters included demographic and anaesthetic data, residual curarization, oxyhemoglobin saturation (SpO<sub>2</sub>) in the recovery room (PACU), episodes of SpO<sub>2</sub> lower than 90% in PACU, unexpected intensive care (ICU) admissions, incidence of atelectasis and pneumonia, re-intubation and duration of hospitalization.

**Results:** Obstructive sleep apnea syndrome (OSAS) was more frequent in the sugammadex group (19% vs. 8%;  $p = 0.026$ ). Total intravenous anesthesia (TIVA) was more frequently associated with sugammadex (33% vs. 16%;  $p = 0.007$ ). There were no differences in postoperative residual curarization, SpO<sub>2</sub> < 90% episodes, reintubation, ICU admissions, pulmonary complications and duration of hospitalization.

**Conclusion:** With the inherent limitations of a retrospective study, the use of sugammadex following laparoscopic sleeve gastrectomy showed no advantage over neostigmine in terms of residual curarization and respiratory complications.

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

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## INTRODUCTION

Postoperative respiratory complications and pulmonary morbidity are associated with prolonged hospitalization, unexpected ICU admissions and mortality. Critical respiratory events (CRE) in the PACU occur frequently (up to 6.9%) [1] and include hypoxemia, upper airway collapse or obstruction, need for reintuba-

tion, pulmonary aspiration of gastric contents as well as apnea, atelectasis, negative pressure pulmonary edema and unexpected ICU admission [2,3]. Rose [4] identified risk factors for CRE including age > 60 years, male gender, diabetes, obesity, emergency surgery, operations longer than four hours, a combination of fentanyl and morphine administration during surgery and atracurium dose > 0.25 mg/kg/h. Ninety four percent of the

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patients received an anticholinesterase agent at the end of surgery. It has been also reported that abdominal and orthopaedic surgical patients have a higher risk for the development of PACU complications [1]. Some of these critical respiratory events are attributable to incomplete reversal of the effect of muscle relaxants [3], since residual relaxation may cause clinically relevant signs and symptoms of muscle weakness. Murphy [5], Plaud [2] and Sauer [6] have demonstrated that even minimal residual block was associated with hypoxaemia in the PACU.

Sugammadex, a reversal agent specific to the aminosteroid muscle relaxants, has been found to reach a peak effect faster than neostigmine [7]. The time to reach a train-of-four ratio (TOFR)  $\geq 90\%$  was 13 minutes with 50  $\mu\text{g}/\text{kg}$  neostigmine and only 1.7 minutes with 2 mg/kg sugammadex [8]. It follows that sugammadex may be better at preventing the occurrence of residual curarization and possibly postoperative respiratory complication when compared to neostigmine.

The present study was intended to determine the incidence of residual curarization and postoperative respiratory complications in patients undergoing laparoscopic sleeve gastrectomy in correlation with the type of muscle relaxant reversal agent (sugammadex vs. neostigmine). The hypothesis was that sugammadex may cause less postoperative residual curarization and respiratory complications.

## ■ MATERIALS AND METHODS

The local IRB (Helsinki committee) approved the study design. A sample size was calculated, based on the assumption that each episode of residual curarization may potentially be associated with a respiratory event/complication. The calculation indicated that a sample size of 150 ( $n=75$  in each group) would have an 80% power to detect a true, between-group difference (neostigmine group vs. sugammadex group) of partial curarization [9].

Anaesthesia was induced with fentanyl 100  $\mu\text{g}$ , midazolam 1 mg, propofol 1-2 mg/kg ("sleep" dose) and rocuronium 0.6 mg/kg both given by total body weight. Anaesthesia was maintained with either TIVA (propofol 100-200  $\mu\text{g}\cdot\text{kg}\cdot\text{min}^{-1}$  plus remifentanyl 0.05-2  $\mu\text{g}\cdot\text{kg}\cdot\text{min}^{-1}$  or fentanyl 25-200  $\mu\text{g}/\text{hr}$  by continuous infusion) or by an inhaled anaesthetic (isoflurane or sevoflurane 0.5-1MAC), 60% nitrous oxide in oxygen and aliquots of fentanyl 50  $\mu\text{g}$ , when deemed necessary. Addition-

ally patients received a slow intravenous infusion of dypirone 1 gram and tramadol 100 mg and boluses of 1 mg morphine up to a total dose of 5 mg. Patients with known OSAS and/or COPD did not receive intraoperative morphine. Patients who received TIVA were monitored with BIS sought to be maintained at 40-60. For patients at risk of aspiration, anaesthesia was induced in a rapid sequence manner with propofol and succinylcholine (dosed by total body weight). Patients with a suspected difficult airway were intubated either awake, fiberoptically or with videolaryngoscopy (GlideScope, Verathon). Most patients received rocuronium to provide surgical relaxation. Patients who received atracurium were not included in the study. The depth of muscle relaxation was assessed qualitatively by counting the TOF twitches with a nerve stimulator. Up to one spontaneous twitch was allowed throughout surgery by adding boluses of rocuronium 10-20 mg if more than one twitch in the train-of-four monitoring, was detected. At the end of surgery, full washout of the inhaled anaesthetic agents was undertaken. If the train of four monitoring was at least two twitches, the effect of rocuronium was reversed by either 2.5 mg neostigmine (control group  $n=67$ ) or by sugammadex 1.5-2 mg $\cdot\text{kg}^{-1}$  (study group,  $n=112$ ) given per total body weight. Patients were extubated when fully awake, able to lift and hold their heads up for at least 5 sec and have a TOF count of four assessed visually as strong twitches. Patients not fulfilling these criteria were extubated in the PACU after fulfilling these criteria. Residual curarization was clinically diagnosed either on the operating table or in the PACU as the patient's inability to lift and hold her/his head up for at least five seconds and/or inability to cough effectively despite receiving a reversal agent. Patients diagnosed with residual curarization received a second dose of either of the reversal agents.

The occurrence of early and late respiratory complications was compared by the type of reversal agent employed. The parameters measured and compared between the groups were: demographic and anaesthetic data, incidence of residual curarization,  $\text{O}_2$  saturation, number of events with  $\text{SpO}_2 < 90\%$ , incidence of airway obstruction, bronchospasm, pulmonary aspiration of gastric contents, apnea or hypoventilation, reintubation, unexpected ICU admissions, atelectasis or pneumonia and duration of hospitalization.

The primary endpoint of the study was the occurrence of residual curarization and the secondary endpoint was the occurrence of respiratory complications as defined above.

## Data analysis

Analysis of data was carried out using SPSS 11.0 statistical analysis software (SPSS Inc., Chicago, IL, USA). The assumptions required for parametric testing were validated using Kolmogorov-Smirnov and Bartlett's tests. The level of significance was set at  $\alpha = 0.05$ . Continuous variables with approximately normal distributions were reported as mean  $\pm$  standard deviation, and continuous variables with distributions significantly deviating from normal were described as median (min-max). The primary and secondary outcomes, incident residual curarization and postoperative respiratory complications were compared by muscle relaxant reversal agent type using the chi square test. Secondly, continuous variables were compared by reversal agent type using the t-test for independent samples or the Mann-Whitney U as appropriate, while categorical variables were compared using the chi square test. A model of post-operative complications was developed using logistic regression analysis. All tests were two-sided and considered significant at  $p < 0.05$ .

## RESULTS

The data of 179 patients undergoing laparoscopic sleeve gastrectomy during the period July 2012 to July 2013 were used in this retrospective observational study. There was no difference between the two study groups when comparing the demographic or morphometric characteristics including the ASA class (Table 1). The incidence of coexisting diseases was similar except for the OSAS which was significantly higher in the sugammadex group ( $p < 0.026$ ). Mallampati score and the incidence of difficult intubation and application of awake fiberoptic intubation were similar in both groups. In both groups, most patients' trachea was extubated on the operating table. There were no significant differences regarding duration of operation, time spent in PACU or duration of hospitalization.

The characteristics of anaesthetic drugs used for induction and maintenance and the postoperative analgesia (Table 2) were similar in both study groups except for higher percentage of use of TIVA ( $p = 0.007$ ) and higher dosage of fentanyl in the sugammadex group ( $p < 0.005$ ). Sevoflurane was used in 7% of each group while the rest of the patients maintained with inhaled anaesthetics received isoflurane. There were no differences in the dosage of other anaesthetic and analgesic drugs employed, nor was any difference in the dosage

**Table 1 – Demographic data by reversal agent**

Variable	Neostigmine n=67	Sugammadex n=112	P
Age- years	42 $\pm$ 12	42 $\pm$ 12	0.717
Sex – Females %	72	70	0.755
Co-existing disease %			
Hypertension	33.7	45.2	0.111
Coronary	0	1.7	0.508
C.O.P.D	7	10.5	0.385
O.S.A.S	8.1	19.3	0.026
Smokers	23.3	26.1	0.742
A.S.A - %			0.898
- A.S.A 2	88.2	86.1	
- A.S.A 3	11.8	13.9	
Weight – kg	120 $\pm$ 20	120 $\pm$ 21	0.992
Height- cm	163 $\pm$ 13	164 $\pm$ 11	0.104
B.M.I – kg/m <sup>2</sup>	43 $\pm$ 5	41 $\pm$ 7	0.590
Mallampati %			0.675
3	6	8	
4	2	4	
Mouth opening <3 cm %	1.2	2.6	0.637
Limited neck extension %	2.3	3.5	0.635
Difficult intubation %	3.5	2.6	0.717
Intubation with Glidescope %	20.9	15.7	0.334
Awake fiberoptic intubation %	0	0.9	0.386
Extubation on the operating table %	96.5	95.7	0.758
Intraoperative fluids - mL	1132 $\pm$ 366	1000 $\pm$ 375	0.858
Duration of surgery- Minutes	99 $\pm$ 37	90 $\pm$ 36	0.142
P.A.C.U stay – Minutes	152 $\pm$ 101	155 $\pm$ 82	0.795
Hospital stay- Days	5 $\pm$ 1	5 $\pm$ 1	0.280

Results are expressed as Mean  $\pm$  SD or percentage

A.S.A – American Society of Anesthesiologists

B.M.I – body mass Index;

C.O.P.D – chronic obstructive pulmonary disease;

O.S.A.S - Obstructive sleep apnea syndrome;

P.A.C.U – Post Anesthesia Care Unit

of rocuronium. There were two intraoperative surgical complications necessitating switch to open procedure, one for bleeding and another one due to technical difficulties. There were no intraoperative anaesthetic complications.

Table 3 shows that there were no statistically significant differences in the incidence of postoperative residual curarization, SpO<sub>2</sub> and respiratory complications and interventions.

**Table 2 – Anesthesia and analgesia data by reversal agent**

Variable	Neostigmine n=67	Sugammadex n=112	P
Induction agent %			0.768
Propofol	97.7	98.3	
Etomidate	2.3	1.7	
Intubation muscle relaxant %			
Succinylcholine	60.9	55.9	0.275
Rocuronium	29.1	44.1	0.150
T.I.V.A %	16.3	33	0.007
Use of fentanyl %	70.9	87	0.005
Total rocuronium dose - mg	67.6±20	66±19	0.201
Rocuronium dose - mg/total body weight	0.56	0.55	
Mean fentanyl dose - mg	0.264±97	0.209±85	0.00
Mean remifentanil dose - mg	0.47±0.22	0.49±0.23	0.241
Intraoperative morphine dose - mg	4.1±1	4.8±2	0.500
P.A.C.U morphine dose - mg	3.7 ± 3.6	4.5±4.2	0.423
P.A.C.U pethidine dose - mg	41±36	34±36	0.156
Surgical ward morphine dose - mg	3.7±3.6	4.5±4.2	0.142
Surgical ward pethidine dose - mg	41.3±36.3	34±36.1	0.156

Mean ± SD or percentage; T.I.V.A – Total Intravenous Anesthesia

**Table 3 – Respiratory complications by reversal agent**

Variable	Neostigmine n=67	Sugammadex n=112	P
Baseline SpO <sub>2</sub>	98.8	98.6	0.590
SpO <sub>2</sub> on P.A.C.U admission	98±1	98±1	0.576
SpO <sub>2</sub> at 30 min in the P.A.C.U	96±2	95±3	0.320
SpO <sub>2</sub> at 60 min in the P.A.C.U	97±0.5	97±1	0.795
Hypoxemia (SpO <sub>2</sub> < 90% with supplemental oxygen %)	0	3.5	0.181
Bronchospasm %	2	3.5	0.761
C.P.A.P required in the P.A.C.U %	7	12.2	0.245
Postoperative reintubation %	1.5	2.5	0.428
Need for second dose of reversal %	8.2	6.1	0.591
P.O.N.V %	41.9	47.8	0.401

Mean ± SD or percentage; C.P.A.P – Continuous Positive Airway Pressure

P.O.N.V – Postoperative Nausea and Vomiting

Re-dosing of reversal of muscle relaxants in case of residual curarization before extubation or weakness in the PACU was performed in 8.2% of the patients in the neostigmine group (re-dosed as 20µg.kg<sup>-1</sup>), half done in the OR and 6.1% in sugammadex patients, all of which were done in the OR (p=0.591). For primary reversal, two of these patients received 1.5 mg.kg<sup>-1</sup> and 1.3 mg.kg<sup>-1</sup> of sugammadex respectively. In the sugammadex group of patients, an additional dose of 1 mg.kg<sup>-1</sup> was added in partially curarized patients.

Seven patients were re-intubated, two for airway obstruction, both from the neostigmine group (one had residual curarization). Five other patients, all in the sugammadex group, were re-intubated for hypoventilation. Two of them had delayed re-intubations, four and eight hours after surgery due to CO<sub>2</sub> retention, attributed to the opioids given in the PACU. None of the patients with hypoventilation had partial curarization. One of the CO<sub>2</sub> retainers had severe OSAS and the other had both OSAS & COPD.

Hypoxaemia in the PACU ( $\text{SpO}_2 < 90\%$  with supplemental oxygen) was recorded in four cases all having been treated with sugammadex. Another two patients were recorded as having delayed hypoxaemia on the ward. All were associated with hypoventilation and all were re-intubated.

There were no patients with negative pressure pulmonary oedema or aspiration. One patient in the sugammadex group was transferred to the ICU due to surgical complication. One patient with atelectasis followed by pneumonia in the neostigmine group required antibiotic therapy.

There was no significant correlation between residual curarization and respiratory complications.

There were no cardiovascular complications. All patients recovered without residual sequelae and were discharged home.

## ■ DISCUSSION

Morbidly obese patients are prone to postoperative respiratory complications, including hypoventilation, hypoxaemia, hypercarbia and airway obstruction [8].

Sugammadex is a relatively new and effective agent for reversal of neuromuscular block and has the potential for prevention of residual curarization and respiratory complications owing to its beneficial pharmacological profile [10] consisting of its ability to remove the relaxant molecule from the synaptic gap.

In this retrospective study the incidence of postoperative residual curarization and respiratory complications in patients undergoing laparoscopic sleeve gastrectomy who received reversal with either sugammadex or neostigmine, were compared, the hypothesis being that sugammadex patients might have less residual muscle weakness and therefore are less prone to postoperative respiratory complications.

Sugammadex was found to have no statistical significant benefits over neostigmine in terms of residual curarization and early or late postoperative respiratory complications. This lack of benefit may at least in part stem from the suboptimal (less than recommended) dose of sugammadex administered to the two patients that developed residual curarization in the sugammadex group.

Published data regarding the rate of postoperative residual curarization are scarce and inconclusive. It

has been estimated to range between 5% and 85% [2,9]. This wide range of incidence can be explained by the variability in the definition of residual curarization, duration of muscle relaxant action, the use and type of neuromuscular monitoring, and the use or avoidance of reversal. The incidence of postoperative residual curarization may therefore be as high as 59% without reversal administration for intermediate-acting muscle relaxants, and approximately 48% when neostigmine is given as the reversal agent [9].

Murphy [3] reported a much lower incidence (0.8%) of critical respiratory event (CRE) as compared to 6.9%, as reported by Hines [1] in PACU patients, perhaps reflecting the use of intermediate rather than long-acting muscle relaxant, followed by neostigmine de-curarization at the end of surgery.

Murphy [5] demonstrated a clear association between CRE and residual curarization, since patients who developed CRE had a lower mean train of four ratio (0.62 vs 0.98).

The incidence of residual curarization and CRE in the PACU may be significantly reduced by intraoperative acceleromyographic monitoring of the neuromuscular function [3]. Residual curarization may affect the function of laryngeal and pharyngeal muscles resulting in impaired laryngeal reflexes and swallowing accompanied by dyspnea, voice change and ineffective coughing. These in turn, might result in silent aspiration and/or ineffective cleansing of secretions from the respiratory tract, complicating with atelectasis and pneumonia [2]. Chest X-rays performed two days postoperatively in patients treated with long-acting relaxants showed an atelectasis rate of 17% in patients with residual paralysis compared to 5% in patients without residual paralysis, suggesting that residual relaxation might contribute to late postoperative pulmonary morbidity such as atelectasis or pneumonia [11]. However, the only patient who developed atelectasis and pneumonia, though he belonged to the neostigmine group, did not apparently have partial curarization and did not require re-dosing of the reversal agent.

Anaesthetic complications have been reported to increase ten-fold when reversal of neuromuscular block was omitted [12]. However, factors other than residual paralysis such as central respiratory depression due to residual effect of opioids and general anaesthetics may also contribute to CRE and mortality. This was in fact the case of most of our patients who had respiratory

complications and required reintubation, mainly because of hypoventilation associated with OSAS and/or COPD.

Laparoscopic sleeve gastrectomy requires appropriate surgical conditions by judicious use of muscle relaxants, although uncertainty remains regarding their dosing in obese patients [13]. Similar uncertainty remains regarding the ideal dosing of sugammadex, which would prevent residual curarization. While some studies [14] recommend dosing sugammadex at 2 mg.kg<sup>-1</sup> total body weight if two twitches are present in the TOF count, Van Lanke [15] found that the appropriate dose should be calculated on the basis of ideal body weight according to the formula "Ideal body weight plus 40% of the excess weight". This means that though some of our patients were suboptimally dosed on a total body weight basis, they still received enough sugammadex according to Van Lanke's recommended dosage. Following neostigmine the time to the recovery to a TOF ratio of 0.9 in the obese patients (14.5 minutes) is significantly longer than in the normal weight group (6.9 min) [7]. Therefore, obese patients are at increased risk from residual curarization postoperatively. Although we expected to find less respiratory complications with sugammadex, the rate of these complications was similar in both groups, which may indicate that other factors rather than muscle weakness caused by residual curarization, might have an impact in the development of postoperative complications. Such factors may include patient's coexisting diseases, such as OSAS or COPD, and the severity of morbid obesity.

The current study has several limitations. First, it was performed retrospectively. Secondly, neostigmine was given as a single dose rather than based on the patient's body weight. Thirdly, some of the sugammadex patients received suboptimal doses of sugammadex. Finally, it was presumed that the patients with OSAS received preferentially more sugammadex due to the anaesthesiologist's concerns about these patients' risk of pulmonary complications, thus causing a bias in the interpretation of the rate of respiratory complications that occurred in the sugammadex group.

Despite all these limitations, the results are considered to be clinically relevant and demonstrate the need for large, prospective studies in order to confirm the benefits of sugammadex in reducing the incidence of postoperative residual curarization and respiratory complications.

## ■ CONCLUSION

With the inherent limitations of a retrospective study, the use of sugammadex following laparoscopic sleeve gastrectomy showed no advantage over neostigmine in terms of residual curarization and respiratory complications.

## ■ CONFLICT OF INTEREST

There are no conflicts of interest

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