Original Article

Emergency use of sugammadex after failure of standard reversal drugs and postoperative pulmonary complications: A retrospective cohort study

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Abstract

Background and Aims: The use of sugammadex instead of neostigmine for the reversal of neuromuscular blockade may decrease postoperative pulmonary complications. It is unclear if this finding is applicable to situations where sugammadex is administered after the administration of neostigmine. The objective of this study was to compare the incidence of a composite outcome measure of major postoperative pulmonary complications in patients who received sugammadex as a rescue agent after neostigmine versus those who received sugammadex alone for reversal of neuromuscular blockade.

Material and Methods: This retrospective cohort study analyzed the medical records of adult patients who underwent elective inpatient noncardiac surgery under general anesthesia and received sugammadex for reversal of neuromuscular blockade, at a tertiary care academic hospital between August 2016 and November 2018.

Results: A total of 1,672 patients were included, of whom 1,452 underwent reversal with sugammadex alone and 220 received sugammadex following reversal with neostigmine/glycopyrrolate. The composite primary outcome was diagnosed in 60 (3.6%) patients. Comparing these two groups, and after adjusting for confounding factors, patients who received sugammadex after reversal with neostigmine had more postoperative pulmonary complications than those reversed with sugammadex alone (6.8% vs. 3.1%, odds ratio, 2.29; 95% confidence interval [CI], 1.25 to 4.18; $P = 0.006$).

Conclusion: The use of sugammadex following reversal with neostigmine was associated with a higher incidence of postoperative pulmonary complications as compared to the use of sugammadex alone. The implications of using sugammadex after the failure of standard reversal drugs should be investigated in prospective studies.

Keywords: Neostigmine, neuromuscular blockade, postoperative pulmonary complications, sugammadex

Introduction

Neuromuscular blocking drugs (NMBDs) are routinely used as part of a balanced general anesthetic to provide muscular relaxation during endotracheal intubation and surgery. The effects of NMBDs are traditionally reversed by administering neostigmine, an acetylcholine esterase inhibitor.[1] Sugammadex, a novel cyclodextrin molecule, provides an alternative for reversing the effects of NMBDs.[2] It selectively binds to and sequesters amino-steroidal NMBDs, thereby reducing the availability of these drugs at the neuromuscular junction.

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Multiple studies have demonstrated that sugammadex has superior efficacy in the reversal of neuromuscular blockade, as compared with neostigmine.[3,4] The incidence of postoperative pulmonary complications (PPCs) may also be lower with the use of sugammadex versus neostigmine.[5] Thus, although sugammadex as a sole reversal agent has been evaluated extensively, its use as a "rescue agent" to reverse neuromuscular blockade after the administration of neostigmine has only been described in case reports.[6,7] It is unclear if sugammadex administration after neostigmine provides the same risk/benefit profile as compared to the use of sugammadex as a sole reversal agent.

The theoretical risk of parasympathetic stimulation from unbound neostigmine released after the administration of sugammadex might predispose patients to a higher risk of postoperative complications.[8] The primary aim of this study was to compare the incidence of PPCs between patients who received sugammadex after the administration of neostigmine versus those who received sugammadex alone for NMBD reversal. Our hypothesis was that patients reversed with neostigmine, followed by rescue sugammadex, will have a higher incidence of PPCs.

Material and Methods

We conducted this single-center, retrospective, observational cohort study after approval by the Institutional Review Board. A waiver of informed consent was granted (study no: 11043, approval date: 11/12/2018). All patients undergoing non-cardiac surgery under general anesthesia from August 2016 (date of initial drug availability at our institution) to November 2018 were identified. Study inclusion criteria were as follows: age ≥18 years, use of rocuronium and/or vecuronium during surgery, and administration of sugammadex during the intraoperative period. Patients undergoing emergency surgery were excluded.[9] The patients' electronic medical records (EMR) including intraoperative anesthesia records were then retrieved and analyzed.

The following data were extracted from the EMR: patient demographics, preoperative comorbidities, the American Society of Anesthesiologist (ASA) physical status classification, smoking status, admission, and discharge date, anesthesia start and end time, all medications administered during surgery, initial peripheral capillary oxygen saturation (SpO_2) before pre-oxygenation in the operating room (OR), and postoperative complications (as defined below). In addition, the last train-of-four (TOF) count (obtained via qualitative neuromuscular monitoring) documented before the administration of the initial neuromuscular blockade reversal agent (sugammadex or neostigmine) was recorded. Surgical procedures were identified using their Current Procedural Terminology (CPT) billing codes. Preoperative comorbidities and postoperative complications were identified using the International Classification of Diseases revision 10 (ICD-10) billing codes and differentiated based on the presence of admission (POA) determination, utilizing the hospital's billing and coding data. All opioid doses were converted to intravenous morphine equivalents. To assess patient comorbidities, as well as identify patients with existing chronic pulmonary disease, we used billing data to calculate the Charlson Comorbidity Index (CCI).[10]

We defined a composite outcome measure of major PPCs, including respiratory failure, pneumonia, and pulmonary edema during the index hospitalization.[11] These outcomes were defined using ICD-10 billing codes. Supplementary Table 1 provides a full list of the codes used to generate our outcome variables. The accuracy of these billing codes to define complications in the surgical population has been validated previously.[12,13] Secondary outcomes included the hospital length of stay, in-hospital mortality, and postoperative intensive care unit (ICU) admission.

Statistical analysis

We used nonparametric tests after verifying that the studied variables were not normally distributed using the Kolmogorov–Smirnov normality test. The level of significance was set at $\alpha = 0.05$. Because the continuous variables in this study were not normally distributed, they were described as median with inter-quartile ranges. Postoperative respiratory complications and other categorical variables were compared by NMBD type using Pearson's Chi-square test or Fisher's exact test. Continuous variables were compared by muscle relaxant reversal agent type using the rank-based nonparametric Mann–Whitney *U* test. We performed a sub-group analysis to assess for the primary outcome in patients with body mass index (BMI) >30 kg/m^2. We used propensity matching for the surgical duration and total intraoperative opioid consumption (nearest neighbor technique with a difference no more than 1% in propensity score) to eliminate the effect of these confounding factors. All tests were two-sided and considered significant at $P < 0.05$. Statistical analysis was performed using IBM SPSS 26.0 (Armonk, NY). Based on post-hoc power analysis, we calculated that a two group χ^2 test with a 5% two-sided significance level will have 72.74% power to detect the difference between a Group 1 proportion, π_1, of 0.068 and a Group 2 proportion, π_2 of 0.031 (odds ratio: 0.438) based on the sample sizes in our analysis.

Results

Between August 10, 2016, and November 30, 2018, 1,906 patients underwent non-cardiac surgery under general endotracheal anesthesia with muscle relaxation using an

amino-steroidal NMBD and received sugammadex for reversal. After excluding patients that were classified as emergent procedures, those younger than 18 years of age, and those with duplicate and incomplete documentation, 1,672 patients were included in the final analysis. Of these patients, 220 received sugammadex after neostigmine/glycopyrrolate administration (NGS group), whereas 1,452 received sugammadex alone (S group) [Figure 1].

Patient characteristics and type of procedures are depicted in Table 1. On comparing the NGS and the S group, there were no differences in age, gender, BMI, ASA physical status, CCI, chronic obstructive pulmonary disease (COPD), restrictive lung disease, asthma, oxygen use, pulmonary hypertension, history of obstructive sleep apnea (OSA), smoking status, and initial SpO_2 between the groups. There was no difference in major surgical procedures between the groups. The duration of surgery was significantly longer in the NGS group (median, 2.6 h [interquartile range [IQR]: 2.0–4.4] vs. 2.6 h [IQR: 1.7–4.0]; $P = 0.020$) [Table 2]. Sugammadex dosing was higher for the S group as compared to the NGS group (median: 2.5 mg/kg [IQR: 2.0–3.8] vs. 2.1 mg/kg [IQR: 1.8–2.7]; $P < 0.001$) and more patients required a second dose of sugammadex in the NGS group than the S group (6% vs. 2%, $P = 0.002$). The use of opioids was higher for the NGS group than in the S group (median 15.0 mg [IQR: 10.0–23.4] vs. 13.4 mg [IQR: 8.4–20.0]; $P < 0.005$). The TOF count was available for 75% of the

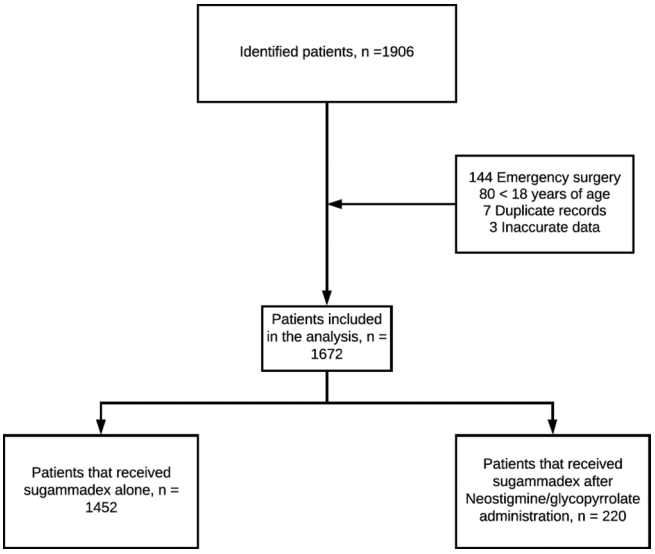

Figure 1: Flowchart of the study

Table 1: Patient characteristics

Variable	NGS (*n*=220)	S (*n*=1452)	*P*
Age in years, median (IQR)	58 (69-42)	58 (69-42)	0.723
Gender, *n* (%)			
Male	98 (45)	637 (44)	0.851
Body mass index (kg/m^2), median (IQR)	31 (41-26)	31 (38-26)	0.344
ASA physical status classification, *n* (%)			
1	6 (3)	32 (2)	0.627
2	56 (25)	379 (26)	0.838
3	143 (65)	949 (65)	0.917
4	15 (7)	92 (6)	0.785
Charlson Comorbidity index, median (IQR)	1 (3-0)	1 (2-0)	0.055
COPD, *n* (%)	47 (21)	324 (22)	0.752
Restrictive lung disease, *n* (%)	0	4 (0.3)	_
Asthma, *n* (%)	22 (10)	205 (14)	0.097
Home oxygen use, *n* (%)	6 (3)	19 (1)	0.106
Pulmonary hypertension, *n* (%)	9 (4)	40 (3)	0.274
Obstructive sleep apnea, *n* (%)	46 (21)	249 (17)	0.173
Smoking status, *n* (%)			
Current smoker	41 (19)	271 (19)	0.992
Former smoker, quit >1 year	53 (24)	341 (23)	0.844
Unknown	8 (4)	50 (3)	0.884
Never smoked before	118 (54)	790 (54)	0.831
Initial SpO_2 (%), median (IQR)	99 (100-97)	99 (100-98)	0.500
Procedure type, *n* (%)			
Thoracic major	12 (5)	62 (4)	0.384
Upper and lower abdomen major	45 (20)	254 (17)	0.299
Other	163 (74)	1136 (78)	0.169

NGS: Neostigmine/glycopyrrolate and Sugammadex; S: Sugammadex only group; IQR: interquartile range; ASA: American Society of Anesthesiologist; COPD: chronic obstructive pulmonary disease, SpO_2: peripheral capillary oxygen saturation. Other procedure type includes minor thoracic and abdominal surgery, head and neck, spine and spinal cord surgery, minor urologic and gynecologic surgery, hip, leg, foot, shoulder, arm, and hand surgery, and radiologic procedures

Table 2: Comparison of intraoperative factors

Variable	NGS (*n*=220)	S (*n*=1452)	*P*
Length of surgery (h), median (IQR)	2.6 (2.0-4.4)	2.6 (1.7-4.0)	0.020
Muscle relaxant used, *n* (%)			
Rocuronium	220 (100)	1,443 (99.4)	
Vecuronium	0	9 (0.6)	
Succinylcholine	20 (9.1)	143 (9.8)	0.724
Total muscle relaxant dose (mg/TBW), median (IQR)			
Rocuronium	1.1 (0.8-1.6)	1.0 (0.8-1.5)	0.008
Reversal agent dose, median (IQR)			
Sugammadex, (mg/TBW)	2.1 (1.8-2.7)	2.5 (2.0-3.8)	<0.001
Neostigmine, (mcg/TBW)	46.8 (35.7-55.6)	-	
>1 Repeat dose of sugammadex, *n* (%)	13 (6)	33 (2)	0.002
Train of Four, median (IQR)	4 (2-4)	4 (1-4)	0.050
IV morphine equivalent dose (mg), median (IQR)	15.0 (10.0-23.4)	13.4 (8.4-20.0)	0.005

NGS, neostigmine/glycopyrrolate and Sugammadex; IQR, interquartile range; mg, milligram; TBW, total body weight; mcg, microgram; IV, intravenous

included patients and was lower in the S group (median: 4 [IQR: 1–4] vs. 4 [IQR: 2–4]; $P = 0.050$).

The total incidence of PPCs was 3.6% (60/1,672). The incidence of PPCs in the NGS and S groups was 6.8% (15/220) and 3.1% (45/1,452), respectively. Patients reversed with sugammadex after the administration of neostigmine/glycopyrrolate were more likely to develop PPCs than those that were reversed with sugammadex alone (odds ratio, 2.29; 95% CI, 1.25 to 4.18, $P = 0.006$). Patients with BMI > 30 had a higher incidence of PPCs in the NGS group than the S group, 9/82 (11%) and 17/567 (3%), $P < 0.001$ [Table 3]. This association was significant even after matching for the surgical duration and total intraoperative opioid consumption. Hospital length of stay and in-hospital mortality were also higher for the NGS group than for the S group (median: 2.2 days [IQR: 1.0–6.2] vs. 1.4 days [IQR: 0.4–4.3), $P < 0.001$) and 2% vs. 0.3%, $P = 0.002$, respectively. The intensive care unit (ICU) admission rate was higher for the NGS group than for the S group, 22% vs. 17%, but did not reach statistical significance ($P = 0.081$).

Table 3: Postoperative pulmonary complications based on body mass index

BMI kg/m²	*n*	NGS and PPC	Sugammadex alone and PPC	*P*
BMI<25	316	2/41	9/275	0.601
BMI 25-30	465	4/58	19/407	0.464
BMI>30	891	9/121	17/770	0.001

BMI, body mass index; NGS, neostigmine/glycopyrrolate and Sugammadex; PPC, postoperative pulmonary complications

Discussion

In this retrospective observational cohort study, we found that patients who received sugammadex after the administration of neostigmine experienced a higher incidence of PPCs, a longer hospital length of stay, and higher in-hospital mortality, as compared to patients who received sugammadex as a sole reversal agent. Given the theoretical risk for uncontrolled parasympathetic activation when sugammadex is administered after neostigmine, and the lack of guidance on the use of sugammadex in this setting, these findings raise concerns.

Sugammadex use has been reported to result in a significant reduction in postoperative residual paralysis as compared to neostigmine, and also a reduction in the incidence of PPCs.[5] Most of these data, however, are derived from studies that used sugammadex as the sole reversal agent. There is limited literature on the use of sugammadex after administration of neostigmine and its impact on PPCs. Cheong *et al.*[14] demonstrated that the combined use of sugammadex and neostigmine may decrease the recovery time and the required dosage of sugammadex to reverse rocuronium-induced moderate neuromuscular blockade. However, the study was limited by its small patient numbers, the inclusion of only healthy ASA class 1 or 2 patients, and a significant difference in body weight between the comparison groups. Isolated reports have also described the emergency use of sugammadex after incomplete reversal from rocuronium-induced neuromuscular blockade with successful outcomes,[6,7] but studies assessing the impact of sugammadex administration in patients that have already received anticholinergic medications are lacking. To our knowledge, this study is the first to assess the impact of the use of sugammadex after standard reversal drugs on PPCs.

The overall incidence of PPCs in our study was 3.6%, which is consistent with the rate of between 2 and 9% reported in the medical literature.[15-17] The recently published STRONGER study also reported a similar incidence of 3.5% in the group reversed with sugammadex.[5] We found a significant difference in the incidence of PPCs between the two comparison groups, with the NGS group having almost

double the incidence of PPCs as compared to the S group. Our incidence of PPCs in the NGS group was higher than that reported in the literature for patients receiving neostigmine as a reversal agent, 11 highlighting the higher risk associated with the use of sugammadex as a rescue agent after standard reversal. Thus, identifying the need to better understand and characterize the use of sugammadex as a "rescue" agent after the administration of neostigmine/glycopyrrolate for reversal of neuromuscular blockade.

Common side effects of neostigmine are related to muscarinic activation, excess accumulation of acetylcholine, and overstimulation of the vagal nerve. This may result in excessive salivation, muscle weakness, increased mucus production, and depressed mentation. These adverse effects may contribute to an increased risk for PPCs. Further, administration of neostigmine/glycopyrrolate, after recovery from the neuromuscular block, increases upper airway collapsibility and impairs genioglossus muscle activation in response to negative pharyngeal pressure,[18] and neostigmine administration has also been linked to higher rates of atelectasis.[19] Hence, unopposed action of neostigmine after the administration of sugammadex may cause or exacerbate adverse respiratory events, a hypothesis that merits future investigation.[20] Longer hospital length of stay and higher in-hospital mortality in patients in the NGS group could be related to the higher incidence of PPCs in this group, as the occurrence of PPCs is a risk factor for postoperative morbidity and mortality.[15,21]

Because the "rescue" use of sugammadex has never been evaluated in the literature and there are no published data and recommendations on appropriate dosing in this setting, we feel that there might be an urge amongst providers to use a lower dose of sugammadex. This could explain the difference in the dose of sugammadex between the two groups in our study. The use of a lower dose of sugammadex in the "rescue" setting may cause an inadequate reversal of neuromuscular blockade, leading to residual muscle paralysis and may also be a potential cause of the observed difference in PPCs between the two groups in our study. Similarly, our study unearthed an unexpectedly high failure rate of neostigmine reversal, at 110 failures per year and it is unclear if this was due to improper dosing of neostigmine or lack of enough time allowed for neostigmine to achieve the peak effect. Although the incidence of the residual neuromuscular blockade has been reported to be as high as 30%,[22,23] it is unclear how much of this could be attributed to dosing and timing of reversal agents and we feel that more research in this arena is needed.

Another major finding in our study was the high incidence of PPCs in obese patients in the NGS group. High BMI is a recognized risk factor for the development PPCs;[24] however, the higher incidence in the NGS group warrants further investigation. It has been reported that recovery to a TOF ratio of 0.9 in obese patients is slower and higher doses of neostigmine (up to 50 μg/kg) may be needed to facilitate faster recovery.[25,26] Neostigmine doses in our study ranged from 30 μg/kg to 60 μg/kg. Inadequate dosing in obese patients could have played a significant role in the development of PPCs.

The study is limited by its retrospective nature and inclusion of data from a single center. Confounding by indication is a likely risk; however, we did not find a difference between the two groups with regard to co-morbid conditions that would have increased the likelihood of both the outcome and the intervention/exposure. The change in the practice of administration of sugammadex over time is another confounding factor. Further, TOF monitoring was not consistently used in our study before the administration of reversal agents. Although this is a major limitation, the use of a monitoring device has been inconsistently used in dosing of reversal agents,[27] and neuromuscular monitoring is not a part of the American Society of Anesthesiologists' Standards for Basic Anesthetic Monitoring. Also, neuromuscular monitoring is not universal across the US academic hospitals, as can be seen in the recently published STRONGER study wherein almost 43% of patients in the neostigmine group and 29% in the sugammadex group had no documentation of TOF within 30 min of extubation.[5] Regardless, the use of neuromuscular monitoring is paramount and should not be undermined in clinical practice, as it has been shown to prevent PPCs.[28,29] In our study, reversal with neostigmine took place after TOF monitoring in most patients. However, data showing the time of last neuromuscular blockade administered before the reversal, whether repeat TOFs were obtained before rescue sugammadex administration in the cohort experiencing incomplete neostigmine reversal, and the time between reversal and extubation remains unknown.

Another major limitation is not knowing the reason for the use of sugammadex as a rescue neuromuscular blockade reversal. It is also unknown why some clinicians opted for using sugammadex instead of repeated administration of neostigmine and glycopyrrolate to a maximum recommended dose. The assumption that the patients with neostigmine could not be extubated for reasons other than residual neuromuscular blockade cannot be refuted. Therefore, we cannot conclude with certainty if the decision to administer rescue sugammadex was carried out based on a pragmatic measure of neuromuscular monitoring or simply clinical suspicion. In addition, giving sugammadex cannot guarantee complete neuromuscular recovery without neuromuscular monitoring, whether it is given alone or as a rescue reversal to neostigmine.[30]

Our findings may also have been impacted by the difference in intraoperative characteristics between the two groups, such as length of surgery and increased narcotic consumption. However, our findings remained consistent even after adjusting for these confounding factors. Considering the conflicting evidence on the impact of renal dysfunction on sugammadex clearance,[31,32] we did not assess for renal impairment in our analysis that potentially might have affected the results. Our institutional policy does not recommend the use of sugammadex in patients with renal failure and sugammadex was not used in this group of patients. The results of our study also highlight that the failure of neostigmine therapy probably has causes that cannot be remedied in every case by the additional administration of sugammadex. This could be due to known influences of multicollinearity or unrecognized confounders. In other words, it is not sufficient to treat a residual neuromuscular blockade, which should probably have been achieved by the additional administration of sugammadex to prevent postoperative pulmonary complications. Thus, indicating that there must be other or additional reasons for the postoperative pulmonary complications than a residual neuromuscular blockade. A few other limitations of this study are associated with other unknown data that can potentially act as cofounding variables that include temperature monitoring, benzodiazepine use, and total intraoperative intravenous fluid administration. Despite these limitations, our observations run counter to previously published data demonstrating the safety of sugammadex rescue after neostigmine and further prospective studies should be performed before recommending routine use of sugammadex after neostigmine administration.

In conclusion, we found that a significant proportion of patients undergoing non-cardiac elective surgery under general anesthesia with neuromuscular blockade receive sugammadex after the administration of traditional reversal agents and these patients have a higher incidence of postoperative pulmonary complications as well as postoperative mortality as compared to those that receive sugammadex alone.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Full list of codes used to generate outcome variables

Diagnosis	ICD-10 codes
Pneumonia	J13, J15.0, J15.1, J15.20, J15.211, J15.212, J 15.4, J15.5, J15.6, J15.8, J15.9, J16.8, J18.0, J18.1, J18.2, J18.8, J18.9
Acute pulmonary edema	J81.0
Acute respiratory failure	J95.821, J96.00, J96.01, J96.02
Acute pulmonary insufficiency	J95.1, J95.2
Respiratory failure	J96.90, J96.91, J96.92
Acute respiratory distress syndrome	J80
Acute respiratory distress	R06.03
Acute/chronic respiratory failure	J96.20, J96.21, J96.22
Pneumonitis	J69.0, J69.1, J69.8

Abbreviations: ICD-10, International Classification of Diseases revision 10 clinical modification