ORIGINAl ReSeArCh

Post-operative respiratory outcomes associated with the use of sugammadex in laparoscopic colorectal cancer surgery: a retrospective, propensity score matched cohort study

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Abstract
Sugammadex can rapidly reverse neuromuscular blockade and has several advantages over cholinesterase inhibitors. It is unclear, however, whether administration of sugammadex in the absence of intraoperative deep neuromuscular blockade has direct clinical benefits. The present study retrospectively assessed the ability of sugammadex to prevent post-operative respiratory adverse events in patients undergoing laparoscopic colorectal surgery. The medical records of patients who underwent laparoscopic colorectal surgery from 2014 to 2018 in a tertiary care hospital were reviewed. Patients who underwent reversal of neuromuscular blockade with sugammadex or pyridostigmine were subjected to propensity score matching. To assess their relative effects on post-operative adverse respiratory events (defined as a composite of \(\text{SpO}_2 < 94\%\) in the post-anesthesia care unit, additional oxygen supplementation during ward transfer or stay, and emergency use of sugammadex in the post-anesthesia care unit), the incidence of these effects was compared in propensity score matched groups of patients treated with sugammadex or pyridostigmine. Of the 602 patients, 210 remained in each group after propensity score matching. The incidence of post-operative respiratory adverse events did not differ significantly in the two groups. These findings suggest that the unrestricted administration of sugammadex not preceded by intra-operative deep neuromuscular blockade does not have clinical benefits, when compared with pyridostigmine, in preventing post-operative respiratory adverse events.

Keywords
Sugammadex; Rocuronium; Neuromuscular blocking agents; Laparoscopic surgery; Post-operative complication

1. Introduction
Sugammadex is a synthetic cyclodextrin molecule that can rapidly reverse neuromuscular blockade induced by steroidal neuromuscular blocking drugs (NMBD) such as rocuronium. Sugammadex acts by encapsulating free rocuronium in plasma, creating a concentration gradient that enables the removal of rocuronium from neuromuscular junctions. Sugammadex also possesses several advantages over traditionally used cholinesterase inhibitors. It is a biologically inactive compound that does not bind to any other receptor in the body \([1, 2]\), thus avoiding undesirable physiological effects, such as tachycardia and arrhythmia, resulting from combined treatment with cholinesterase inhibitors and anticholinergics \([3]\).

Post-operative respiratory adverse events due to residual neuromuscular blockade remain a constant concern to anesthesiologists. This is especially true during deep neuromuscular blockade, as the dose of rocuronium needs to be significantly increased. Although sugammadex has been shown to efficiently prevent such complications after the use of deep neuromuscular blockade \([4–7]\), it remains unclear whether treatment with sugammadex has clinical benefits in the absence of intra-operative deep neuromuscular blockade. This study therefore evaluated the effects of sugammadex on the incidence of post-operative respiratory adverse events in the absence of routine deep neuromuscular blockade.

2. Methods
This retrospective observational study was approved by the Institutional Review Board of Chungnam National University...
Hosptial (CNUH 2019-11-040, Chairperson Prof. KS Suh) on 29 November 2019, and the trial was registered at the Clinical Research Information Service, a clinical trial registry in South Korea (CRIS, identifier: KCT0004551). Informed consent was waived, due to the retrospective design of the study. This article adheres to the applicable STROBE guidelines [8].

### 2.1 Data collection

The electronic medical records of patients who underwent laparoscopic colorectal cancer surgery, performed by a single experienced surgeon from 2014 to 2018 in a tertiary care hospital, were reviewed retrospectively. Patients were excluded if they had undergone robotic surgery or colorectal cancer surgery combined with surgery on other organs; were directly transferred to the intensive care unit after surgery; or were administered neuromuscular blocking agents other than rocuronium. Patients with insufficient records (incomplete or missing information on administration of a neuromuscular blocking or reversing agent) were also excluded. Only patients who received sugammadex as the primary reversal agent were regarded as having been treated with sugammadex.

Patient characteristics (demographic and clinical) and post-operative outcomes were recorded. Demographic characteristics included age, sex, height, weight, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, smoking status, and comorbidities. Liver cirrhosis was identified by its disease code and renal dysfunction was defined as a pre-operative estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m². The records of pre-operative consultations with gastroenterologists and pulmonologists were regarded as surrogate markers of associated comorbidities. Clinical characteristics included the date of surgery, type of procedure (anterior resection, colectomy, low anterior resection), the attending anesthesiologist (A, B, C, others), the duration and type of anesthesia (inhalation or total intravenous), the dose (weight-adjusted) and administration method (bolus or continuous infusion) of rocuronium, and the interval between the last dose of rocuronium and reversal agent. Anesthesiologists who administered anesthesia to fewer than 10% of patients were designated as ‘others’. The duration of anesthesia was defined as the interval between the beginning of induction and the time

### Table 1. Demographic and clinical characteristics of all patients and of propensity score matched patients.

<table>
<thead>
<tr>
<th></th>
<th>Before matching</th>
<th>After matching</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pyridostigmine</td>
<td>Sugammadex</td>
</tr>
<tr>
<td>(n = 289)</td>
<td>(n = 313)</td>
<td></td>
</tr>
<tr>
<td>Sex (Male/Female)</td>
<td>175/114</td>
<td>201/112</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65.0 [57.0; 73.0]</td>
<td>68.0 [61.0; 75.0]</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.7 [21.8; 26.1]</td>
<td>24.3 [21.7; 26.2]</td>
</tr>
<tr>
<td>ASA &gt; 2</td>
<td>29 (10.0%)</td>
<td>60 (19.2%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>76 (26.3%)</td>
<td>65 (20.8%)</td>
</tr>
<tr>
<td>Gastroenterologic comorbidity</td>
<td>50 (17.3%)</td>
<td>60 (19.2%)</td>
</tr>
<tr>
<td>Pulmonary consultation</td>
<td>21 (7.3%)</td>
<td>44 (14.1%)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>7 (2.4%)</td>
<td>14 (4.5%)</td>
</tr>
<tr>
<td>Anesthesia duration (min)</td>
<td>200.0 [170.0; 230.0]</td>
<td>205.0 [180.0; 251.0]</td>
</tr>
<tr>
<td>Procedure</td>
<td>0.02</td>
<td>0.031</td>
</tr>
<tr>
<td>Anterior resection</td>
<td>101 (34.9%)</td>
<td>109 (34.8%)</td>
</tr>
<tr>
<td>Colectomy</td>
<td>76 (26.3%)</td>
<td>80 (25.6%)</td>
</tr>
<tr>
<td>Low anterior resection</td>
<td>112 (38.8%)</td>
<td>124 (39.6%)</td>
</tr>
<tr>
<td>TIVA</td>
<td>5 (1.7%)</td>
<td>24 (7.7%)</td>
</tr>
<tr>
<td>Rocuronium infusion</td>
<td>2 (0.7%)</td>
<td>30 (9.6%)</td>
</tr>
<tr>
<td>Rocuronium dose (mg/kg)</td>
<td>1.2 [1.0; 1.4]</td>
<td>1.3 [1.1; 1.5]</td>
</tr>
<tr>
<td>Last rocuronium interval (min)</td>
<td>49.0 [35.0; 62.0]</td>
<td>50.0 [35.0; 62.0]</td>
</tr>
</tbody>
</table>

Results expressed as mean ± SD, median [IQR], or number (%). Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologist physical status; eGFR, estimated glomerular filtration rate; TIVA, total intravenous anesthesia; SMD, standardized mean difference.
the patient left the operating room. Post-operative outcomes included extubation time (the interval between administration of reversal agent and extubation); length of stay in the post-anesthesia care unit (PACU); SpO2 in the PACU; additional post-operative oxygen supplementation; post-operative nausea and vomiting; length of post-operative hospital stay; and need for reoperation.

### 2.2 Outcome measures

The primary outcome was the incidence of post-operative respiratory adverse events stratified by the use of sugammadex. Respiratory adverse events were defined as a composite of SpO2 < 94% in the PACU, additional oxygen supplementation during ward transfer or stay, and emergency use of sugammadex in the PACU. The need for oxygen supplementation was determined by the attending physician (an anesthesiologist in the PACU or a surgeon in the ward). In our institution, oxygen is initially provided to patients with SpO2 < 94% in room air, and those with a decreasing trend of SpO2 if no signs of severe respiratory compromise are observed. Secondary post-operative outcomes included time to extubation, durations of PACU and hospital stay, post-operative nausea and vomiting, and need for reoperation.

### 2.3 Statistical analysis

All statistical analyses were performed using R software (version 3.6.3, R Project for Statistical Computing, Vienna, Austria). To account for possible selection bias and confounding factors, 1:1 propensity score matching was performed using the MatchIt package (3.0.2) in R. The dependent variable was use of sugammadex, scored as 1, versus use of a cholinesterase inhibitor (pyridostigmine), scored as 0. Nearest neighbor matching with a 0.1 caliper was performed, with patient characteristics (age, sex, BMI, ASA > 2, smoking, and comorbidities) and clinical factors (type of procedure, duration and type of anesthesia, dose and method of administration of rocuronium, and the interval between the last dose of rocuronium and the first dose of reversal agent) designated as covariates to be corrected. Standardized mean differences were calculated to validate matching balance, with a difference < 0.1 indicating that the two groups were sufficiently balanced.

After validating the balance, the normality of continuous data was assessed using the Shapiro-Wilk test. If normality was satisfied, the results were expressed as mean ± SD and groups were compared by independent t-tests. If normality was not satisfied, the results were expressed as median (IQR), and groups were compared using Kruskal-Wallis Rank sum tests. Categorical data were expressed as number (%) and compared using χ²-squared or Fisher’s exact test, as appropriate. For all calculations, a two-tailed P-value < 0.05 was considered.
TABLE 2. Incidence of respiratory adverse events in the propensity score matched groups.

<table>
<thead>
<tr>
<th></th>
<th>Pyridostigmine (n = 210)</th>
<th>Sugammadex (n = 210)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory adverse event</td>
<td>21 (10.0%)</td>
<td>27 (12.9%)</td>
<td>0.443</td>
</tr>
<tr>
<td>Desaturation (SpO₂ &lt; 94%)</td>
<td>4 (1.9%)</td>
<td>10 (4.8%)</td>
<td>0.174</td>
</tr>
<tr>
<td>Additional O₂ supply</td>
<td>17 (8.1%)</td>
<td>23 (11.0%)</td>
<td>0.406</td>
</tr>
<tr>
<td>Emergency sugammadex use</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>1</td>
</tr>
</tbody>
</table>

Results expressed as number (%).

TABLE 3. Post-operative outcomes in the propensity score matched groups.

<table>
<thead>
<tr>
<th></th>
<th>Pyridostigmine (n = 210)</th>
<th>Sugammadex (n = 210)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extubation time (min)</td>
<td>9.0 [7.0; 10.0]</td>
<td>8.0 [6.0; 10.0]</td>
<td>0.028</td>
</tr>
<tr>
<td>PACU stay (min)</td>
<td>44.0 [35.0; 53.0]</td>
<td>45.0 [38.0; 52.0]</td>
<td>0.369</td>
</tr>
<tr>
<td>PONV</td>
<td>14 (6.7%)</td>
<td>13 (6.2%)</td>
<td>1</td>
</tr>
<tr>
<td>Hospital stay (day)</td>
<td>6.0 [5.0; 7.0]</td>
<td>6.0 [5.0; 7.0]</td>
<td>0.261</td>
</tr>
<tr>
<td>Re-operation</td>
<td>9 (4.3%)</td>
<td>9 (4.3%)</td>
<td>1</td>
</tr>
</tbody>
</table>

Results expressed as median [IQR] or number (%). Abbreviations: PACU, post-anesthesia care unit; PONV, post-operative nausea and vomiting.

3. Results

During the study period, 711 patients underwent laparoscopic colorectal cancer surgery; of these, 109 were excluded (43 patients underwent robotic surgery, 4 patients were directly transferred to the intensive care unit, 22 patients received combined surgery, and 40 patients had insufficient medical records). Of the 602 remaining patients, 313 received sugammadex and 289 received pyridostigmine. Propensity score matching selected 210 pairs of patients (Fig. 1). Their demographic and clinical characteristics are shown in Table 1. Each covariate had an acceptable standardized mean difference (< 0.1) after matching.

The primary outcome, incidence of postoperative respiratory adverse events, did not differ between the two groups (21/210 in the pyridostigmine group, and 27/210 in the sugammadex group, $P = 0.443$) (Table 2). In addition, there were no differences between these groups for each respiratory adverse event. Other post-operative outcomes are shown in Table 3. The extubation time was significantly longer in the pyridostigmine than in the sugammadex group (9.0 [7.0; 10.0] min vs. 8.0 [6.0; 10.0] min, $P = 0.028$), but there were no other significant differences in outcomes between the propensity score matched groups. Changes in the rate of sugammadex administration and the composition of the anesthesiologists before propensity score matching are shown in Fig. 2. There was an increasing trend in the use of sugammadex during the study period along with the change in the composition of the anesthesiologists.

4. Discussion

The present study evaluated the benefits of routine sugammadex administration in patients undergoing laparoscopic colorectal cancer surgery without intra-operative deep neuromuscular blockade. Our results showed no significant differences in the incidence of post-operative respiratory adverse events and other post-operative outcomes between propensity matched groups of patients treated with sugammadex or pyridostigmine. Although extubation time was significantly shorter with the use of sugammadex, its clinical significance is questionable.

Several studies have reported that sugammadex reduces post-operative respiratory complications. For example, sugammadex reduced in-hospital rates of post-operative respiratory adverse events after general and otolaryngologic surgery [12]. Sugammadex was also found to reduce the incidence of mechanical ventilation in the PACU due to residual neuromuscular blockade from 0.63% to 0.20% [13]. However, the definition of post-operative respiratory complications varies among studies, and the effects of sugammadex have not been well studied using the recently revised definition of post-operative pulmonary complications [9]. The present study differs from previous studies in that the effects of sugammadex were evaluated using this revised definition [9].

Residual neuromuscular blockade is associated with post-operative respiratory adverse events, such as hypoxemia and upper airway obstruction [14–16]. Sugammadex was shown to be superior to cholinesterase inhibitors in reducing residual neuromuscular blockade [17–20] and shortening the recovery time from rocuronium-induced neuromuscular blockade [19, 21]. Moreover, a meta-analysis found that sugammadex shortened times to discharge from the operating room and PACU [22]. Other studies, however, found that the pharmacologic advantages of sugammadex over cholinesterase inhibitors did not translate into actual clinical benefits. For example, a recent randomized trial comparing sugammadex and neostigmine showed that, although sugammadex reduced residual neuromuscular blockade, post-operative pulmonary function and atelectasis did not differ in the two groups of
FIGURE 2. Rates of sugammadex use by individual anesthesiologists over time. The left vertical axis indicates reversal agents (upper block; S: sugammadex, lower block; P: pyridostigmine). The right vertical axis indicates the year. The horizontal axis indicates the composition of the anesthesiologists in each year. Vertical partitions for each year indicate the individual anesthesiologists during that year. The horizontal partition in each anesthesiologist column indicates the rate of sugammadex use in each year by the anesthesiologist. The number of patients anesthetized by anesthesiologists with a high preference for sugammadex (B, C, others) increased over time, whereas the number anesthetized by anesthesiologist with a low preference for sugammadex (A) decreased.

patients [20]. Moreover, a large scale multicenter study found that sugammadex was not superior to neostigmine in preventing post-operative pulmonary complications [23]. Similarly, the present study found that sugammadex did not improve post-operative respiratory outcomes when compared with pyridostigmine.

Routine administration of sugammadex may be beneficial, however, in certain clinical situations. For example, sugammadex has been shown to efficiently reduce respiratory complications during the use of deep neuromuscular blockade [1, 24] and to benefit patients undergoing relatively short surgical procedures, such as laryngeal microsurgery, when spontaneous recovery from neuromuscular is hardly expected [25, 26]. A recent retrospective study also found that sugammadex was associated with reduced rates of post-thymectomy myasthenic crisis in patients with myasthenia gravis [27].

Currently, except for emergency situations, such as reversal immediately after rocuronium-induced neuromuscular blockade, and specific clinical situations [25–27], there are no absolute indications for the use of sugammadex. Therefore, clinical practice regarding the use of sugammadex in the absence of deep neuromuscular blockade can vary among physicians. Although the patient characteristics did not change significantly over time, the use of sugammadex increased steadily throughout the entire study period, being used in most patients in 2018. Based on variations and changes in physician
preference, the increased use of sugammadex over time was associated with individual preference and changes in staff at our institution. Because year and anesthesiologist preference were multicollinear in their effects on the use of sugammadex, these factors were intentionally omitted from the matching process. It has been recommended that variables dependent merely on policy or time factors should not be included in the propensity score matching process [28].

This study had several limitations. First, due to its retrospective design, the data quality and accuracy may be compromised. Detailed information about patient comorbidities, the extent of the surgery (e.g., tumor size, blood loss), and opioid usage during and after surgery were unavailable, which may have affected study outcomes. Although pre-operative consultation and anesthesia time were investigated, true patient comorbidities and the extent of surgery were undetermined. Second, all patients were from a single center, thus limiting the generalizability of these results. Finally, neuromuscular monitoring was not performed, and the doses of the reversing agents were not quantitated. Although this may be a more general and realistic reflection of clinical practice, care should be taken when comparing our results with those of studies in which neuromuscular blocking agents and reversal agents were administered quantitatively.

5. Conclusions
The administration of sugammadex without preceding intraoperative deep neuromuscular blockade does not reduce postoperative respiratory adverse events compared with pyridostigmine. These results suggest that sugammadex should be used when clear clinical benefits can be expected (e.g., deep neuromuscular blockade). Future studies evaluating indications for the use of sugammadex are necessary.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
This retrospective observational study was approved by the Institutional Review Board of Chungnam National University Hospital (CNUH 2019-11-040, Chairperson Prof. KS Suh) on 29 November 2019, and the trial was registered at the Clinical Research Information Service, a clinical trial registry in South Korea (CRIS, identifier: KCT0004551). Informed consent was waived due to the retrospective design of the study.

AUTHORS’ CONTRIBUTIONS
BH, CL and SHY designed and supervised the research. CO and YJ wrote the manuscript and performed data analysis and visualization. SS, SY and SJ performed the data investigation. WC supervised the methodology and manuscript writing.

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CONFLICT OF INTEREST
The authors declare no competing interests.

REFERENCES


