Effect of Sugammadex on Postoperative Myasthenic Crisis in Myasthenia Gravis Patients: Propensity Score Analysis of a Japanese Nationwide Database

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BACKGROUND: In myasthenia gravis (MG) patients, postoperative myasthenic crisis, and residual neuromuscular blocking agent (NMBA) can cause respiratory failure that requires mechanical ventilation. However, it remains unclear whether the use of sugammadex for NMBA reversal reduces postoperative myasthenic crisis in MG patients undergoing surgery. We analyzed the association between use of sugammadex and postoperative myasthenic crisis in patients with MG using a national inpatient database.  

METHODS: Adult patients with MG who received thymectomy under general anesthesia were identified in the Japanese Diagnosis Procedure Combination database from July 1, 2010 to March 31, 2016. Patients who received sugammadex (sugammadex group) were compared with those who did not receive sugammadex (control group). The primary outcome was postoperative myasthenic crisis, and the secondary outcomes were postoperative pneumonia, tracheostomy, 28-day mortality, total hospitalization costs, and length of stay after surgery. Propensity scores were estimated by logistic regression based on the following variables: age; sex; body mass index (BMI); smoking index; history of cancer; Charlson comorbidity index (CCI); type of thymectomy; time from hospital admission to surgery; use of plasma exchange, immunosuppressants, corticosteroids, anticholinesterase, and oral benzodiazepine before surgery; type of hospital; and treatment year. The outcomes were compared using stabilized inverse probability of treatment weighting (IPTW) analyses to obtain good between-group balance.  

RESULTS: Of 795 patients identified, 506 patients received sugammadex and 289 patients did not. After stabilized IPTW, the sugammadex group was associated with a decrease in postoperative myasthenic crisis (22/507 [4.3%] vs 25/288 [8.7%]; odds ratio [OR], 0.48; 95% confidence interval [CI], 0.25–0.91), but not associated with a decrease in postoperative pneumonia (5/507 [1.0%] vs 7/288 [2.4%]; OR, 0.44; 95% CI, 0.17–1.14) or tracheostomy (7/507 [1.4%] vs 10/288 [3.5%]; OR, 0.38; 95% CI, 0.12–1.22) compared with the control group. The sugammadex group had significantly lower median (interquartile range) total hospitalization costs ($13,186 [$11,250–$16,988] vs $14,119 [$11,713–$20,207]; P < .001) and median length of stay after surgery (10 [8–15] vs 11 [8–18] days; P < .001), compared with the control group.  

CONCLUSIONS: In this retrospective observational study, sugammadex was associated with reductions in postoperative myasthenic crisis and total hospitalization costs in adult patients with MG who received thymectomy. Given the present findings, sugammadex should be routinely administered for MG patients undergoing thymectomy. (Anesth Analg 2020;130:367–73)

KEY POINTS  
• Question: Does the administration of sugammadex decrease the frequency of postoperative myasthenic crisis in myasthenia gravis (MG) patients undergoing thymectomy?  
• Findings: In a nationwide retrospective cohort, we found that the use of sugammadex for neuromuscular blocking agent (NMBA) reversal was associated with a lower odds of postoperative myasthenic crisis.  
• Meaning: The administration of sugammadex may be preferable choice for MG patients undergoing thymectomy.

Myasthenia gravis (MG) is an autoimmune disorder of neuromuscular junctions, most commonly involving antiacetylcholine receptor antibodies, and characterized by high sensitivity to nondepolarizing neuromuscular blocking agents (NMABs). Thymoma is observed in 10%–15% of patients affected by MG.1 Although thymectomy is a standard treatment for MG, anesthetic management...
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is complicated. Anesthesiologists need to administer minimal or no NMBA because patients with MG may have higher risks of postoperative residual NMBA and postoperative pneumonia than patients without MG. Furthermore, myasthenic crisis, a life-threatening respiratory failure caused by weakness of the upper airway or respiratory muscles, has similar clinical manifestations to postoperative residual NMBA. Patients who present with myasthenic crisis require intubation because of poor airway protection, inadequate secretion clearance, and hypoventilation.

Sugammadex reduces the activity of steroidal NMBA such as rocuronium and vecuronium by encapsulating these agents. Unlike anticholinesterase, sugammadex does not increase acetylcholine in neuromuscular junctions and does not interfere with the perioperative anticholinesterase level. Therefore, sugammadex may be an ideal drug for reversal of muscle paralysis in patients with MG. Although several case series studies have described the clinical consequences of using sugammadex in MG patients, data have been lacking on the associations between sugammadex and postoperative complications.

We hypothesized that the use of sugammadex for reversal of muscle paralysis is associated with reduced postoperative myasthenic crisis and respiratory complications. The purpose of the present study was to evaluate our hypothesis using data from a Japanese national inpatient database. The study did not focus on interactions between the body and the drug.

METHODS
The study was approved by the Institutional Review Board of The University of Tokyo. The requirement for informed consent was waived because of the anonymous nature of the data. This article adheres to the applicable the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Data Source
This was a retrospective cohort study conducted in the Japanese Diagnosis Procedure Combination database from July 1, 2010 to March 31, 2016. The database includes nationwide inpatient administrative claims and discharge data in Japan. All 82 academic hospitals are obliged to participate in the database, while community hospitals can participate voluntarily. All clinical data for individual patients are recorded at discharge by their attending physicians. To optimize the accuracy of the recorded data, the responsible physicians refer to medical charts and electronically submit the data using a uniform data entry format. The database includes the following information: main diagnosis, comorbidities present at admission, and complications after admission recorded with International Classification of Diseases, Tenth Revision (ICD-10) codes accompanied by text data in Japanese; surgical interventions and medical procedures with original Japanese codes; patient characteristics (age, sex, weight, height); daily records of drugs and devices used during hospitalization; type of hospital (academic or nonacademic); length of stay; and discharge status.

Sugammadex
Since January 2001, sugammadex has been covered by the Japanese health insurance system for NMBA reversal. At present, it is widely used in Japan because it brings about rapid reversal of NMBA, is only contraindicated in patients with known hypersensitivity, and is fully available without restriction.

Patient Selection
We identified patients who were admitted with a diagnosis of MG (ICD-10 code, G70.0) and received thymectomy under general anesthesia. We included patients ≥20 years of age. We excluded patients with a written diagnosis of “suspected” MG to improve the adequacy of patient selection and those who received surgery at ≥14 days after admission to unify the patient background characteristics. The eligible patients were categorized into 2 groups: patients who received sugammadex during surgery (sugammadex group) and patients who did not (control group).

Variables and Outcomes
The following variables were compared between the 2 groups to check the differences in patient background characteristics: age; sex; body mass index (BMI); smoking index; history of cancer; Charlson comorbidity index (CCI); type of thymectomy; time from hospital admission to surgery; use of plasma exchange, immunosuppressants, corticosteroids, anticholinesterase, and oral benzodiazepine before surgery; type of hospital; and treatment year. BMI was categorized by the World Health Organization definitions as underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), obese (≥30 kg/m²), and missing. The CCI is a method for predicting mortality by classifying or weighting comorbidities. The CCI was defined by 17 comorbidities related to clinical conditions recorded in charts and has been validated in many populations. Many researchers have developed coding algorithms using International Classification of Diseases, Ninth Revision (ICD-9) or ICD-10 codes. As a result, the CCI is widely used to control for confounding by comorbidities in observational studies. We categorized type of thymectomy as transsternal thymectomy or videoscopic thymectomy and hospital types as academic or nonacademic.

The primary outcome was postoperative myasthenic crisis, defined as respiratory failure requiring prolonged mechanical ventilation after thymectomy.
(≥3 days) or reintubation within 30 days after thymectomy.12,13 The secondary outcomes were postoperative pneumonia, tracheostomy, 28-day mortality, total hospitalization costs, and length of stay after surgery. Postoperative pneumonia was identified by recorded ICD-10 codes (J10–J18).

Statistical Analysis
Continuous variables are presented as means (standard deviation) or medians (interquartile range). Categorical variables are presented as counts (percentage).

We adjusted for confounding between the sugammadex and control groups using propensity score methods instead of multivariable analysis because the event of postoperative myasthenic crisis was expected to be rare and a multivariable model for association between exposure and outcome would not be feasible. To estimate the propensity scores, a logistic regression model was used with the following baseline variables suspected to be related to both the exposure and outcome:14 age; sex; BMI; smoking index; history of cancer; CCI; type of thymectomy; time from hospital admission to surgery; use of plasma exchange, immunosuppressants, corticosteroids, anticholinesterase, and oral benzodiazepine before surgery; type of hospital; and treatment year. We examined the balance in baseline covariates that could affect sugammadex and postoperative myasthenic crisis before and after inversely weighting by the propensity score (ie, stabilized inverse probability of treatment weighting [IPTW]) using absolute standardized differences, with differences of >10% regarded as imbalanced.15 We assessed the normality of continuous variables using graphical displays and the Kolmogorov–Smirnov test. We also illustrated the distributions of propensity scores before and after stabilized IPTW. We controlled for measured confounding factors by stabilized IPTW, using the average treatment effect (ATE). The ATE measures the difference in average outcomes between the treated and the controlled subjects in the matched population. Stabilized IPTW creates a pseudo data set in which the distribution of potentially confounding variables is balanced between the treatment and control groups.16 The sum of weights in the treated group and the sum of weights in the control group are equal, mimicking a 1:1 allocation.

To examine the odds ratios (ORs) and 95% confidence intervals (CIs) for postoperative myasthenic crisis, postoperative pneumonia, and tracheostomy, we performed a multivariable logistic regression analysis after stabilized IPTW.17,18 In the database used in this research, data derived from multiple hospitals were structured by 2 strata: hospitals and patients. The use of sugammadex was expected to vary by hospital preference.19 We therefore fit the regression model with a generalized linear model with a cluster–robust variance estimator using unique hospital identifiers to adjust for clustering of patients within hospitals after stabilized IPTW. No other variables were included in the generalized linear model. Total hospital costs and length of stay after surgery were compared by the Mann-Whitney U test.

Two sensitivity analyses were performed. First, we defined the exclusion criteria as patients who received surgery at ≥7 days or ≥28 days after admission rather than ≥14 days. ORs and 95% CIs were calculated. Second, we calculated the E-value. The E-value is related to evidence for causality in observational studies that are potentially subject to confounding, according to a recent report.20 The second sensitivity analysis was conducted by calculating the E-value, which represents the minimum strength of association that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment–outcome association.

We assumed a proportion of postoperative myasthenic crisis of 10% and defined a clinically important difference as 4%, assuming a 2-sided α error of .05 and a power of .8.13 As a result, 721 cases were required for each arm of the study. All statistical analyses were performed using IBM SPSS Statistics for Windows version 23.0 (IBM, Armonk, NY) and Stata Statistical Software: Release 15 (Stata Corp, College Station, TX). Two-tailed values of P < .05 were considered significant.

RESULTS
We identified 1158 MG patients who underwent thymectomy. Of these, 795 patients were eligible for the study, comprising 506 patients in the sugammadex group and 289 in the control group (Figure 1).
The baseline characteristics are shown in Table 1. Compared with the control group before stabilized IPTW, the sugammadex group was significantly more likely to receive videoscopic surgery and less likely to receive corticosteroids, anticholinesterase, academic hospital admission, and treatment in 2010. With the use of the stabilized IPTW method, a pseudo data set was created with 795 patients (507 and 288 subjects in the sugammadex and control groups, respectively). All baseline characteristics were well balanced between the 2 groups. Figure 2 shows the distributions of propensity scores in the sugammadex and control groups before and after stabilized IPTW. After stabilized IPTW, the distribution of propensity scores was similar between the sugammadex and control groups.

In the stabilized IPTW analyses, the sugammadex group was associated with significantly decreased odds of postoperative myasthenic crisis (sugammadex versus control: 4.3% vs 8.7%; OR, 0.48; 95% CI, 0.25–0.91; P = .02) compared with the control group. The sugammadex group was not associated with a decreased odds of postoperative pneumonia (OR, 0.44; 95% CI, 0.17–1.14; P = .09) or tracheostomy (OR, 0.38; 95% CI, 0.12–1.22, P = .94) (Table 2). The sugammadex group had significantly lower median (interquartile range) total hospitalization costs ($13,186 [$11,250–$16,988] vs $14,119 [$11,713–$20,207]; P < .001) and median length of stay after surgery (10 [8–15] vs 11 [8–18] days; P < .001), compared with the control group.

The first sensitivity analysis showed that sugammadex remained significantly associated with postoperative myasthenic crisis in patients who received surgery at <28 days (OR, 0.55; 95% CI, 0.30–1.09; P = .09) and was not associated with postoperative myasthenic crisis in patients who received surgery at <7 days (OR, 0.50; 95% CI, 0.23–1.08). The second sensitivity analysis showed that the E-value for the observed estimate of the association between sugammadex

Table 1. Baseline Characteristics of the Patients Before and After Stabilized Inverse Probability of Treatment Weighting

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted Groups</th>
<th>Adjusted Groups</th>
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<tbody>
<tr>
<td></td>
<td>Sugammadex (n = 506)</td>
<td>Control (n = 289)</td>
</tr>
<tr>
<td>Age, mean (standard deviation)</td>
<td>55.0 (14.1)</td>
<td>53.9 (14.8)</td>
</tr>
<tr>
<td>Sex (male), n (%)</td>
<td>235 (46.4)</td>
<td>144 (49.8)</td>
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<tr>
<td>Body mass index (kg/m²), n (%)</td>
<td>&lt;18.5</td>
<td>35 (6.9)</td>
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<tr>
<td></td>
<td>18.5–24.9</td>
<td>321 (63.4)</td>
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<tr>
<td></td>
<td>25.0–29.9</td>
<td>107 (21.1)</td>
</tr>
<tr>
<td></td>
<td>≥30</td>
<td>36 (7.1)</td>
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<tr>
<td>Missing</td>
<td>7 (1.4)</td>
<td>4 (1.4)</td>
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<tr>
<td>Smoking, n (%)</td>
<td>Nonsmoker</td>
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<td>Former or current smoker</td>
<td>191 (37.7)</td>
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<td></td>
<td>Unknown</td>
<td>32 (6.3)</td>
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<td>History of cancer, n (%)</td>
<td>0</td>
<td>264 (52.2)</td>
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<td></td>
<td>≥1</td>
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<td>Type of thymectomy surgery</td>
<td>Transsternal thymectomy</td>
<td>366 (72.3)</td>
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<tr>
<td></td>
<td>Videoscopic thymectomy</td>
<td>140 (27.7)</td>
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<tr>
<td>Time from hospital admission to surgery in days, mean (standard deviation)</td>
<td>4.4 (2.5)</td>
<td>4.6 (2.8)</td>
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<td>Preoperative medical therapy, n (%)</td>
<td>Plasma exchange</td>
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<td></td>
<td>Immunosuppressant</td>
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<td></td>
<td>Corticosteroid</td>
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<td></td>
<td>Anticholinesterase</td>
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<tr>
<td></td>
<td>Academic hospital, n (%)</td>
<td>234 (46.2)</td>
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<tr>
<td>Treatment year, n (%)</td>
<td>2010</td>
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<tr>
<td></td>
<td>2011</td>
<td>51 (10.1)</td>
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<td>177 (35.0)</td>
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<td></td>
<td>2015</td>
<td>152 (30.0)</td>
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Abbreviation: D, standardized difference.
DISCUSSION

Using a national inpatient database in Japan, this study investigated the effect of sugammadex for NMBA reversal in patients with MG who underwent thymectomy. Sugammadex was associated with significant reductions in postoperative myasthenic crisis and total hospitalization costs in this study.

Two previous studies have examined the effect of sugammadex in patients with MG. A recent retrospective large cohort study reported lower risks for adverse pulmonary outcomes in American Society of Anesthesiologists physical status classes III and IV patients after reversal with sugammadex compared with neostigmine or no reversal drug.\(^2\)\(^1\) Regarding MG, a case series of 117 patients showed no desaturation (oxygen saturation [\(\text{SpO}_2\]) \(\leq 95\%\) in room air), no elevation of carbon dioxide (\(\text{PCO}_2\); 10% above baseline), no reintubation, and no clinical signs of acquired bronchopneumonia.\(^8\) However, there are no data on the association between sugammadex and postoperative myasthenic crisis. To our knowledge, this was the first study to examine the association between sugammadex and postoperative myasthenic crisis in patients with MG.

The strength of the present study was the evaluation of sugammadex for MG patients who received thymectomy using a large retrospective study. The study showed that the sugammadex group was associated with a significant decrease in the odds of postoperative myasthenic crisis in comparison with the control group and the sensitivity analyses supported the main analysis. This may be clinically plausible because sugammadex has a different mechanism from anticholinesterase. Sugammadex immediately binds to free intravascular rocuronium, leading to formation of a stable complex that can be excreted and removed in the urine. Meanwhile, the efficacy of anticholinesterase is limited by a ceiling effect, in that profound neuromuscular blockade cannot be reversed.\(^2\)\(^2\) Moreover, anticholinesterase use is associated with a risk of cholinergic crisis. Therefore, if neuromuscular weakness occurred after anticholinesterase was given to MG patients, it would be difficult to distinguish among residual NMBA, myasthenic crisis, or cholinergic

| Table 2. Outcomes in the Stabilized Inverse Probability of Treatment Weighting Groups |
|-----------------------------------|---|---|-----------|---------|
|                                    | Sugammadex (\(n = 507\)) | Control (\(n = 288\)) | OR\(^a\) (95% CI) | \(P\)   |
| Primary outcome                   |                            |                        |                    |
| Postoperative myasthenic crisis\(^b\) | 22 (4.3)                  | 25 (8.7)                | 0.48 (0.25–0.91)   | .02     |
| Secondary outcomes               |                            |                        |                    |
| Postoperative pneumonia           | 5 (1.0)                    | 7 (2.4)                 | 0.44 (0.17–1.14)   | .09     |
| Tracheostomy                      | 7 (1.4)                    | 10 (3.5)                | 0.38 (0.12–1.22)   | .11     |
| 28-day mortality                 | 0 (0)                      | 4 (1.4)                 | NA                  | NA      |

Data are presented as n (%) or OR (95% CI). Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.
\(^a\)ORs were calculated by a generalized linear model with a cluster-robust variance estimator using unique hospital identifiers after IPTW.
\(^b\)Postoperative myasthenic crisis was defined as respiratory failure requiring prolonged mechanical ventilation after thymectomy (\(\geq 3 \text{d}\)) or reintubation within 30 days after thymectomy.
This study indicates that sugammadex should be used for MG patients who receive thymectomy for reversal of muscle paralysis after surgery rather than anticholinesterase. The market price of sugammadex is much higher than that of neostigmine. Sugammadex (200 mg) costs approximately $100, while neostigmine (2 mg) costs approximately $2.50 in Japan. However, our study showed that sugammadex was associated with significantly reduced total hospitalization costs compared with the control group. Moreover, the shorter length of stay after surgery contributed to the decrease in total hospital costs in the sugammadex group. Even though the price of sugammadex is high, it can reduce total hospitalization costs.

This study has some limitations. First, although we investigated nationwide data using stabilized IPTW, the study cannot adjust for unmeasured confounders. However, we obtained consistent point estimations of the ORs in the first sensitivity analysis. Moreover, the second sensitivity analysis, using the E-value, showed that the OR of postoperative myasthenic crisis in the sugammadex group compared with the control group was 0.48 (95% CI, 0.25–0.91), with an E-value of 3.59 (lower 95% CI, 1.43). This means that the observed OR of 0.48 could be explained away by an unmeasured confounder associated with both the treatment and the outcome with a risk ratio of 3.59 each, net of the measured confounders. Furthermore, the CI for the observed effect could be moved to include the null by an unmeasured confounder associated with both the treatment and the outcome with a risk ratio of 1.43 each, net of the measured confounders. Therefore, even if this study had unmeasured confounding, it would not alter the conclusion. Furthermore, it may be difficult to perform randomized trials in MG patients because of the rarity of the disease. Second, data for symptoms, severity, duration of MG, pulmonary function tests before and after surgery, and acetylcholine receptor antibody test results were not included in the database. Third, it was difficult to examine the pharmacodynamics and pharmacokinetics of sugammadex based on the properties of the database. Finally, sugammadex was not associated with a decrease in postoperative pneumonia in the study. The proportion of postoperative pneumonia may have been underestimated because we extracted postoperative pneumonia using recorded ICD-10 codes. Despite these limitations, the study provides new knowledge about N MBA reversal during thymectomy in MG patients.

In conclusion, the present study using a large nationwide database demonstrated that sugammadex use for N MBA reversal was associated with decreased odds of postoperative myasthenic crisis and contributed to a reduction in total hospitalization costs in patients with MG who received thymectomy. Sugammadex could help improve the strategies for postoperative myasthenic crisis while saving hospitalization costs. Given the present findings, sugammadex should be routinely used for MG patients undergoing thymectomy.

DISCLOSURES

Name: Hideyuki Mouri, MD.
Contribution: This author helped design the study, analyze and interpret the data, and prepare the manuscript.

Name: Taisuke Jo, MD, PhD.
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Contribution: This author helped analyze and interpret the data.

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Contribution: This author helped collect and interpret the data. All authors approved the final manuscript.

Name: Hideo Yasunaga, MD, PhD.
Contribution: This author helped design the study; collect, analyze, and interpret the data; and prepare the manuscript.

This manuscript was handled by: Ken B. Johnson, MD.

REFERENCES


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