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ORIGINAL RESEARCH ARTICLE

Safety of sugammadex for myasthaenia gravis patients undergoing general anaesthesia: a retrospective database study

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Abstract

Background: Using neuromuscular blocking drugs (NMBDs) for patients with myasthaenia gravis remains a challenge in perioperative management. Sugammadex has enabled the safe use of NMBDs. We investigated whether the adverse outcomes, and the treatment used for myasthaenic crises and tracheotomy, are affected by NMBD use in patients with myasthaenia gravis under general anaesthesia.

Methods: Patients with myasthaenia gravis who underwent general anaesthesia were retrieved from the Diagnostic Procedure Combination/Per-Diem Payment systems in Japan between 1 January 2010 and 30 November 2020. This database did not contain information on the severity of myasthaenia gravis (Osserman classification). Patients who received rocuronium and sugammadex were compared with those who did not receive NMBDs after propensity-score matching. We excluded patients who underwent emergency or cardiac surgery or tracheal intubation before anaesthesia. The primary outcome was receipt of postoperative treatment used for myasthaenic crises.

Results: Among 2304 surgical patients with comorbid myasthaenia gravis, propensity-score matching identified 788 patients administered rocuronium and sugammadex and 449 not administered NMBDs. On comparing the treatment used for myasthaenic crises, we found no significant difference between the two groups (6.2% *vs* 5.3%; hazard ratio, 1.14; 95% confidence interval, 0.70–1.85).

Conclusions: Use of rocuronium and sugammadex in patients with myasthaenia gravis did not significantly affect the receipt of postoperative treatment used for myasthaenic crises compared with no use of NMBDs. As well as the severity of myasthaenia gravis was not fully adjusted, it is unclear whether intraoperative administration of rocuronium with the use of sugammadex postoperatively is acceptable and further investigations are needed.

Keywords:: autoimmune disease; general anaesthesia; myasthaenia gravis; neuromuscular blocking drugs; neuromuscular disease; rocuronium; sugammadex

Myasthaenia gravis is a neuromuscular disease caused by autoimmune attack of acetylcholine receptors (AChRs) at the neuromuscular junction, resulting in a decrease in the number of AChRs and a neuromuscular transmission disorder.[1,2] It is commonly stated that myasthaenia gravis increases the sensitivity of patients to non-depolarising neuromuscular blocking drugs (NMBDs), and that the frequency of postoperative complications, including myasthaenic crisis, increases with the use of NMBDs.[3] Because the sensitivity to NMBDs of patients with myasthaenia gravis has been ascribed to the number of AChRs in each individual, the use of NMBDs in general anaesthesia requires neuromuscular monitoring and the calculation of an optimal dose of NMBDs.[4] If there are residual effects of the NMBD at the end of surgery, it is necessary to reverse them so as to minimise the risk of postoperative complications.

Sugammadex, a neuromuscular blocking agent-binding agent that rapidly reverses the effects of aminosteroid NMBDs,

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Table 1 Patient, hospital, and surgical characteristics.

	Full cohort			Matched cohort		
	RB+sugammadex (n = 1169)	No NMBD (n = 455)	SMD	RB+sugammadex (n = 788)	No NMBD (n = 449)	SMD
Age (years)	63.7 (15.0)	62.1 (16.1)	0.10	62.3 (15.9)	62.4 (16.1)	0.00
Male sex	523 (44.7)	190 (41.8)	0.06	339 (43.0)	188 (41.9)	0.02
BMI (kg/m^2)	23.6 (4.1)	23.1 (4.2)	0.12	23.3 (4.1)	23.2 (4.2)	0.03
Smoking history	385 (32.9)	149 (32.7)	0.07	226 (28.7)	135 (30.1)	0.04
Ocular type	70 (6.0)	24 (5.3)	0.03	46 (5.8)	24 (5.3)	0.02
Charlson comorbidity index			0.20			0.03
0	622 (53.2)	283 (62.2)		476 (60.4)	278 (61.9)	
1, 2	435 (37.2)	147 (32.3)		261 (33.1)	146 (32.5)	
3, 4	99 (8.5)	19 (4.2)		43 (5.5)	19 (4.2)	
≥5	13 (1.1)	6 (1.3)		8 (1.0)	6 (1.3)	
Preoperative medicine						
Immunosuppressive drugs	383 (32.8)	191 (42.0)	0.19	307 (39.0)	186 (41.4)	0.05
Steroids	931 (79.6)	345 (75.8)	0.09	608 (77.2)	341 (75.9)	0.03
Cholinesterase inhibitors	620 (53.0)	247 (54.3)	0.03	445 (56.5)	244 (54.3)	0.04
Operative Anaesthetic agent						
Inhalation	838 (71.7)	312 (68.6)	0.07	569 (69.7)	309 (68.8)	0.02
Operation type			0.25			0.07
Thoracotomy	471 (40.3)	158 (34.7)		274 (34.8)	158 (35.2)	
Abdominal surgery	328 (28.1)	53 (11.6)		179 (22.7)	53 (11.8)	
Others	370 (31.7)	244 (53.6)		335 (42.5)	238 (53.0)	
Thymectomy	379 (32.4)	143 (31.4)	0.02	250 (31.7)	143 (31.8)	0.00
Hospital information						
Training hospital	946 (80.9)	368 (80.9)	0.00	638 (81.0)	363 (80.8)	0.0
Year			0.19			0.06
2010	5 (0.4)	2 (0.4)		4 (0.5)	2 (0.4)	
2011	15 (1.3)	9 (2.0)		11 (1.4)	7 (1.6)	
2012	22 (1.9)	17 (3.7)		20 (2.5)	17 (3.8)	
2013	56 (4.8)	18 (4.0)		48 (6.1)	17 (3.8)	
2014	75 (6.4)	49 (10.8)		64 (8.1)	48 (10.7)	
2015	110 (9.4)	48 (10.5)		82 (10.4)	46 (10.2)	
2016	130 (11.1)	56 (12.3)		83 (10.5)	56 (12.5)	
2017	189 (16.2)	69 (15.2)		126 (16.0)	69 (15.4)	
2018	197 (16.9)	73 (16.0)		127 (16.1)	73 (16.3)	
2019	202 (17.3)	59 (13.0)		122 (15.5)	59 (13.1)	
2020	168 (14.4)	55 (12.1)		101 (12.8)	55 (12.2)	

Data are presented as n (%), except age and Body Mass Index, which are presented as mean±standard deviation.
RB, rocuronium bromide; NMBD, neuromuscular blocking drugs; SMD, standardised mean difference.

was approved for use in Japan in 2010 and in the US in 2015.[5] A recent study limited to patients with post-thymectomy myasthaenia gravis reported that anaesthetic management with rocuronium reversed by sugammadex was not associated with an increased risk of respiratory complications.[6,7] However, as thymectomy is recommended in patients with myasthaenia with a short duration of disease,[8,9] most patients who undergo thymectomy surgery are in the early stages of disease onset. Furthermore, a significant number of myasthaenic crises reportedly occur in the context of surgical procedures, particularly thymectomies, and often lead to prolonged postoperative tracheal intubation and extended hospital stays.[10] Post-thymectomy patients may have different backgrounds and outcomes compared with patients with myasthaenia gravis undergoing other surgical procedures. The safety of anaesthetic management with rocuronium reversed with sugammadex in patients with myasthaenia gravis undergoing non-thymectomy surgery needs to be investigated.

Our primary aim was to examine whether the incidence of adverse outcomes in myasthaenia gravis patients undergoing any surgical procedure is affected by the use of NMBDs using data from a nationwide large inpatient database. The main outcomes included the postoperative treatment used for myasthaenic crises (tracheal intubation, continuous ventilator management for more than 3 postoperative days, use of steroid pulses, plasma exchange, and immunoglobulin preparations) and tracheotomy.

Methods

The ethics board of Kyoto University Graduate School and Faculty of Medicine approved this retrospective study on 30 November 2016 (approval number R0885). There was no requirement to obtain informed consent because of the anonymised nature of the data.

Data source

This study's dataset was provided by Medical Data Vision (MDV) Co., Ltd. (Tokyo, Japan).[11] The MDV database uses the Diagnostic Procedure Combination (DPC) Payment System/Per-Diem payment System in Japan. The database contains data from more than 400 acute hospitals and more than 30

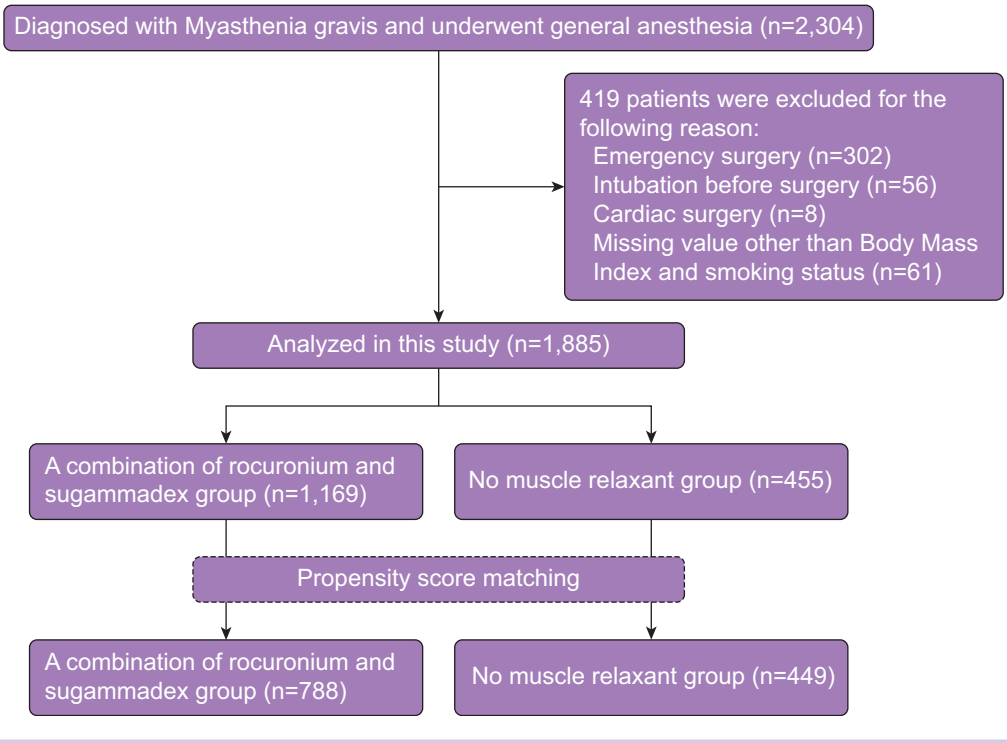

Fig 1. Study flow diagram.

million patients in Japan. It includes data on patient characteristics, such as age, gender, BMI, self-reported smoking history, International Classification of Diseases, 10th Edition (ICD-10) clinical diagnosis codes, and Japan-specific standardised procedure codes. It also contains data on administrative claims, such as drug prescription information coded according to medical procedures recorded using Japan-specific standardised procedure codes (K codes), and the WHO Anatomical Therapeutic Chemical Classification (ATC).

Study population

This study included the records of all patients with myasthaenia gravis who underwent general anaesthesia during their hospitalisation between 1 January 2010 and 30 November 2020. Myasthaenia gravis was identified using ICD-10 codes at the time of admission. We selected patients who were prescribed a combination of rocuronium and sugammadex and those who received no NMBDs; we excluded patients who underwent tracheal intubation before anaesthesia and those who underwent emergency or cardiac surgery. Patients with incomplete data for the index procedure were also excluded. Services, procedures, and medications used to identify general anaesthesia, surgery, and prescribed drugs were retrieved.

Study variables

Patient characteristics and hospital information (age, sex, BMI, smoking history, and type of hospital) were collected. Comorbidities, including coronary artery disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, chronic kidney disease, and diabetes mellitus, were identified using the respective ICD-10 codes. Comorbidities were scored and evaluated using the Charlson Comorbidity Index.[12] Procedure-related variables included the type of surgery (thymectomy, thoracotomy, abdominal surgery, or other procedures). Because of the structure of the database, neuromuscular monitoring data were not available. Furthermore, it would be appropriate to use the Osserman classification to eliminate the effects of different severities of myasthaenia gravis, but this variable could also not be extracted from the database. To adjust for the differences in the severity of myasthaenia gravis between the two groups, we identified ocular myasthaenia gravis and oral medications for myasthaenia gravis prescribed before surgery and the type of hospital (training or non-training).

Outcome definitions

Myasthaenic crisis could not be identified from the database as it has no specific diagnostic code. Since tracheal intubation, continuous postoperative ventilator management for at least 3 days, steroid pulses, plasma exchange, or immunoglobulin preparations are used to treat myasthaenic crisis,[13] we defined these as the composite endpoint "treatment used for myasthaenic crises." Referring to previous studies, steroid pulse therapy was defined as the use of hydrocortisone equivalent of at least 2500mg day^{-1} for 3 consecutive days.[14] The secondary outcomes were tracheostomy, discharge destination classification, and postoperative length of stay. All outcomes were identified using the relevant procedural or ATC codes.

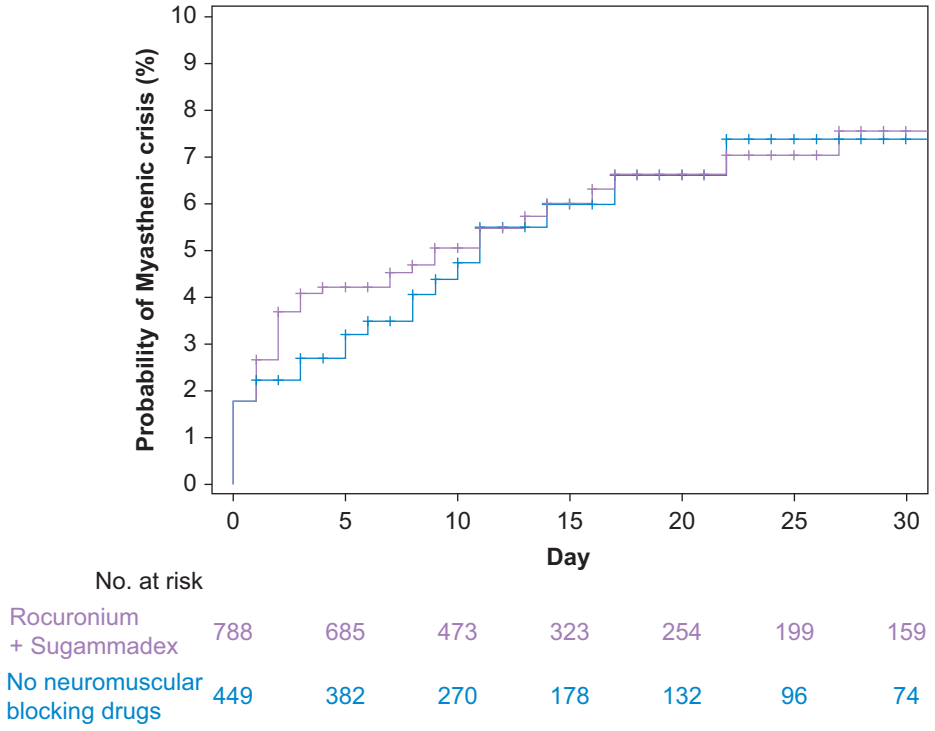

Fig 2. The cumulative incidence rate curves for the treatment used for myasthaenic crises (the treatment of tracheal intubation, continuous postoperative ventilator management for at least 3 days, treatment with plasma exchange, steroid pulse therapy, and immunoglobulin therapy), according to group.

Statistical analysis

The data are expressed as median for categorical variables or skewed data. Continuous variables that are normally distributed are represented by the mean and standard deviation. We conducted a 1:2 propensity-score matching for minimal differences in clinical characteristics between the two groups. The factors included in the model for propensity-score matching are listed in Table 1. All missing BMI, smoking history and preoperative medication data were imputed using the multiple imputation method.[15] The two groups were matched based on the logit of the propensity-score (calliper set to 0.20) by using nearest-neighbour matching, with an algorithm matching one group (no NMBD group) to the other (the rocuronium and sugammadex combination group). A standardised mean difference of >0.1 indicated a meaningful imbalance.[16] The outcomes were assessed using the Wilcoxon and Fisher's exact tests and the Cox proportional hazard model. The Kaplan–Meier method was used to generate cumulative incidence curves. Death was considered a competing risk factor in the analyses. A *P*-value <0.05 was defined as statistically significant, and we used the statistical software SAS (version 9.4; SAS Institute, Cary, NC, USA).

Sensitivity analyses

To validate the study in the Cox proportional hazards model, we performed logistic regression analyses for all patients. We performed subgroup analyses for patients who underwent thymectomy and those who did not in order to exclude the effect of thymectomy, which may worsen the symptoms of myasthaenia gravis.[17,18] Propensity-score matching was repeated for each subgroup according to the operation type.

Results

The initial cohort, which included patients who were diagnosed with myasthaenia gravis and underwent general anaesthesia, comprised 2304 patients. Among these, 419 patients were excluded because of tracheal intubation the day before surgery (n = 56), emergency surgery (n = 302), cardiac surgery (n = 8), or missing values for variables other than BMI, smoking status, and premedications (n = 61). The remaining 1885 patients were analysed in this study, 1169 of whom received a combination of rocuronium and sugammadex during general anaesthesia, whereas 455 received no NMBDs. After propensity-score matching, data from 788 and 449 patients were obtained for the combination and no NMBD groups, respectively (1237 patients in total, Fig 1). The two groups after propensity-score matching were well balanced for the baseline characteristics of the patients and type of hospital (Table 1).

Outcome analysis

In the dataset obtained after propensity-score matching, three and two patients died during hospitalisation in the combination of rocuronium and sugammadex and no NMBD groups, respectively. The cumulative incidence of treatment used for

Table 2 Patient outcomes.

	RB+sugammadex (n = 788)	No NMBD (n = 449)	HR (95% confidence interval)	P-value
Treatment used for myasthaenic crises	49 (6.2)	24 (5.3)	1.14 (0.70–1.85)	0.60[a]
Reintubation	15 (1.9)	3 (0.7)		
PVM	3 (0.4)	1 (0.2)		
Plasma exchange	10 (1.4)	4 (1.0)		
Immunoglobulin	24 (3.4)	11 (2.7)		
Steroid pulse	20 (2.8)	9 (2.2)		
Tracheotomy	9 (1.1)	2 (0.4)	2.51 (0.55–11.6)	
Discharged to home	712 (90.4)	411 (91.5)	0.87 (0.58–1.30)	
Postoperative length of stay (days)	13 (8–28)	12 (8–24)		0.19[b]

Data are presented as n (%), except for postoperative length of stay, which is presented as median (interquartile range).
RB, rocuronium bromide; NMBD, neuromuscular blocking drugs; HR, hazard ratio; PVM, postoperative ventilator management for at least 3 days.
[a] Log rank test.
[b] Wilcoxon rank-sum test.

myasthaenic crises by group is shown in Figure 2. Survival analysis using Cox regression showed no significant difference between the groups (*P*=0.60). There were no significant differences in the receipt of treatment used for myasthaenic crises (6.2% *vs* 5.3%; hazard ratio, 1.14; 95% confidence interval, 0.70–1.85). The two groups also exhibited no differences in the secondary outcomes, including the median postoperative length of stay, or in the rates of tracheostomy or discharge destination classification (Table 2).

Sensitivity analysis

Logistic regression analysis showed no significant difference in the primary outcome (receipt of postoperative treatment used for myasthaenic crises) (odds ratio 1.04, 95% confidence interval 0.62–1.74), as did the Cox proportional-hazards model. From the 522 patients who underwent thymectomy, we created a propensity-score -matched sub-cohort (n = 368) comprising 227 patients who received a combination of rocuronium and sugammadex (out of 379) and 141 who did not receive NMBDs (out of 143). A similar procedure was repeated for the subgroup of 1102 patients who underwent surgery other than thymectomy: we created a propensity-score -matched sub-cohort (n = 824) comprising 518 patients who received a combination of rocuronium and sugammadex (out of 790) and 306 who did not receive NMBDs (out of 312). The baseline characteristics of the two groups, according to whether they underwent thymectomy, before and after propensity-score matching are shown in Supplementary Tables 1 and 2. After propensity-score matching, the two groups showed no significant difference in patient characteristics, except for the year in the group that underwent thymectomy and the operation type in the group that underwent surgery other than thymectomy. There were no significant differences in all outcomes between the rocuronium and sugammadex combination and no NMBD groups after propensity-score matching, either in the post-thymectomy group or in the non-thymectomy group (Tables 3 and 4).

When the patients were analysed separately depending on whether they had undergone thymectomy, the incidence of receipt of treatment used for myasthaenic crises after thymectomy was higher ($P < 0.0001$) at 11.8% (n = 62) than in the non-thymectomy cases (2.4%, n = 26).

Discussion

In this analysis of data from 1240 patients with myasthaenia gravis who had undergone general anaesthesia, the combination of rocuronium and sugammadex did not change receipt of treatment used for myasthaenic crises or tracheostomy.

Table 3 Patient outcomes for those who underwent thymectomy.

	RB+sugammadex (n = 229)	No NMBD (n = 142)	HR (95% confidence interval)	P-value
Treatment used for myasthaenic crises	21 (9.2)	16 (11.3)	0.84 (0.44–1.59)	0.59[a]
Reintubation	7 (3.1)	2 (1.4)		
PVM	2 (0.9)	0 (0.0)		
Plasma exchange	8 (3.5)	4 (2.8)		
Immunoglobulin	11 (4.8)	6 (4.2)		
Steroid pulse	10 (4.4)	8 (5.6)		
Tracheotomy	6 (2.6)	0 (0.0)	NA	
Discharged to home	209 (91.3)	134 (94.4)	0.62 (0.27–1.46)	
Postoperative length of stay (days)	11 (9–27)	12 (9–23)		0.13[b]

Data are presented as n (%), except for postoperative length of stay, which is presented as median (interquartile range).
RB, rocuronium; NMBD, neuromuscular blocking drugs; HR, hazard ratio; NA, not applicable.
[a] Log rank test.
[b] Wilcoxon rank-sum test.

Table 4 Patient outcomes for those who underwent surgery other than thymectomy.

	RB+sugammadex (n = 520)	No NMBD (n = 307)	HR (95% confidence interval)	P-value
Treatment used for myasthenic crises	10 (1.9)	8 (2.6)	0.69 (0.27–1.75)	0.44[a]
Reintubation	4 (0.8)	1 (0.3)		
PVM	2 (0.4)	1 (0.3)		
Plasma exchange	0 (0.0)	0 (0.0)		
Immunoglobulin	3 (0.6)	5 (1.6)		
Steroid pulse	3 (0.6)	1 (0.3)		
Tracheotomy	2 (0.4)	2 (0.7)	0.57 (0.08–3.88)	
Discharged to home	465 (89.4)	277 (90.2)	0.92 (0.57–1.46)	
Postoperative length of stay (days)	14 (8–29)	13 (6–24)		0.03[b]

Data are presented as n (%), except for length of stay, which is presented as median (interquartile range).
RB, rocuronium; NMBD, neuromuscular blocking drugs; HR, hazard ratio.
[a] Log rank test.
[b] Wilcoxon rank-sum test.

These results are consistent with those of a previous study, which showed that the use of rocuronium and sugammadex was not associated with an increase in respiratory complications in patients with myasthaenia gravis limited to post-thymectomy.[6] However, most previous studies were limited to postoperative patients undergoing thymectomy, and there are few reports of analyses including postoperative patients undergoing other surgical procedures. The postoperative course of thymectomy may be different from that of other procedures as myasthaenia symptoms may worsen after thymectomy.[17,18] In the sensitivity analysis, patients who underwent thymectomy tended to receive more treatment used for myasthaenic crises than patients who underwent other surgical procedures. Patients with myasthaenia gravis may require general anaesthesia in situations other than thymectomy and anaesthesiologists are often unsure whether to use NMBDs during general anaesthesia in these patients. The present study covered all types of surgery and addressed the limited scope of previous studies.

We performed a sensitivity analysis, grouping patients according to whether they were post-thymectomy or not, to examine the results in further detail. There were no statistically significant differences in receipt of treatment used for myasthaenic crises, tracheostomy, discharge to home, or length of hospital stay postoperatively, whether after thymectomy or other procedures, which was consistent with the results of the main analysis. To further verify the results of the propensity-score matching analysis, we also performed a logistic regression analysis using the same explanatory variables, which yielded similar results. Our results indicate that the use of NMBDs may be acceptable in surgeries requiring muscle relaxation, even if the patient has myasthaenia gravis. However, the data in this study are limited, and optimal individualised dose adjustment is necessary when using NMBDs, with reference to neuromuscular monitoring.

Study limitations

First, the DPC database did not include data for potentially relevant confounding factors that are not claimable by insurance, such as the use of neuromuscular monitoring or the skill level of the surgeon or anaesthesiologist. Therefore, no adjustment was made for these confounding factors, and the results should be interpreted with care. Neuromuscular monitoring is essential, especially when using NMBDs for patients with myasthaenia gravis. The anaesthesiologist should tailor the dose of rocuronium and sugammadex reversal according to neuromuscular monitoring in myasthaenic patients. The lack of this information may underestimate the potential usefulness of the rocuronium and sugammadex combination.

Second, the DPC database did not contain information on the severity of myasthaenia gravis (degree and frequency of dysarthria, limb muscle weakness, and respiratory impairment, Osserman classification or Myasthaenia Gravis Foundation of America score, and presence of anti-AChR antibody positivity). The possible bias here is unidirectional: rocuronium is likely to be used in less severely ill patients and therefore the results of the rocuronium and sugammadex combination group may be misleadingly good. We attempted to adjust for the severity of myasthaenia by identifying myasthaenia gravis of the ocular type and whether the patients were being treated with steroids, anticholinesterase drugs, or immunosuppressive drugs. However, we cannot rule out the possibility of inappropriate evaluation of myasthaenia gravis severity causing some bias.

Third, minor early postoperative complications could not be extracted from the database because of the absence of symptom coding (e.g. eyelid drooping, blurred vision) Therefore, we could not evaluate minor postoperative changes and the impact of NMBD administration strategies on minor complications.

In light of these limitations, especially the lack of neuromuscular monitoring, interpretation of the results requires great caution, and there are concerns about applying the results of this study directly to clinical practice.

Conclusions

In this retrospective database study evaluating patients with myasthaenia gravis undergoing different types of surgical procedure with general anaesthesia, the combination of rocuronium and sugammadex did not result in increased postoperative adverse events, including treatment used for myasthaenic crises, in comparison with the number of events associated with no use of NMBDs. However, because of data that were not available from the database, it is unclear whether rocuronium administration with the postoperative

use of sugammadex is acceptable in surgeries where NMBDs are essential during the surgery, and this will require further investigation.

Authors' Contributions

Study conception and design: IN, MT, HY, CK, KK
Data collection: IN, MT
Data analysis: IN, MT
Scientific writing: IN, MT, HY, CT, KK
Study supervision: MT, HY, CT, KK
All the authors critically reviewed the manuscript.
All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Declarations of interest

In the past 5 years, the corresponding author has received honoraria from Astellas, Taisho Pharmaceutical, Hikari Pharmaceutical, Eisai, Mitsubishi Tanabe Pharma, Takeda Pharmaceutical Company Limited, Sanofi K.K., and consultation fees from Olympus, Kyowa Hakko Kirin, Kaken Pharmaceutical, and Otsuka Pharmaceuticals. There are no patents, products in development, or marketed products relevant to those companies to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjao.2022.100092.

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