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The effect of neuromuscular reversal agent on postoperative pain after laparoscopic gastric cancer surgery

Comparison between the neostigmine and sugammadex

Tak Kyu Oh, MD[a], Eunjeong Ji, PhD[b], Hyo-Seok Na, MD, PhD[a,*]

Abstract

Use of sugammadex for neuromuscular block reversal is associated with fewer postoperative complications than neostigmine; however, the effects on postoperative pain outcomes are largely unknown. In this retrospective study, we investigated the relationship between neuromuscular reversal agents and postoperative pain-related outcomes following laparoscopic gastric cancer surgery.

We reviewed the electronic health records of patients who underwent laparoscopic gastric cancer surgery between January 2010 and June 2017. Patients were divided into a sugammadex group and a neostigmine group, according to the neuromuscular block reversal agent used. We compared the pain outcomes in the first 3 days postoperatively (POD 0–3), length of hospital stay, and postoperative complications (Clavien-Dindo grade ≥II).

During the study period, 3056 patients received sugammadex (n = 901) or neostigmine (n = 2155) for neuromuscular reversal. After propensity score matching, 1478 patients (739 in each group) were included in regression analysis. In linear regression analysis, intravenous morphine equivalent consumption (mg) during POD 0 to 3 was higher in the sugammadex group than in the neostigmine group [coefficient 103.41, 95% confidence interval (CI): 77.45–129.37; $P < .001$]. However, hospital stay was shorter (coefficient: −0.60, 95% CI −1.12 to −0.08; $P = .025$) and postoperative complication rate was lower (odds ratio: 0.20, 95% CI 0.07–0.58; $P = .003$) in the sugammadex group.

In this retrospective study, patients undergoing laparoscopic gastric cancer surgery who received sugammadex for neuromuscular block reversal exhibited greater postoperative analgesic requirements than those who received neostigmine but had a shorter hospital stay and a lower postoperative complication rate. A randomized and blinded study should be conducted in the future to confirm the findings of the present study.

Abbreviations: CI = confidence interval, IRB = Institutional Review Board, IV = intravenous, NRS = numeric rating scale, PCA = patient-controlled analgesia, POD = postoperative day, SNUBH = Seoul National University Bundang Hospital, TOF = train-of-4.

Keywords: laparoscopy, pain, postoperative, stomach neoplasms

1. Introduction

Laparoscopic surgery has the advantages of being less invasive, causing less postoperative pain, and allowing more rapid recovery than conventional laparotomy surgery. When performing laparoscopic surgery, deep neuromuscular block is preferred to secure optimal surgical space.[1–3] However, deep intraoperative neuromuscular block can delay neuromuscular reversal; moreover, there is a potential problem of residual postoperative paralysis when a cholinesterase inhibitor is used as the reversal agent. Sugammadex (Bridion, Merck Sharp and Dohme, Oss, The Netherlands) is generally regarded as an optimal agent for the reversal of deep neuromuscular block by rocuronium.

A number of studies have evaluated the efficacy of sugammadex for the reversal of rocuronium-induced neuromuscular block without residual paralysis.[4] However, there is a paucity of studies regarding the effect of sugammadex on postoperative pain. An important study in this area was performed by Castro et al, who reported that sugammadex resulted in lower postoperative pain than neostigmine after laparoscopic bariatric surgery.[5] However, their study was limited to assessment of the intensity of pain for 1 hour postoperatively; therefore, it is difficult to extend their findings to the entire postoperative recovery period. Further, differences in the severity of postoperative pain and analgesic consumption, in cases where neuromuscular reversal was achieved by sugammadex or a conventional cholinesterase inhibitor, remain poorly elucidated.

This study was undertaken to determine the relationship between reversal agents and postoperative pain-related out-

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[a] Department of Anesthesiology and Pain Medicine, [b] Medical Research Collaborating Center, Seoul National University Bundang Hospital, Seongnam, Republic of Korea.

[*] Correspondence: Hyo-Seok Na, Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, 166, Gumi-ro, Bundang-gu, Seongnam, 13620, Republic of Korea (e-mail: hsknana@gmail.com).

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comes, including opioid consumption and pain scores, following laparoscopic gastric cancer surgery. Secondary objectives included evaluation of the relationships between reversal agent used and both length of hospital stay and postoperative complication rate in these patients.

2. Methods

This retrospective observational study was approved by the Institutional Review Board (IRB) at Seoul National University Bundang Hospital (SNUBH) (Approval number: B-1802–451–101, Approval date: February 12, 2018, Ethical committee: IRB of SNUBH, Seongnam-si, Gyeonggi-do 13620, South Korea). The requirement for informed patient consent was waived because of the retrospective non-interventional study design. Our data were obtained from the electronic health records stored in the "Bundang hospital Electronic System for Total Care" at SNUBH for 8 years.[6] Electronic health records were reviewed for patients aged 20 years or older who underwent elective laparoscopic surgery for stomach cancer between January 2010 and June 2017. Exclusion criteria were as follows: incomplete medical documentation; single-port laparoscopic surgery which might reduce postoperative pain[7]; use of cisatracurium as a neuromuscular blocking agent; intraoperative conversion to an open approach; concomitant resection of other organs outside the abdominal cavity; reoperation performed during the first 3 postoperative days (POD 0–3); and history of chronic opioid use for preoperative pain. Before the study period, our surgical team at SNUBH had performed a lot of gastric surgeries using a standardized multi-port laparoscopy-guided technique under general anesthesia.[8] As a result of these extensive exclusion criteria, those patients who had preoperative pain or received any preoperative cancer therapy were excluded from our final analyses.

2.1. Anesthesia and analgesia protocol for laparoscopic gastric cancer surgery

All patients received 1 to 3 mg of intravenous (IV) midazolam as premedication before entering the operating room and 1.5 to 2.5 $mg\,kg^{-1}$ of propofol for the induction of anesthesia. An inhalation agent (desflurane or sevoflurane) and continuous remifentanil infusion were used for maintenance of anesthesia. Rocuronium was used for endotracheal intubation and intraoperative muscle relaxation, except in patients with end-stage renal disease. Rocuronium-induced neuromuscular block was generally adjusted to target a deep (train-of-4 [TOF] 0) or moderate (TOF 1–3) block. Upon completion of surgery, sugammadex (≥4 $mg\,kg^{-1}$) or neostigmine (0.04–0.06 $mg\,kg^{-1}$) plus glycopyrrolate (0.01–0.02 $mg\,kg^{-1}$) was used for reversal of muscle relaxation, depending both on the total amount of rocuronium administered intraoperatively and the postoperative TOF response using a peripheral nerve stimulator.

IV patient-controlled analgesia (PCA) was used for postoperative pain management and generally consisted of fentanyl 8 to 15 $\mu g\,mL^{-1}$ at a total volume of 100 mL, in accordance with the patient's age and underlying conditions. The IV PCA was set to deliver a continuous basal infusion of 1 $mL\,h^{-1}$ and a bolus of 1 mL, with a lockout time of 10 to 15 minutes. Most patients used the total amount of IV PCA within POD 0 to 2, and additional opioid analgesics were prescribed by physicians upon request by each patient. Generally, acetaminophen or a nonsteroidal anti-inflammatory agent was not used until POD 3. In addition, the infiltration of local anesthetic into the wound was not performed in our institution for laparoscopic gastric cancer surgeries.

2.2. Outcome variables

The following data were collected for the study: age, sex, body mass index, durations of both surgery, and anesthesia (min), total gastrectomy, transfusion of packed red blood cell in POD 0, mean rocuronium dosage, incidence of postoperative admission to the intensive care unit, agent used for the reversal of neuromuscular block, postoperative opioid consumption, postoperative pain scores, postoperative complications (Clavien-Dindo grade ≥II, i.e., requiring pharmacological or surgical treatment, and/or exhibiting life-threatening complications or death),[9] length of hospital stay after surgery; and preoperative comorbidity (including American Society of Anesthesiologists physical status, Charlson Comorbidity Index, diabetes mellitus, hypertension, ischemic heart disease, neurological disease, chronic obstructive pulmonary disease, chronic kidney disease, and liver disease).

Mean rocuronium dosage ($\mu g\,kg^{-1}\,min^{-1}$) was calculated by dividing the total amount (μg) of rocuronium used for induction and maintenance by body weight (kg) and duration of anesthesia (min). The amount of postoperative opioid used was converted to IV morphine equivalents (mg) using a standard conversion ratio [10] (Supplementary Table 1, http://links.lww.com/MD/D70). A Numeric Rating Scale (NRS; 0–10) score was used to assess postoperative pain. Registered nurses measured NRS pain scores at least 6 times each day; the mean value of all measured NRS pain scores for a given day (POD 0, 1, 2, or 3) was recorded as the NRS pain score for that day. All data were collected by a medical records technician from the Medical Informatics Team at SNUBH who was blinded to the study objectives. All study investigators were also blinded to the data until the main statistical outcomes were derived.

Patients in whom sugammadex was used for reversal of rocuronium were placed within the sugammadex group and those in whom neostigmine was used were placed within the neostigmine group. The primary outcome of the study was the difference in severity of pain (indicated by morphine equivalent consumption and NRS pain scores on POD 0–3) after laparoscopic gastric cancer surgery between the sugammadex and neostigmine groups. The secondary outcomes were the differences in length of hospital stay and postoperative complication rate between the 2 groups.

2.3. Statistical analysis

Student *t* test and Pearson Chi-squared test were used to compare continuous and categorical variables, respectively, between the sugammadex and neostigmine groups. We performed propensity score matching to balance the covariates in the 2 groups to meet the condition of standardized mean difference (SMD) <0.1 [11]. All patients were matched at a 1:1 ratio with caliper 0.25 by the nearest neighbor method without replacement. We then performed linear regression analyses to detect differences in morphine equivalent consumption, NRS pain scores on POD 0 to 3, and length of hospital stay between the 2 groups. Additionally, we performed binary logistic regression analyses to characterize differences in the postoperative complication rate between the 2 groups after propensity score matching. All statistical analyses were performed using R software (version 3.3.2, R Development Core Team, Vienna, Austria). A P value $<.05$ was considered statistically significant.

Table 1

Patient characteristics between sugammadex and neostigmine-treated groups before propensity score matching in patients who underwent laparoscopic gastric cancer surgery.

Variable	Before propensity score matching			After propensity score matching		
	Sugammadex N = 901	Neostigmine N = 2,155	SMD	Sugammadex N = 739	Neostigmine N = 739	SMD
Age, yr			0.150			0.098
20–49	153 (16.9%)	422 (19.6%)		123 (16.6%)	125 (16.9%)	
50–69	470 (52.2%)	1,162 (53.9%)		392 (53.1%)	387 (52.4%)	
≥70	278 (30.8%)	571 (26.5%)		224 (30.3%)	227 (30.7%)	
Sex: male	648 (71.9%)	1,463 (67.9%)	0.088	520 (70.4%)	519 (70.2%)	0.003
Body mass index, kg m^{-2}	23.4 (3.6)	23.1 (3.5)	0.082	23.3 (3.6)	23.4 (3.9)	0.043
Duration of surgery, min	199.26 (64.8)	194.8 (65.8)	0.068	198.8 (60.5)	202.0 (81.6)	0.044
Duration of anesthesia, min	236.3 (66.0)	234.0 (67.46)	0.035	236.4 (61.8)	239.2 (83.4)	0.039
Transfusion of pRBC in POD 0	25 (2.8%)	72 (3.3%)	0.042	18 (2.4%)	25 (3.4%)	0.050
Total gastrectomy	395 (43.8%)	865 (40.1)	0.085	259 (35.0)	270 (36.5)	0.035
Postoperative ICU admission	36 (4.0%)	57 (2.6%)	0.075	28 (3.8%)	26 (3.5%)	0.014
Preoperative comorbidity						
ASA physical status			0.038			0.025
1,2	854 (94.8%)	2,060 (95.6%)		703 (95.1%)	699 (94.6%)	
>3	47 (5.2%)	95 (4.4%)		36 (4.9%)	40 (5.4%)	
Charlson Comorbidity Index			0.011			0.02
1,2	732 (81.2%)	1,760 (81.7%)		597 (80.8%)	591 (80.0%)	
>3	169 (18.8%)	395 (18.3%)		142 (19.2%)	148 (20%)	
Diabetes mellitus	131 (14.5%)	328 (15.2%)	0.019	109 (14.7%)	107 (14.5%)	0.008
Hypertension	272 (30.2%)	681 (31.6%)	0.031	232 (31.4%)	235 (31.8%)	0.009
Ischemic heart disease	53 (5.9%)	110 (5.1%)	0.034	41 (5.5%)	41 (5.5%)	<0.001
Neurologic disease	29 (3.2%)	64 (3.0%)	0.014	23 (3.1%)	26 (3.5%)	0.023
COPD	19 (2.1%)	51 (2.4%)	0.017	15 (2.0%)	19 (2.6%)	0.036
Chronic kidney disease	15 (1.7%)	44 (2.0%)	0.028	12 (1.6%)	12 (1.6%)	<0.001
Liver disease	64 (7.1%)	122 (5.7%)	0.059	36 (4.9%)	55 (7.4%)	0.021
Mean ROC dosage, $\mu g\ kg^{-1}\ min^{-1}$	9.4 (4.5)	7.4 (3.2)	0.509	8.4 (3.6)	8.2 (3.7)	0.052

Presented as mean (standard deviation) or number (percentage).

ASA = american society of anesthesiologists, COPD = chronic obstructive lung disease, ICU = intensive care unit, POD = postoperative day, pRBC = packed red blood cell, ROC = rocuronium, SMD = standardized mean difference.

3. Results

Between January 2010 and June 2017, 4871 patients aged 20 years or older underwent elective laparoscopic gastric surgery at our institution. Of those patients, 1815 were excluded as presented in Figure 1. After exclusion, a total of 3056 patients were enrolled in the study (901 and 2155 patients in the sugammadex and neostigmine groups, respectively). Finally, after propensity score matching to adjust for unbalanced covariates between the two groups, data describing 1478 patients (n = 739 in each group) were available for analysis.

3.1. Patient characteristics before and after propensity score matching

Before propensity score matching, there were significant differences in sex, body mass index, incidence of admission to the postoperative intensive care unit, and mean rocuronium dosage administered between the sugammadex and neostigmine groups (Table 1). All variables were well-balanced (SMD <0.1) after propensity score matching. Supplementary Figure 1, http://links.lww.com/MD/D70 shows the propensity scores for the covariates after propensity score matching.

3.2. Postoperative pain outcomes

After propensity score matching, morphine equivalent consumption during POD 0 to 3 was greater in the sugammadex group than in the neostigmine group (659.5 ± 234.8 mg vs 556.0 ± 272.9 mg; $P < .001$; Table 2). In addition, the NRS pain scores on POD 2 and 3 were higher in the sugammadex group than in the neostigmine group (3.9 ± 0.9 vs 3.7 ± 1.0, $P = .001$ on POD 2 and 3.4 ± 0.8 vs 3.1 ± 1.0, $P < .001$ on POD 3; Table 2).

Table 3 shows the results of linear regression analysis performed after propensity score matching. There was a significant increase by 103.41 (mg) in morphine equivalent consumption on POD 0 to 3 in the sugammadex group (coefficient 103.41, 95% confidence interval [12] 77.45–129.37; $P < .001$). Moreover, NRS pain scores on POD 2 and 3 increased significantly by 0.17 and 0.28, respectively, in the sugammadex group (coefficient 0.17, 95% CI 0.07–0.27, $P < .001$ on POD 2 and coefficient 0.28, CI 0.18–0.37, $P < .001$ on POD 3).

3.3. Postoperative hospital stay and complications

After propensity score matching, the postoperative hospital stay was shorter in the sugammadex group than in the neostigmine group (6.6 ± 4.2 days vs 7.2 ± 5.9 days; $P = .025$); postoperative complication rate (Clavien-Dindo grade ≥II) was also lower in the sugammadex group (0.5% vs 2.7%; $P < .001$), as shown in Table 2.

Table 4 shows the results of linear regression analysis for length of hospital stay after surgery and postoperative complications after propensity score matching: length of hospital stay decreased by 0.6 day in the sugammadex group, when compared with the neostigmine group (coefficient −0.60, 95% CI −1.12 to

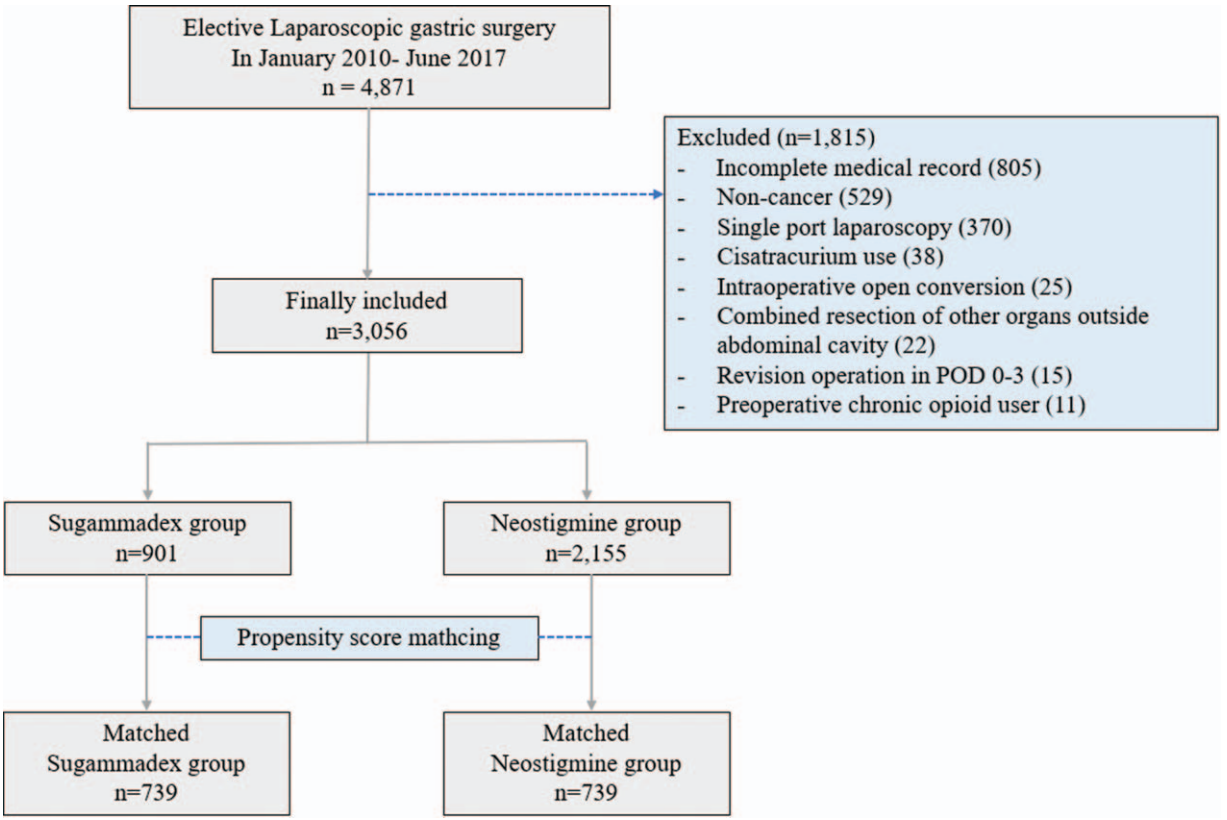

Figure 1. Flow chart depicting patient selection protocol in this study.

−0.08, $P=.025$); similarly, postoperative complication rate decreased by 80% in the sugammadex group (odds ratio 0.20, 95% CI 0.07–0.58, $P=.003$).

4. Discussion

In this study, we found that postoperative morphine equivalent consumption on POD 0 to 3 was considerably greater when neuromuscular block was reversed by sugammadex than by neostigmine. Furthermore, NRS pain scores on POD 2 and 3 were slightly higher in the sugammadex group than in the neostigmine group. However, the sugammadex group tended to have a slightly shorter hospital stay and showed a considerably lower risk of postoperative complications (Clavien-Dindo grade ≥II) than the neostigmine group.

This study focused on whether rapid and complete reversal of neuromuscular block by sugammadex could affect postoperative pain. We could not identify the precise mechanism; however, there are reports of muscle tension in the abdominal wall associated with abdominal pain [13] and relaxation of skeletal

Table 2

Postoperative pain outcomes, postoperative complications, and length of hospital stay before and after propensity score matching.

	Before propensity score matching			After propensity score matching		
Variable	**Sugammadex N = 901**	**Neostigmine N = 2155**	***P* value**	**Sugammadex N = 739**	**Neostigmine N = 739**	***P* value**
Morphine equivalent in POD 0–3, mg	661.0 (240.0)	544.1 (261.1)	<.001	659.5 (234.8)	556.0 (272.9)	**<.001**
NRS pain score						
POD 0	5.0 (1.2)	5.3 (1.9)	<.001	5.0 (1.2)	5.2 (2.0)	.154
POD 1	4.4 (1.2)	4.3 (1.1)	.005	4.4 (1.1)	4.5 (1.3)	.064
POD 2	3.9 (1.0)	3.6 (1.0)	.005	3.9 (0.9)	3.7 (1.0)	**.001**
POD 3	3.4 (0.9)	3.0 (1.0)	.001	3.4 (0.8)	3.1 (1.0)	**<.001**
Length of hospital stay, day	6.6	6.8	.264	6.6 (4.2)	7.2 (5.9)	**.025**
Postoperative complication*	5 (0.6%)	42 (1.9%)	.004	4 (0.5%)	20 (2.7%)	**.001**

Presented as mean (SD) or number (percentage).

* Postoperative complication includes only the cases ≥II in Clavien-Dindo classification.

NRS = numeric rating scale, POD = postoperative day.

Table 3

Linear regression analysis for postoperative pain outcomes after propensity score matching.

Dependent variable	Coef	95% confidence interval		*P* value
		Lower limit	Upper limit	
Morphine equivalent consumption in POD 0–3				
Sugammadex group (vs neostigmine group)	**103.41**	77.45	129.37	**<.001**
NRS pain score on POD 0–3				
Sugammadex group (vs. neostigmine group)				
POD 0	−0.12	−0.29	0.046	.154
POD 1	−0.12	−0.24	0.01	.064
POD 2	**0.17**	0.07	0.27	**<.001**
POD 3	**0.28**	0.18	0.37	**<.001**

NRS = numeric rating scale, POD = postoperative day, ROC = rocuronium; Coef, coefficient.

Table 4

Linear regression analysis for length of hospital stay and logistic regression analysis for occurrence of postoperative complication (≥ II in Clavien-Dindo classification) after propensity score matching.

Variable		95% confidence interval		*P*-value
		Lower limit	Upper limit	
Length of hospital stay after surgery	**Coef***			
Sugammadex (vs neostigmine)	−0.60	−1.12	−0.08	.025
Occurrence of postoperative complication	**OR***			
Sugammadex (vs neostigmine)	0.20	0.07	0.58	.003

Coefficient* and OR*: Sugammadex group (versus Neostigmine group).
Coef = coefficient, OR = odds ratio, ROC = rocuronium.

muscle reducing nociceptive pain.[14] Reversal of neuromuscular block by sugammadex would restore muscle strength more rapidly and completely. Therefore, in the present study, patients in the sugammadex group may have felt more severe pain in the acute postoperative period than those in the neostigmine group, resulting in higher postoperative morphine equivalent consumption.

Our findings are in contrast with those of Castro et al[5] who reported less immediate acute postoperative pain in sugammadex-treated patients than in neostigmine-treated patients. Some parameters might lead to different results in our study as compared to the study by Castro et al.[5] First, the primary outcomes of the 2 studies are different. The study by Castro et al. did not assess the consumption of analgesics and the evaluation period was limited to approximately 90 postoperative minutes, whereas our study mainly focused on the consumption of morphine equivalents during POD 0 to 3. Considering that complete excretion of sugammadex by the kidney takes more than 24 hours,[15] the evaluation period for postoperative pain outcome was too short in the study by Castro et al. Second, the participants of the study by Castro et al were morbidly obese. Given that morbidly obese patients show hypoalgesia in response to noxious electrical stimuli,[16] postoperative pain data obtained from them cannot be generalized to all adult patients. Finally, we analyzed the postoperative pain after laparoscopic gastric cancer surgery, while the study by Castro et al focused on postoperative pain after bariatric surgery. The difference in surgery characteristics might also have caused the results to differ between our study and the study by Castro et al However, information regarding the impact of sugammadex on pain outcomes after both laparoscopic bariatric surgery and gastric cancer surgery is lacking, and more studies should be conducted in the future.

In addition to the above study, there have been several studies of postoperative pain as a secondary outcome, depending upon the neuromuscular reversal agent used.[12,17,18] One study reported less postoperative pain in sugammadex-treated patients than in neostigmine-treated patients.[17] However, differences in intraoperative neuromuscular block states achieved by these 2 agents could affect the postoperative pain outcome because low-pressure pneumoperitoneum in the sugammadex group might reduce postoperative pain after laparoscopic surgery. In 2 other studies, intraoperative neuromuscular block state and postoperative pain were reported to be similar irrespective of the neuromuscular block reversal agent used.[12,18] In this study, patients in the sugammadex group also received more rocuronium intraoperatively, before propensity score matching. However, the rocuronium dose was balanced to be equal between the 2 groups after propensity score matching, and finally, the postoperative analgesic consumption and NRS pain score were still higher in the sugammadex group.

Our present findings highlight the clinical relevance of perioperative management in patients receiving sugammadex as a neuromuscular reversal agent. Notably, sugammadex is viewed as an essential reversal agent for rocuronium-induced neuromuscular block.[19] Moreover, deep neuromuscular block is incorporated within various types of laparoscopic surgeries.[2] We found that length of hospital stay and complication rate after laparoscopic gastric cancer surgery decreased in the sugammadex group, consistent with previous reports.[4] However, our findings suggest that effective pain management should be implemented for patients receiving sugammadex during the acute postoperative period. Multimodal analgesic methods, including epidural analgesia or a transversus abdominis plane block, may provide better pain control without increasing opioid consumption.

This study had some limitations. First, due to its retrospective design, many confounders needed to be controlled by propensity score matching. However, propensity score matching can only reduce the effect of the known confounders. Unmeasured confounders and selection bias might have affected the results of this study. Second, although most opioid-based pain control measures used in our study consisted of fentanyl-based IV PCA, various types of opioids were used for rescue analgesia. Thus, standard conversion ratios were used to calculate morphine equivalent consumption. Second, deriving a postoperative pain score for the day from a mean of several estimates all obtained by a team of nurses might cause the inaccuracy of NRS pain score in our study, as each nurse may interact differently with each patient. However, it is unquestionable that patients who felt severe pain required more amount of rescue analgesics, which was considerably higher in the sugammadex group than in the neostigmine group. Third, this study was performed at a single center, so the results cannot be generalized. Nevertheless, this study is the first study to show that in cases involving reversal by sugammadex after laparoscopic gastric cancer surgery, more careful analgesia monitoring should be utilized than in cases involving the use of neostigmine. Additionally, the results of our study can provide an appropriate rationale for prospective studies.

In conclusion, in this retrospective study, the postoperative analgesic requirement might be increased in patients who received sugammadex for reversal of neuromuscular block after laparoscopic gastric cancer surgery. A future prospective and randomized blinded study is required to obtain more convincing evidence regarding the effect of sugammadex on postoperative pain in the same intraoperative neuromuscular block state.

Author contributions

Conceptualization: Tak Kyu Oh, Hyo-Seok Na.
Data curation: Tak Kyu Oh, Hyo-Seok Na.
Formal analysis: Eunjeong Ji.
Writing – original draft: Tak Kyu Oh.
Writing – review & editing: Hyo-Seok Na.

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