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Use of sugammadex in lung cancer patients undergoing video-assisted thoracoscopic lobectomy

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Background: This study aimed to retrospectively evaluate the use of sugammadex in patients undergoing video-assisted thoracoscopic surgery (VATS) lobectomy.
Methods: Data were obtained from medical record review of patients who underwent VATS lobectomy from January 2013 to November 2014. Fifty patients were divided into two groups: the sugammadex group (group S, n = 19) was administered sugammadex 2 mg/kg, while the pyridostigmine group (group P, n = 31) received pyridostigmine 20 mg with glycopyrrolate 0.2 mg or atropine 0.5 mg. The primary endpoint measure was the overall incidence of postoperative pulmonary complications including prolonged air leak, pneumonia, and atelectasis. The secondary endpoint measures were the length of postoperative hospital stay and duration of chest tube insertion.
Results: The overall incidence of postoperative pulmonary complications in patients in group S was significantly lower compared with that of group P (5 [26.3%] vs. 17 [54.8%]; P = 0.049). Also, the durations of chest tube insertion (5.0 [4.0–7.0] vs. 7.0 [6.0–8.0] days; P = 0.014) and postoperative hospital stay (8.0 [8.0–10.0] vs. 10.0 [9.0–11.0] days; P = 0.019) were shorter in group S compared with group P. Administration of sugammadex was associated reduced with postoperative pulmonary complications (OR: 0.22; 95% CI: 0.05–0.87; P = 0.031).
Conclusions: The use of sugammadex, compared with pyridostigmine, showed a significantly reduced overall incidence of postoperative pulmonary complications and decreased duration of chest tube use and postoperative hospital stay in patients undergoing VATS lobectomy, suggesting that sugammadex might be helpful in improving clinical outcomes in such patients.

Key Words: Effect, Sugammadex, Thoracoscopic lobectomy, VATS lobectomy.

Introduction

A patient's muscles must be relaxed during laparoscopic surgery to secure a good field of view and operating space for the surgeon. Deep muscle relaxation reduces the surgical field pressure and makes the operation easier [1-3]. Until recently, cholinesterase inhibitors, such as pyridostigmine and neostigmine, have been administered to reverse muscle relaxants. These drugs increase the concentration of acetylcholine in the neuromuscular junction and compete with non-depolarized muscle relaxants at the receptor to reverse muscle relaxation [4]. However, cholinesterase inhibitors may still cause acute respiratory events, such as hypoxemia, airway obstruction, and postoperative

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pulmonary complications, because they are not direct muscle relaxation antagonists [5-8]. Additionally, unpleasant symptoms, such as muscle weakness, longer post-anesthesia care unit stays, and delayed tracheal extubations may occur [9].

Sugammadex is the first selective relaxant binding agent, which is a synthetically modified gamma-cyclodextrin. Sugammadex reverses muscle relaxation quickly and safely from deep anesthesia levels by binding directly with steroidal neuromuscular blocking agents, such as rocuronium or vecuronium without residual muscle relaxation [8,10,11]. Therefore, the use of sugammadex for neuromuscular blockade reversal can be expected to enable deep breathing and help restore pulmonary function as soon as possible. We hypothesized that these effects would result in decreased postoperative pulmonary complications that have been reviewed in lobectomy studies such as pneumonia, atelectasis, and prolonged air leak [12-15].

This study sought to retrospectively evaluate the use of sugammadex in patients undergoing thoracoscopic lobectomy.

Materials and Methods

This study was approved by the Institutional Review Board (IRB) for the patients who were transported to the intensive care unit (ICU) after general anesthesia in the central operating suite from January 1, 2013 to November 30, 2014 (IRB No. 14-231).

This study was conducted following the guidelines of the STROBE statement [16]. The data were retrospectively obtained from medical record review of patients. The inclusion criteria were the following: 1) patients older than 20 years; 2) American Society of Anesthesiologists (ASA) physical status classifications I, II, and III; and 3) patients operated on via video-assisted thoracoscopic surgery (VATS) lobectomy. Cases converted to open surgery or bilateral surgery were excluded.

In our hospital, neuromuscular function is monitored at the adductor pollicis muscle using the train of four (TOF) during VATS lobectomy. According to protocol for reversal of muscle relaxant, a single bolus dose of traditional reversal (pyridostigmine 20 mg with glycopyrrolate 0.2 mg or atropine 0.5 mg) or sugammadex 2 mg/kg is administered if spontaneous recovery has reached the reappearance of a second twitch in response to TOF stimulation. Neuromuscular monitoring continues until the end of anesthesia and at least until recovering a TOF ratio of 0.9, which is considered sufficient for safe extubation. Postoperative care including chest tube use, duration of ventilator use, ICU stay and postoperative hospital stay are routinely implemented according to VATS lobectomy protocol at the Department of Thoracic and Cardiovascular Surgery. All patients received 0.9 mg/kg of rocuronium for induction, and maintenance vecuronium was administered. Patient controlled analgesia for postoperative pain control consisted of fentanyl 5 μg/kg/h for all patients.

Fifty patients who underwent VATS lobectomy were divided into two groups: the sugammadex group (group S, n = 19) was administered sugammadex 2 mg/kg, while the pyridostigmine group (group P, n = 28) received a single bolus dose of traditional reversal (pyridostigmine 20 mg with glycopyrrolate 0.2 mg or atropine 0.5 mg). Because sugammadex has only been used since January 2014 at our institution, group P and group S represent data collected before and after this time point, respectively.

Anthropometric information, comorbidities, preoperative arterial blood gas analysis (ABGA), pulmonary function tests (PFTs), chest X-ray, and chest computed tomography findings were confirmed by examining the medical records. Tumor stages, locations of the lobectomy sites, anesthesia and operation times, the administration of sugammadex, intraoperative ABGA, and time to extubation after termination of anesthesia were investigated using the anesthesia and operative records. Tumor type and the surgical margin of the incision site were confirmed. Intraoperative hypoxia was defined as a saturation less than 95% oximetry or arterial oxygen partial pressure less than 80 mmHg during surgery. The primary endpoint measure was the overall incidence of postoperative pulmonary complications including prolonged air leak, pneumonia, and atelectasis as confirmed from progress and discharge records. Postoperative pulmonary complications was observed during the entire period from the operation to the day of discharge. A prolonged air leak was defined as an air leak present on postoperative day 4. Atelectasis and pneumonia were diagnosed based on radiologic readings of postoperative chest X-ray. The secondary endpoint measures were the length of postoperative hospital stay and duration of chest tube insertion. These factors were also confirmed by examining progress records.

All measured values were statistically analyzed using SPSS ver. 21.0 software (IBM Corp., Armonk, NY, USA). For continuous variables, the data distribution was firstly evaluated for normality using the Kolmogorov-Smirnov test. As age, body mass index, operation and anesthetic durations passed the normality test, they were analyzed using the t-test. Since the length of ventilation, ICU stay, chest tube duration, and postoperative hospital stay did not pass the normality test, they were analyzed using the Mann–Whitney *U* test. ASA physical status, comorbidities and specific complications were analyzed using the chi-square and Fisher's exact tests. In addition, univariate and subsequent multivariate binary logistic regression analyses were performed to identify demographic and clinical variables associated with complications. Variables with $P < 0.2$ in the univariate logistic regression analysis were entered into the multivariate logistic regression analysis using backward selection. P values < 0.05 were considered significant.

Results

A total of 54 patients were included. Three cases that converted to open surgery, and one case that underwent bilateral surgery were excluded. The remaining 50 patients were divided into group P (n = 31) and group S (n = 19). No significant differences were found between the two groups in demographic and clinical variables including the majority of the comorbidities. Only diabetes presented a statistically significant difference; i.e., more patients in group P had histories of diabetes compared with the patients in group S (38.7% vs. 10.5%; P = 0.031) (Table 1). Postoperative hypoxia did not occur in the two groups.

Our primary endpoint, the overall incidence of postoperative pulmonary complications in patients, was significantly lower in group S compared with that of group P (5 [26.3%] vs. 17 [54.8%]; P = 0.049); however, no statistically significant differences in any of the specific complications were observed between the two groups (Table 2). A subsequent multivariate regression analysis revealed that administration of sugammadex was associated with reduced postoperative pulmonary complications (odds ratio: 0.22; 95% CI: 0.05–0.87; P = 0.031) (Table 3).

The secondary endpoints, duration of chest tube insertion and length of postoperative hospital stay, showed statistically significant differences. The duration of chest tube insertion (5.0 [4.0–7.0] vs. 7.0 [6.0–8.0] days; P = 0.014) and postoperative hospital stay (8.0 [8.0–10.0] vs. 10.0 [9.0–11.0] days; P = 0.019) were significantly shorter in group S than group P (Table 2).

Atrial fibrillation, pulmonary embolism, myocardial infarction, cerebrovascular accident, renal failure, re-operation, and death did not occur in either group. One group P experienced

Table 1. Patient Characteristics

	Group P (n = 31)	Group S (n = 19)	P value
Age (yr)	61.2 ± 11.8	62.7 ± 8.3	0.632
Sex (M/F)	16/15	10/9	0.944
BMI (kg/m^2)	23.7 ± 3.0	23.7 ± 3.7	0.610
ASA (1 and 2/3)	15/16	9/10	0.944
Operation time (min)	238.2 ± 38.1	243.7 ± 37.3	0.623
Anesthetic time (min)	310.6 ± 42.9	315.8 ± 40.5	0.676
Hypoxia OP	15 (48.4)	9 (47.4)	0.944
Past Medical History	18 (58.1)	9 (47.4)	0.461
Hypertension	11 (35.5)	5 (26.3)	0.500
DM	12 (38.7)	2 (10.5)	0.031
Previous lung OP	1 (3.2)	1 (5.3)	1.000
CVA	4 (12.9)	0 (0.0)	0.284
IHD	3 (9.7)	1 (5.3)	1.000
COPD	0 (0)	2 (10.5)	0.140
Atrial fibrillation	0 (0)	2 (10.5)	0.140

Data are presented as mean ± SD or number of patients (%). Group P: Pyridostigmine administration, Group S: Sugammadex administration. BMI: body mass index, ASA: American Society of Anesthesiologists physical status classification, OP: operation, DM: diabetes mellitus, CVA: cerebrovascular accident, IHD: ischemic heart disease, COPD: chronic obstructive pulmonary disease.

Table 2. Postoperative Complication and Length of Postoperative Care

	Group P (n = 31)	Group S (n = 19)	P value
Complication	17 (54.8)	5 (26.3)	0.049
Prolonged air leak	1 (3.2)	1 (5.3)	1.000
Pneumonia	7 (22.6)	3 (15.8)	0.722
Atelectasis	11 (35.5)	2 (10.5)	0.095
Mechanical ventilation (day)	0 (0–0)	0 (0–0)	0.434
Chest tube insertion (day)	7.0 (6.0–8.0)	5.0 (4.0–7.0)	0.014
ICU stay (day)	2.0 (2.0–2.0)	2.0 (2.0–2.0)	0.263
PostOP hospital stay (day)	10.0 (9.0–11.0)	8.0 (8.0–10.0)	0.019

Data are presented as number of patients (%) or median and 25–75% IQR. Group P: Pyridostigmine administration, Group S: Sugammadex administration. ICU: intensive care unit, postOP: postoperative.

Table 3. Associations between Demographic and Clinical Variables and Postoperative Complications

	PostOP complication (−) (n = 28)	PostOP complication (+) (n = 22)	Univariate		Multivariate	
			OR (95% CI)	P value	OR (95% CI)	P value
Age (yr)	60.1 ± 11.1	63.9 ± 9.5	1.04 (0.98–1.10)	0.203		
BMI (kg/m^2)	23.9 ± 3.4	23.5 ± 3.1	0.96 (0.81–1.15)	0.671		
Male	16 (57.1)	10 (45.5)	1.60 (0.52–4.93)	0.413		
Sugammadex	14 (50.0)	5 (22.7)	0.29 (0.09–1.02)	0.053	0.22 (0.05–0.87)	0.031
ASA class 3	12 (42.9)	14 (63.6)	2.33 (0.74–7.34)	0.148	2.96 (0.82–10.68)	0.098
DM	5 (17.9)	9 (40.9)	3.19 (0.88–11.54)	0.078	1.40 (0.30–6.49)	0.665
Hypertension	7 (25.0)	9 (40.9)	2.08 (0.62–6.94)	0.235		
Prelung OP	1 (3.6)	1 (4.5)	1.29 (0.08–21.78)	0.862		
CVA	2 (7.1)	2 (9.1)	1.30 (0.17–10.05)	0.801		
IHD	1 (3.6)	3 (13.6)	4.26 (0.41–44.17)	0.224		
Atrial fibrillation	2 (7.1)	0 (0.0)		0.999		
COPD	1 (3.6)	1 (4.5)	1.29 (0.08–21.78)	0.862		
OP hypoxia	14 (50.0)	10 (45.5)	0.83 (0.27–2.55)	0.750		
Operation time (min)	233.8 ± 38.7	248.6 ± 35.1	1.01 (1.00–1.03)	0.167	1.02 (1.00–1.04)	0.090
Anesthetic time (min)	305.5 ± 42.4	321.6 ± 39.8	1.01 (1.00–1.02)	0.178	0.99 (0.95–1.04)	0.716

Data are presented as mean ± SD or number of patients (%) and odds ratios (OR) with 95% CI. BMI: body mass index, ASA: American Society of Anesthesiologists physical status classification, DM: diabetes mellitus, OP: operation, CVA: cerebrovascular accident, IHD: ischemic heart disease, COPD: chronic obstructive pulmonary disease.

sick sinus syndrome after surgery, but this patient had underlying asymmetric sinus node dysfunction.

Discussion

Several studies have compared the effect of sugammadex versus cholinesterase inhibitors, such as pyridostigmine or neostigmine in the postanesthesia care unit (PACU). These studies have shown that the use of sugammadex has reduced postoperative residual curarization (PORC) in the PACU [6,10]. This study showed that the incidence of postoperative pulmonary complications was lower and the duration of postoperative hospital stay was shorter in the patients undergoing lobectomy with suggamadex treatment.

In this study, respiratory complications including prolonged air leak, pneumonia, and atelectasis occurring after lobectomy were evaluated, and we thought that the use of sugammadex as a neuromuscular blockade reversal reduced overall pulmonary complications. Although sugammadex has been shown to reduce the total number of postoperative complications, there were no significant differences in specific pulmonary complications. This is thought to be due to the limitation of the number of subjects. We only had a sample size of 50 patients. In studies comparing thoracoscopic surgery and thoracotomy, respiratory and cardiovascular complications, especially atrial fibrillation, were common [12-15], but cardiovascular problems were rarely observed in this study. However, the decrease in complication rate is similar to the result of other studies in which the frequency of critical respiratory events is decreased due to the use of sugammadex. Martinez-Ubieto et al. [6] examined whether the TOF level, type of neuromuscular blocking agents (NMBAs) and reversal agents used, and respiratory events in the PACU were associated with an increased incidence of pneumonia and atelectasis during hospital admission. By studying critical respiratory event percentages for each of the groups identified by type of NMBAs and reversal agents used, significant differences were observed between the rocuronium-sugammadex group (1.1%) compared to the rocuronium group (9.7%) and the cisatracurium-neostigmine group (8.7%).

The decrease in the duration of chest tube insertion and postoperative hospital stay in this study may also be the result of reduced postoperative pulmonary complication. Sugammadex induces rapid reversal, quick restoration of normal skeletal muscle function and achivement of deep breaths without residual muscle relaxation, which reduces the incidence of atelectasis, help to restore pulmonary function [8,10,11], and allows the chest tube to be removed as soon as possible. These factors may reduce the length of postoperative hospital stay.

The extra few minutes of reversal advantage could translate into real clinical benefits. Studies have been reported that residual muscle relaxation progresses to respiratory complications such as pneumonia or atelectasis during hospital stays. Martinez-Ubieto et al. [6] demonstrated that the presence of PORC in the PACU shows a significant association with the development of postoperative critical respiratory events such as pneumonia, atelectasis and that the use of sugammadex significantly reduces the incidence of PORC in the PACU. Grosse-Sundrup et al. [17] demonstrated a significantly higher incidence of pulmonary

complications within seven postoperative days associated with the use of intermediate acting NMBAs. The authors inferred that the lingering effects of NMBAs are likely to have caused respiratory compromise in vulnerable patients. Another study reported that pulmonary outcomes deteriorated significantly in patients over 60 years of age with ASA physical status of 3 or 4 who were administered neostigmine or no reversal agent, but almost no detrimental effects were reported in the group that was administered sugammadex [18].

In this study, we could not confirm an association between sugammadex use and cardiovascular complications. However, a study comparing the use of sugammadex versus neostigmine in a patient with obstructive sleep apnea [7], reported that circulation-related complications including bradycardia, tachycardia, hypotension, hypertension, and arrythmia were significantly reduced in the group using sugammadex compared to the group using neostigmine. (5.4% vs. 37.8%). They assumed that circulation-related complications in patients who were given neostigmine might be associated with the later improvement in neuromuscular conduction. Therefore, in this study, the use of sugammadex can be considered to reduce cardiovascular complications that commonly occur in patients undergoing lobectomy. The action mechanism of sugammadex is dependent on the chemical encapsulation of the neuromuscular blocking agent molecule and does not involve a direct interaction with the cholinergic system. Comparatively, the administration of pyridostigmine leads to increased airway resistance and bradycardia and the administration of atropine or glycopyrrolate leads to tachycardia. Therefore, sugammadex may decrease pneumonia-causing secretions and cardiovascular disease [19,20].

This study examined the effect of the use of sugammadex in the postoperative period, but not in the PACU. However, data on residual curarization recorded after ICU transfer could not be confirmed. Only, there were no reintubations in the ICU, suggesting that there were no serious complications due to residual curarization. The most common complication after tracheal extubation is coughing. Though coughing is usually not a complication in itself, coughing may increase arterial pressure, heart rate and intraocular or intracranial pressure, and ineffective or persistent coughing might be associated with complications such as laryngospasm [21]. Therefore, it is a limitation of this study that we could not confirm minor respiratory events due to residual curarization such as coughing.

We began using the sugammadex in our hospital during the second half of 2013, and this measure has been used mainly with patients who are being transported to the ICU since 2014 for the prevention of hypoventilation during the transfer to the ICU. Thus, this study was divided into two groups based on January 2014. For this reason, this study may have limitations as a retrospective study because there is a possibility that a variable is dependent on the progress of time. However, anesthesia management and perioperative management were performed according to the Department of Anesthesiology and the Department of Thoracic and Cardiovascular Surgery protocols. Since the operations were performed by a specialist who has performed the operation since the late 1990s, the difference in the operator's skill level is expected to be minimal. In addition, there was no change in the drug during the study period, and there was no case of delayed recovery due to infection at the surgical site. Therefore, this study seems to have no difference in patient care in accordance with the protocol between the two groups, despite its retrospective nature.

In conclusion, the use of sugammadex, compared with pyridostigmine, showed a significant reduction in the overall incidence of postoperative pulmonary complications and decreased the duration of chest tube use and postoperative hospital stay in patients undergoing VATS lobectomy, suggesting that sugammadex might be helpful in improving clinical outcomes in such patients. However, large-scale of prospective studies are needed to demonstrate the beneficial effects of sugammadex.

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