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Sugammadex for reversing neuromuscular blockages after lung surgery

A systematic review and meta-analysis

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Abstract

Background: This study determined whether sugammadex was associated with a lower risk of postoperative pulmonary complications and improved outcomes in lung surgeries.

Methods: A systematic literature search was conducted using PubMed, Embase, Web of Science, and the Cochrane Library from January 2000 to March 2022. The characteristics of lung surgeries using sugammadex treatment compared with control drugs and postoperative outcomes were retrieved. The primary outcome was estimated through a pooled odds ratio (OR) and its 95% confidence interval (CI) was identified using a random-effects model.

Results: From 465 citations, 7 studies with 453 patients receiving sugammadex and 452 patients receiving a control were included. The risk of postoperative pulmonary complication (PPCs) was lower in the sugammadex group than in the control group. Also, it showed that the effect of sugammadex on PPCs in the subgroup analysis was significantly assessed on the basis of atelectasis or non-atelectasis. Furthermore, subgroup analysis based on the relationship between high body mass index (BMI) and PPCs also showed that sugammadex had less occurrence in both the high BMI (defined as BMI ≥ 25) and low BMI groups. No difference in length of hospital stay (LOS) between the two groups was observed.

Conclusion: This study observed that although reversing neuromuscular blockages with sugammadex in patients undergoing thoracic surgery recorded fewer PPCs and shorter extubation periods than conventional reversal agents, no difference in LOS, postanaesthesia care unit (PACU) stay length and chest tube insertion duration in both groups was observed.

Abbreviations: BMI = body mass index, CI = confidence interval, LOS = length of hospital stay, OR = odds ratio, PACU = postanaesthesia care unit, PPC = postoperative pulmonary complication, SMD = standard mean difference.

Keywords: enhanced recovery after surgery, lobectomy, lung surgery, meta-analysis, neostigmine, postoperative pulmonary complications, sugammadex, VATS

1. Introduction

During the administration of general anesthesia, muscle relaxants are used to facilitate the surgery processes. Subsequently, after surgery, reversal agents, such as acetylcholinesterase inhibitors or sugammadex, are administered to recover respiratory muscle power and remove the endotracheal tube. However, compared with acetylcholinesterase inhibitors, sugammadex is associated with a significantly faster reversal of neuromuscular blockade and shortened discharge from the odds ratio (OR) to the postanaesthesia care unit (PACU) in general surgeries.[1–3] It has also been reported that patients receiving sugammadex had fewer side effects than those given neostigmine.[4] In another recent study,[5] no significant difference was observed between sugammadex and neostigmine based on the risk of the composite postoperative pulmonary complications outcome. Nevertheless, the effect of sugammadex in reducing PPCs remains controversial.[6,7]

Lung cancer is the leading cause of cancer deaths worldwide.[8] The number of surgeries for benign lung tumors or cancers is also growing increasingly. Literature has reported PPC's prevalence in thoracic surgery.[9,10] Specifically, however, patients undergoing thoracic surgery may be at a higher risk of incomplete neuromuscular recovery.[11,12] Hence, a residual block is proposed to increase the incidence of prolonged lung atelectasis and PPCs. In these surgeries, even mild PPCs were associated with increased early postoperative mortality, ICU admissions and length of stay (ICU & hospital).[13] Therefore, the reversal of neuromuscular blockade after lung surgery is essential.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Recently, using sugammadex after thoracic surgeries has become more common. However, the association between sugammadex reversal and avoidance of PPCs in thoracic surgery remains unclear. Therefore, this study evaluated the impact of sugammadex on postoperative outcomes of thoracic surgery. The first human study for sugammadex was conducted on healthy volunteers and published in 2005.[14] Based on this fact, we searched databases from 2000.

2. Material and Methods

Details of the protocol for this systematic review and meta-analysis have been registered on PROSPERO (CRD42022321409).

2.1. Search strategy

Three authors (WT Hsu, CM Hsu, JL Yang) independently searched the PubMed, web of science, Cochrane library, and Embase databases for eligible publications from January 2000 to March 2022, using the following keywords: "thoracic surgery", "video-assisted thoracoscopy", "pneumonectomy", "lobectomy", "lung resection surgery", "thoracotomy", "wedge resection", "sugammadex", and "bridion". Only published prospective and retrospective cohort studies that reported using sugammadex compared with a control drug (neostigmine or other cholinesterase inhibitors) in lung surgery were included. However, reviews, editorials, letters to editors, case reports, commentaries, articles that did not specify the surgery type, articles whose full text was unavailable in the English language, irretrievable articles, and articles published before 2000 were excluded.

2.2. Data extraction

This systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] First, 2 authors (JL Yang and ML Shen) independently evaluated the titles and abstracts, retrieved full text articles and selected the studies. Then, discrepancies were resolved by consulting the other 2 authors (KB Chen and CM Hsu).

Primary outcomes included PPCs and length of hospital stay (LOS). LOS was defined as the number of days from the date of surgery to discharge. However, secondary outcomes included postoperative extubation time, length of PACU stay, and duration of chest tube insertion. While extubation time was defined as the time from surgery end until the patient fulfilled the criteria for safe extubation, length of PACU stay was defined as the duration of stay in PACU from admission to discharge. Additionally, the duration of chest tube insertion was defined as the number of days from the date of surgery to the removal of the chest tube.

2.3. Methodological quality assessment

The methodological quality of all included studies was independently assessed by 2 authors (YW Lai and JL Yang) using the modified Jadad scale.[16] The modified Jadad scale comprises eight items to evaluate randomization, blinding, withdrawals, dropouts, inclusion, and exclusion criteria, adverse effects and statistical analysis. The total score for each article was 0 to 8. A score lower than three means low quality of the trial.

2.4. Statistical analysis

All statistical analyses and meta-analyses were performed using the review manager 5 software (version 5.4, The Nordic Cochrane Centre, Copenhagen, Denmark). Subsequently, we performed a pairwise meta-analysis using an inverse variance random-effect model according to the recommendations of the Cochrane Handbook[17]; this was because some factors including differences in surgery type and outcome definitions may cause inter-study heterogeneity. Pooled effect estimates were also obtained by calculating the standard mean difference (SMD) in outcomes for continuous variables and ORs for dichotomous variables along with their respective 95% confidence intervals (CIs). Then, heterogeneity was assessed using the I square (I^2) statistics and the related P value. Additionally, subgroup meta-analyses for PPCs assessed with atelectasis and without atelectasis, evaluated with early postoperative chest radiographic abnormalities and postoperative hypoxic episodes and residual neuromuscular blockade were conducted for the potential sources of heterogeneity between studies. Afterward, another subgroup analysis was performed for the high body mass index (BMI) (defined as ≥25) and low BMI groups to examine whether BMI's treatment effect was affected. Lastly, sensitivity analyses were conducted to assess the robustness of the findings by excluding retrospective studies. We did not conduct a publication bias analysis because of the lower than ten studies reviewed in this meta-analysis.

A P value less than 0.05 was considered statistically significant for the analysis of effect sizes, and if the $I^2 > 50\%$, the heterogeneity was considered high.

2.5. Ethics and dissemination

The ethical approval was not necessary for this meta-analysis.

3. Results

3.1. Study characteristics

Among the 465 potentially relevant citations from literature searching, 7 studies (1 prospective cohort, 3 retrospective cohorts, 3 randomized controlled trials) were identified to meet our inclusion criteria. We illustrated the study selection process with a PRISMA flow diagram in Figure 1. This review included 905 patients. from the 7 studies, we observed that 453 patients received sugammadex (178, 39.3% female) and 452 patients received a control (189, 41.8% female).The studies included were conducted between 2017 and 2021. Detailed characteristics of the included studies are shown in Table 1. The analyzed PPCs included prolonged air leak, pneumonia, atelectasis,[18,19,21,23] postoperative hypoxic episodes,[12,22] early postoperative chest radiographic abnormalities[20] and incidence of residual neuromuscular blockade during both tracheal extubation and PACU admission.[12] The modified Jadad scores for the methodological quality assessment of each selected study are illustrated in Table 2.

3.2. Incidence of postoperative pulmonary complications

Seven studies were included in the meta-analysis of PPCs, with 453 patients receiving sugammadex and 452 receiving a control. Results showed statistically significant less complications in the sugammadex group. (OR: 0.45, 95% CI: 0.32–0.63, $P < .001$, $I^2 = 0\%$) (Fig. 2a) Subgroup analysis also showed that the sugammadex group had less occurrence in PPCs whether assessed with atelectasis (OR: 0.47, 95% CI: 0.30–0.76, $P = .002$) or without atelectasis (which assessed with early postoperative chest radiographic abnormalities, incidence of postoperative hypoxic episodes and residual neuromuscular blockade) (OR: 0.43, 95% CI: 0.26–0.69, $P < .001$). Finally, we conducted a subgroup analysis for the relationship between BMI (≥25 defined as high BMI) and the incidence of PPCs, which revealed a reduced occurrence of sugammadex in both the high BMI (OR: 0.42, 95% CI: 0.24–0.73, $P = .002$) and low BMI groups (OR: 0.47, 95% CI: 0.31–0.72, $P < .001$) (Table 3).

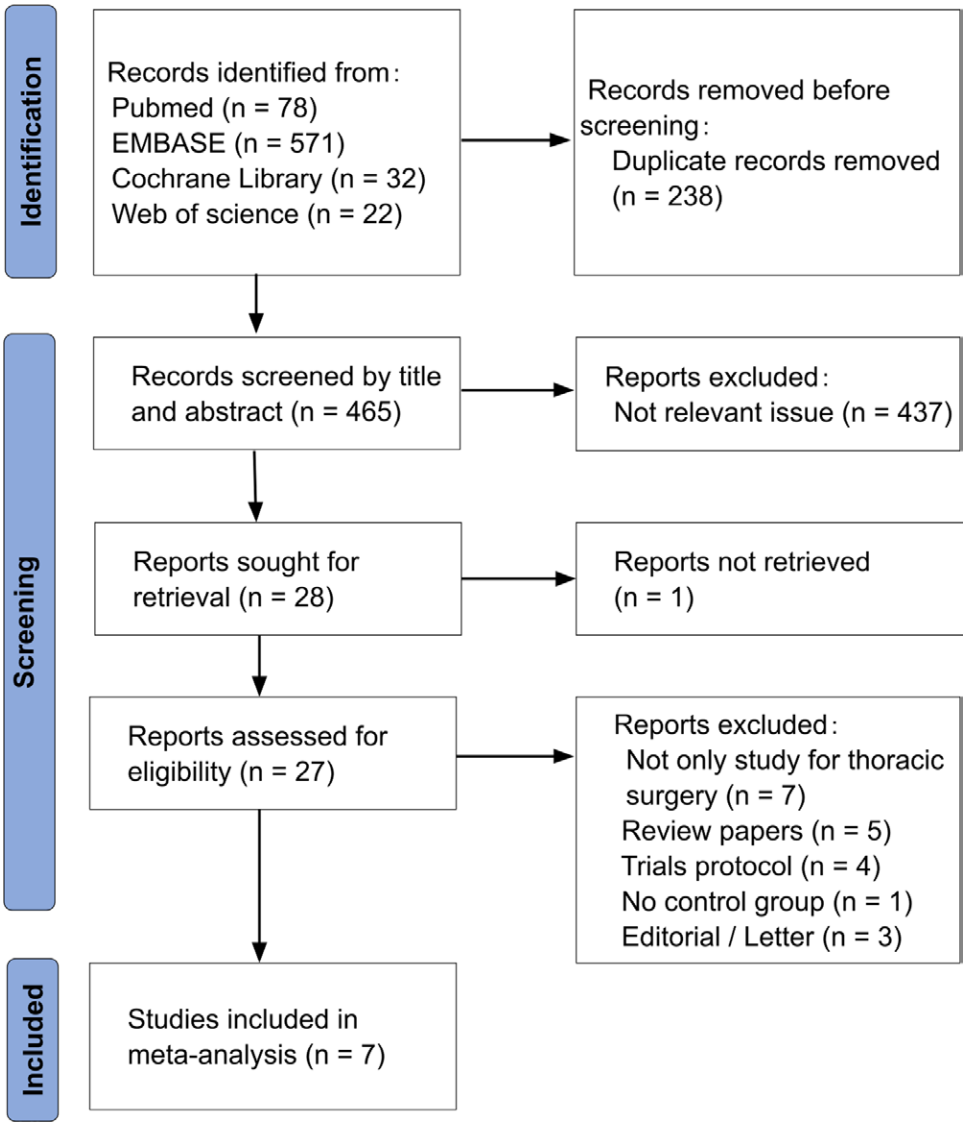

Figure 1. PRISMA diagram of the study selection process for the systemic review and meta-analysis.

3.3. Total length of hospital stay

Three studies were included in the analysis of total LOS, reporting 192 patients receiving sugammadex and 205 receiving a control. Results showed no difference in LOS between the 2 groups (SMD = –0.28, 95% CI; –0.81 to 0.25, $P = .29$, $I^2 = 81\%$) (Fig. 2b).

3.4. Extubation time

The four studies that assessed the time from surgery end to extubation showed that the sugammadex group was associated with a shorter extubation time (SMD –1.0; 95% CI: –1.74 to 0.28, $P = .007$, $I^2 = 93\%$) (Fig. 2c).

3.5. Total rocuronium dose administration

Five studies measured the total dose of rocuronium administered throughout the operation. Results of the meta-analysis indicated no significant difference between both reversal groups (SMD; 0.3; 95% CI:–0.05 to 0.81, $P = .09$, $I^2 = 85\%$) (Fig. 2d).

3.6. Length of PACU stay

Two studies were included that analyzed the length of PACU stay. Results showed no significant difference between both reversal groups (SMD: –0.19, 95% CI: –0.54 to 0.17, $P = .30$, $I^2 = 56\%$) (Fig. 2e).

3.7. Duration of chest tube insertion

Analysis of the 2 studies that reported the duration of chest tube insertion indicated no significant difference between both reversal groups (SMD: –0.43; 95% CI: –1.33 to 0.47, $P = .35$, $I^2 = 84\%$) (Fig. 2f).

3.8. Sensitivity analysis for incidence of postoperative pulmonary complications

We also conducted sensitivity analyses by excluding the three retrospective studies included for this review. Then, sensitivity analysis for the remaining four prospective studies regarding the incidence of PPCs was conducted (OR 0.42, 95% CI: 0.25–0.71, $P = .001$, $I^2 = 0\%$). Results showed a similar incidence to the

Table 1

General characteristics of the selected studies.

Authors & yr	Journal	Country	Study design	Comparison	N	Female (%)	Age, mean ± SD	BMI, mean ± SD	Surgery	Outcomes	
										PPC evaluation parameters	Others
Cho HC, 2017[18]	Korean Journal of Anesthesiology	Korea	Retrospective cohort study	Sugammadex Pyridostigmine	19 31	47.4 48.4	62.7 ± 8.3 61.2 ± 11.8	23.7 ± 3.7 23.7 ± 3.0	VATS lobectomy	Atelectasis, prolonged air leak, pneumonia	LOS, duration of chest tube insertion, length of ICU stay
Çitil AB, 2019[19]	Journal of cardiovascular-thoracic anesthesia and intensive care society	Turkey	Parallel RCT	Sugammadex Neostigmine	30 30	33.3 36.7	51 ± 10.2 52 ± 9.6	23 ± 4.0 23 ± 3.0	Lobectomy, pneumectomy, wedge	Atelectasis, pneumonia	Extubation time, total rocuronium dose, length of ICU stay
Lee DK, 2020[20]	Turkish Journal of Medical Sciences	Korea	Retrospective cohort study	Sugammadex Pyridostigmine	90 69	33.3 27.5	59.5 ± 9.5 59.7 ± 9.2	23.16 ± 3.23 23.14 ± 2.99	VATS lobectomy	Early post-operative chest radiographic abnormalities	Extubation time, total rocuronium dose
Lee TY, 2020[21]	Anesth Pain Med	Korea	Parallel RCT	Sugammadex Neostigmine	46 47	34.8 46.8	63.8 ± 9.7 65.5 ± 8.6	25.5 ± 3.6 24.1 ± 3.3	VATS lobectomy	Atelectasis, prolonged air leak, Pneumonia, desaturation, reintubation	LOS, total rocuronium dose, duration of chest tube insertion, length of ICU stay
Moon TS, 2020[22]	Journal of Clinical Anesthesia	USA	Parallel RCT	Sugammadex Neostigmine	44 48	50.0 45.8	53.1 ± 14.4 49.9 ± 13.8	*28.4 (25.1–31.0) *30.4 (24.6–35.1)	VATS lobectomy, wedge, others	Post-operative hypoxic episodes	Extubation time, total rocuronium dose, length of PACU stay
Murphy GS, 2021[12]	Anesthetic Clinical Pharmacology	USA	NRCT	Sugammadex Neostigmine	97 100	61.9 65.0	68 ± 12 63 ± 13	**77 ± 20/ ***168 ± 10 **75 ± 18/ ***168 ± 11	VATS	Post-operative hypoxic episodes, incidence of residual neuromuscular blockade	Extubation time, total rocuronium dose
Song SW, 2021[23]	Journal of Cardiothoracic Surgery	Korea	Retrospective observational study	Sugammadex Pyridostigmine	127 127	24.4 27.6	*67.0 (60.0–72.0) *66.0 (59.5–71.0)	*23.5 (21.3–25.7) *23.1 (21.5–25.5)	Lobectomy	Atelectasis	LOS, length of PACU stay

Note. BMI = body mass index, LOS = length of hospital stay, ICU = intensive care unit, N = numbers, NRCT = non-randomized control trial, PACU = post-anesthesia care unit, PPC = postoperative pulmonary complication, RCT = randomized control trial, VATS = video-assisted thoracic surgery.

*no SD data available;

**Weight;

***Height.

Table 2

Modified Jadad scores of the included studies.

Included studies	a. Was the study described as randomized?	b. Was the method of randomization appropriate?	c. Was the study described as blinding?*	d. Was the method of blinding appropriate?	e. Was there a description of withdrawals and dropouts?	f. Was there a clear description of the inclusion and exclusion criteria?	g. Was the method used to assess adverse effects described?	h. Were the methods of statistical analysis described?	Total
Cho HC, 2017[18]	0	0	0	0	1	1	1	1	4
Çitil AB, 2019[19]	1	1	1	1	1	1	1	1	8
Lee DK, 2020[20]	0	0	1	0	1	1	1	1	5
Lee TY, 2020[21]	1	1	1	1	1	1	1	1	8
Moon TS, 2020[22]	1	1	1	1	1	1	1	1	8
Murphy GS, 2021[12]	0	0	0	0	1	1	1	1	4
Song SW, 2021[23]	0	0	0	0	1	1	1	1	4

Note: a, e, f, g, h: Yes: +1, No: 0; b, d: Yes: +1, No: −1, Not described: 0; c: double-blind: +1; single-blind: +0.5, No: 0.
The total score for each article ranged from 0 to 8; a score of 7 or 8 was considered to be of high quality, 4 to 6 of moderate quality and 1 to 3 of low quality.

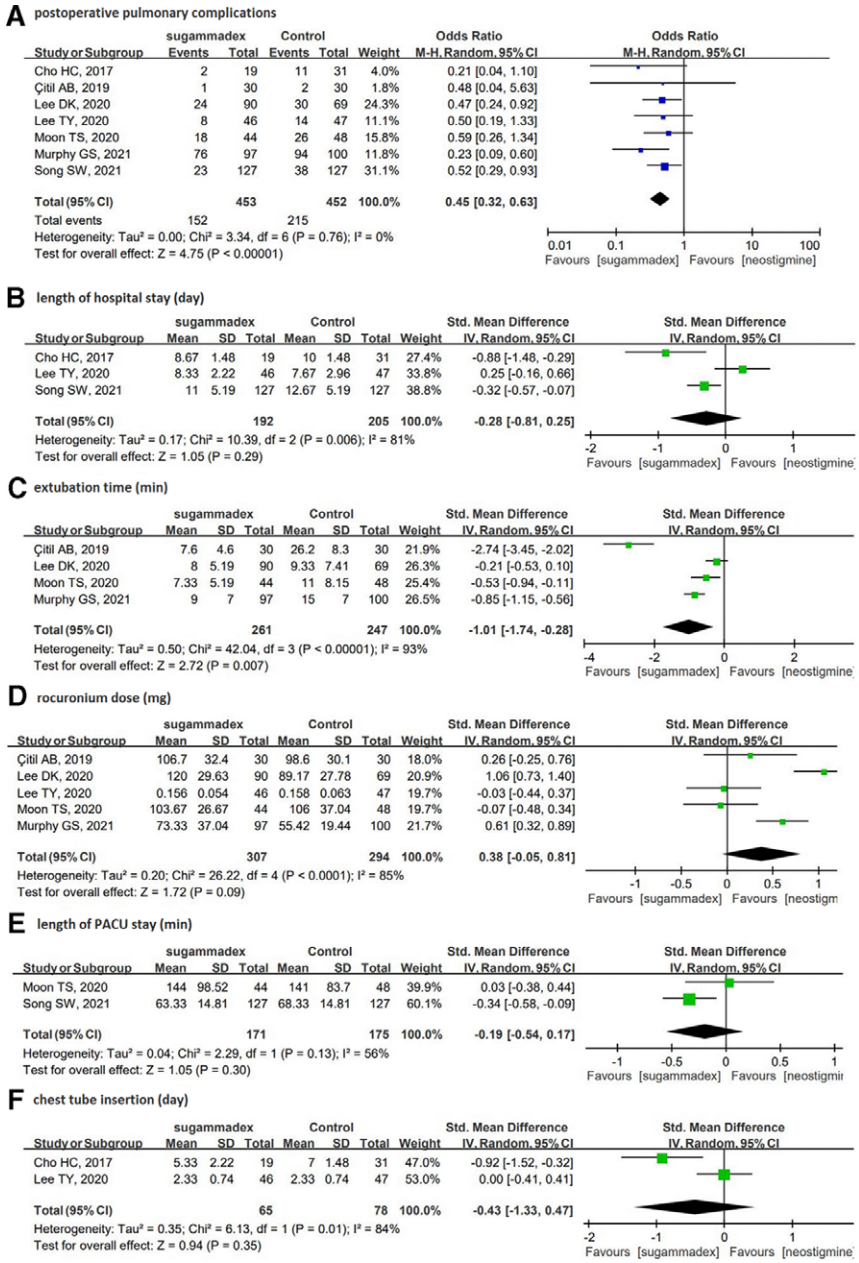

Figure 2. Forest plots comparing sugammadex use versus control on (**a**) postoperative pulmonary complications; (**b**) length of hospital stay (days); (**c**) total rocuronium dose (mg); (**d**) extubation time (minutes); (**e**) length of PACU stay (minutes); (**f**) duration of chest tube insertion (days).

Table 3

Results of subgroup meta-analysis of post-operative pulmonary complications.

Subgroups		Odds ratio	95% confidence interval		*P* value
			Lower limit	Upper limit	
PPCs assessment parameters	Atelectasis mainly	0.47	0.3	0.76	.002
	Early post-operative chest radiographic abnormalities, incidence of post-operative hypoxic episodes and residual neuromuscular blockade	0.43	0.26	0.69	.0006
BMI	≧25	0.42	0.24	0.73	.002
	<25	0.47	0.31	0.72	.0004

BMI = body mass index, PPCs = post-operative pulmonary complication.

main analysis (OR 0.45, 95% CI: 0.32–0.63, $P < .001$, $I^2 = 0\%$), indicating that the main result was robust.

4. Discussion

This meta-analysis observed that sugammadex administration after lung surgery decreased the incidence of PPCs. We also demonstrated that although using sugammadex to reverse muscle relaxation after lung surgery was faster, recovery, and extubation times were shorter than using neostigmine. Moreover, LOS, PACU stay length, and chest tube insertion duration had no significant difference.

During noncardiac surgeries, a previous study showed that sugammadex was associated with a 30% reduced risk of PPCs.[24] In colon surgery, however, no difference in postoperative outcomes with the use of sugammadex was observed.[25] Based on our extensive literature search, this research is the first meta-analysis to evaluate the effect of sugammadex in lung surgery. In this study, we focused on the population of patients undergoing lung surgery, considered a higher risk of PPCs.[9] Sugammadex seemed to reduce PPCs without changing the LOS because PPCs were a leading cause of poor surgical outcomes.[13,26] Therefore, using sugammadex for lung surgery is considered beneficial.

Since no standardized definition of PPC[5] exists, we integrated them using a standard definition according to Abbott et al [27] Then, we conducted a subgroup analysis of atelectasis and non-atelectasis. Results showed that the sugammadex group had a lesser occurrence of atelectasis and non-atelectasis PPCs.

The anesthetic management of obese patients can be challenging because of their altered anatomy and physiology. Studies have reported that approximately 18% of obese patients undergoing surgery experience PPCs, almost twice the risk among average or overweight patients.[28] A BMI of ≥25 was one of the independent risk factors for PPCs in lung cancer patients who underwent VATS lung surgeries.[29] Notably, our result showed the benefit of reducing the incidence of PPCs using sugammadex in patients who underwent lung surgery in both the high (≥25) and low BMI (<25) groups.

Bradycardia and hypotension induced through sugammadex after VATS surgery have been reported previously.[30] The mechanism underlying the decrease in heart remained unknown; however, Kounis syndrome or hypersensitivity appeared to be the most plausible mechanism.[31,32] Both sugammadex and neostigmine were associated with serious adverse events in <1% of patients, and data showed that there was little to no difference in the risk of serious adverse events.[4,33]. The use of anticholinergic agents including atropine and glycopyrrolate to treat bradycardia, and vasopressors (ephedrine, norepinephrine, and epinephrine) to treat hypotension should be considered. Although sugammadex effectively prevents postoperative residual neuromuscular blockade, anesthesiologists should consider it as a causative agent of cardiac arrest during surgery.

The study's strength was that we focused on lung surgery and analyzed PPCs. Subgroup analysis was also performed for atelectasis and non-atelectasis. Additionally, we conducted another subgroup analysis to examine whether the treatment effect was affected by BMI. Then, we used modified Jadad scores to assess the selected studies' methodological quality, which showed moderate to high-quality results. We also performed a sensitivity analysis by excluding the retrospective studies.

However, several limitations to this study were encountered. First, all included trials showed heterogeneity in the types of lung surgery, the different ranges of lung resection could affect the outcomes.[29] Second, surgical complications such as massive intraoperative blood loss[34] were not evaluated in the present study, which could influence the outcome. Third, owing to the fact that the reports included in the present meta-analysis did not include the pertinent information, we did not perform further analysis on the independent risk factors of PPC after VATS surgeries, such as chronic obstructive pulmonary disease,[35] smoking, preoperative $FEV_1 \leq 60\%$, $PaO_2 \leq 60$ mm Hg, intraoperative crystalloids ≥6 mL/kg/h, duration of surgery ≥2 hours.[9,36–38] Additionally, this study did not analyze some side effects of reversal agents (such as postoperative nausea and vomiting, bradycardia, and so forth).

In conclusion, we observed that although reversal with sugammadex in patients undergoing thoracic VATS surgery had lesser PPCs and shorter extubation periods than other conventional reversal agents, in obese and non-obese patients. No difference was observed between LOS, length of PACU stay and duration of chest tube insertion existed in both groups.

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Author contributions

Conceptualization, Jia-Li Yang; methodology, Mei-Ling Shen; formal analysis, Wei-Ti Hsu; investigation, Wei-Ti Hsu; resources, Yu-Wen Lai; data curation, Yu-Wen Lai; writing—original draft preparation, Jia-Li Yang; writing—review and editing, Kuen-Bao Chen; supervision, Chieh-Min Hsu. All authors have read and agreed to the published version of the manuscript.

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