Chinese Medical Journal®

Superiority of sugammadex in preventing postoperative pulmonary complications

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Abstract

Background: Postoperative pulmonary complications often lead to increased mortality and financial burden. Residual paralysis plays a critical role in postoperative pulmonary complications. This meta-analysis was performed to determine whether sugammadex overmatches neostigmine in reducing postoperative pulmonary complications.

Methods: PubMed, Embase, Web of Science, Medline through Ovid, Cochrane Library, Wanfang, China National Knowledge Infrastructure, and Chinese BioMedical Literature Databases were searched from their inception to 24 June, 2021. Random effects models were used for all analyses. Cochrane risk of bias tool was used to assess the quality of RCTs, while Newcastle Ottawa Quality Assessment Scale was used to assess for the quality of cohort studies.

Results: Seventeen studies were included in the meta-analysis. Pooled data from cohort studies showed reversing neuromuscular blocking with sugammadex had less risk of compound postoperative pulmonary complications (relative risk [RR]: 0.73; 95% confidence interval [CI]: 0.60–0.89; $P = 0.002$; $I^2 = 81\%$), pneumonia (RR: 0.64; 95% CI: 0.48–0.86; $I^2 = 42\%$) and respiratory failure (RR: 0.48; 95% CI: 0.41–0.56; $I^2 = 0\%$). However, pooled data from RCTs did not show any difference between the two groups in pneumonia (RR: 0.58; 95% CI: 0.24–1.40; $I^2 = 0\%$) and no respiratory failure was reported in the included RCTs. The difference was not found between sugammadex and neostigmine about atelectasis in pooled data from either RCTs (RR: 0.85; 95% CI: 0.69–1.05; $I^2 = 0\%$) or cohort studies (RR: 1.01; 95% CI: 0.87–1.18; $I^2 = 0\%$).

Conclusion: The evidence of superiority of sugammadex was limited by the confounding factors in cohort studies and small scale of RCTs. Whether sugammadex precedes neostigmine in preventing pulmonary complications after surgery is still unknown. Well-designed RCTs with large scale are needed.

Registration: PROSPERO (https://www.crd.york.ac.uk/PROSPERO/); CRD 42020191575

Keywords: Sugammadex; Neostigmine; Pulmonary complications; Pneumonia; Paralysis

Introduction

Postoperative pulmonary complications occur in nearly 5% of patients undergoing surgeries and increase mortality rate and financial burden.[1-3] Neuromuscular blocking (NMB) agents are widely used for most general anesthetic procedures as they provide ideal muscle paralysis for surgery. However, NMB agents are associated with postoperative pulmonary complications because of residual neuromuscular block after operations.[4]

Neostigmine takes effect by inhibiting cholinesterase competitively and is commonly used to reverse NMB. However, it has cholinergic side effects and is not suitable for deep blocks due to the ceiling effect.[5] The new reversal agent, sugammadex, has advantages over neostigmine as it can encapsulate and inactivate unbound aminosteroid NMB agents; thus, it has better effects in reversing NMB and lowering the risk of residual paralysis.[6] In addition, these superiorities may decrease the incidence of postoperative pulmonary complications.[7] However, previous meta-analyses only show sugammadex reverses NMB more efficiently with less adverse events, such as dry mouth or bradycardia, and shorter discharge duration than neostigmine,[8-10] but the impact of sugammadex on clinical pulmonary outcomes out of the recovery room is still unknown.

It is important for clinical practice to understand whether the incidence rate of postoperative pulmonary complications is lower in sugammadex than in neostigmine. Therefore, we performed a systematic review and meta-

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002381

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Chinese Medical Journal 2023;136(13)
Received: 02-08-2022; **Online:** 28-03-2023 **Edited by:** Jing Ni

analysis to compare their rates of postoperative pulmonary complications.

Methods

The protocol for this systematic review was registered with PROSPERO (https://www.crd.york.ac.uk/PROSPERO/), the international prospective register of systematic reviews (CRD 42020191575), and Preferred Reporting Items for Systematic Review and Network Meta-analyses 2020 recommendations were followed.[11,12]

Eligibility criteria

The identified studies were checked for eligibility criteria according to the patients, intervention, control, outcomes, and studies principles. The inclusion criteria were as follows: (1) patients ≥18 years old, (2) intervention: using sugammadex for NMB reversal, (3) control: using neostigmine for NMB reversal, and (4) outcomes: the primary outcome was the incidence of the compound postoperative pulmonary complication, as defined by authors in the original studies. According to the European perioperative clinical outcome (EPCO) guidelines, these complications include respiratory infection, respiratory failure, pleural effusion, atelectasis, pneumothorax, bronchospasm, and aspiration pneumonitis.[13] The data would be excluded if the definition defined in original studies exceeded those in the EPCO guidelines, such as upper airway obstruction, sleep apnea, and respiratory depression. The compound pulmonary complication is a composite result. The second outcomes were the incidence of specific postoperative pulmonary complications, including pneumonia, respiratory failure, and atelectasis. According to the definition of respiratory failure,[14] desaturation with arterial oxygen saturation of not <90% was not included as respiratory failure. (5) types of studies: randomized controlled trials (RCTs) and cohort studies. Exclusion criteria were non-clinical studies; studies lacking data about postoperative pulmonary complications defined in our study; case reports; reviews; or conference papers.

Literature search

We searched PubMed, Embase, Web of Science, Medline, Cochrane Library, Wanfang, China National Knowledge Infrastructure, and Chinese BioMedical Literature Databases from their inception date to 24 June 2021. A comprehensive search strategy was employed using relevant search terms selected from Medical Subject and Entry Terms. The databases were explored using a search algorithm with Boolean operators: "(sugammadex OR selective relaxant binding agents OR BRIDION gamma-cyclodextrins OR org25969) AND (neostigmine OR neuromuscular blocking agents)".

Study selection and data collection

Two authors (HBL and RL) evaluated the titles, abstracts, and full articles retrieved by the search strategy, and then selected the researches independently. We contacted the authors of some studies for missing data. Data were extracted and recorded in a standard table. The extracted characteristics included author name, publication year, sample size, patients' age, gender, study design, surgery type, doses of sugammadex and neostigmine, ventilation parameters, preoperative pulmonary conditions, evaluation time of pulmonary complications, and definition of the compound pulmonary complication. The data collection was performed by the two authors separately and the third author (SJC) only intervened when discrepancies occurred.

Statistical analyses

Review Manager version 5.3 (RevMan; The Cochrane Collaboration, Copenhagen, Denmark) was used for this meta-analysis. Dichotomous outcomes were calculated with a risk ratio and 95% confidence interval (CI). The same outcomes that were observed in at least two studies were included in the meta-analysis. Considering the significant methodological heterogeneity, separate meta-analyses were performed for RCTs and cohort studies. Contact authors for the original data when important data could not be obtained in the published paper. We utilized the random effects model for all data analysis considering clinical heterogeneity among the included studies. Heterogeneity was assessed using the I^2 statistic. A threshold value of $P < 0.1$ was used to determine the presence of heterogeneity, which would be existed if $I^2 > 50\%$ and significant if $I^2 > 75\%$.[15] If heterogeneity existed, meta-regression was performed with at least ten included studies,[16] while subgroup analyses were performed with <10 included studies. Advanced age and smoke are risk factors for postoperative pulmonary complications,[17] the incidence of smoke is higher in male than female, and different doses of sugammadex has different abilities to reverse deep NMB.[18] Therefore, subgroup analysis was carried out based on age (age <60 years and age ≥60 years) or gender (percentage of male >60%, between 40–60%, <40%, and not reported) or treatment doses of sugammadex (≤2 mg/kg, >2 mg/kg, and not reported). Potential publication bias was evaluated by Egger's tests if at least three studies were included.[19] A funnel plot was made if at least ten studies were included. Sensitivity analyses were performed to test the robustness of the results with heterogeneity. We excluded RCTs that were identified with high risk of bias or cohort studies which scored with Newcastle Ottawa Scale (NOS) no more than seven and altered effect measures to perform sensitivity analyses.

Quality assessment and risk of bias

The quality of the research was assessed independently by two reviewers. Cochrane risk of bias tool was used to assess the quality of RCTs,[20] while NOS was used to assess the quality of cohort studies.[21] Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to analyze the quality of evidence for outcomes derived from the same research type.[22]

Results

A total of 4656 recorded studies were initially identified. After removing duplicates and screening titles and abstracts, 179 full-text articles were selected for eligibility.

At last, 17 studies were included in the systematic review [Figure 1A].

Study characteristics

Table 1 summarizes the characteristics of the 17 included studies, including nine RCTs,[23-31] two prospective cohort trials,[3,32] and six retrospective cohort trials.[2,33-37] Supplementary Table 1, http://links.lww.com/CM9/B167 shows the definition of the compound pulmonary complication and preoperative pulmonary conditions in the included studies. Four studies matched preoperative pulmonary conditions in the neostigmine and sugammadex groups.[2,35-37] There were seven studies that compared the preoperative pulmonary condition between the two groups.[23,24,26-28,33,34] Among them, one study found a higher rate of preoperative obstructive sleep apnea syndrome in the sugammadex group.[34] There were six studies that did not mention the comparison between groups.[3,25,29-32]

Risk of bias and quality of evidence

The risk of bias assessment is summarized in Figure 1B. Seven RCTs poorly described the allocation concealment and five RCTs poorly described the blinding method. One RCT was at high risk of selective reporting bias because of the inconsistent outcomes between this article and the registered protocol. The risk of bias in all cohort studies was mainly about the comparability between the sugammadex and neostigmine groups, and the demonstration that outcome of interest was not present at the start of studies [Supplementary Table 2, http://links.lww.com/CM9/B167]. None of the RCTs and prospective studies has reported a loss of follow-up >15%.

Compound postoperative pulmonary complication

A total of ten studies described the compound pulmonary complication.[2,3,23,27,31-33,35-37] However, the definition in three studies contained complications beyond the definition of the compound postoperative pulmonary complication mentioned in the method and was not included for analysis of the compound pulmonary complication.[23,27,36] Ultimately, we selected six cohort studies consisting of 56,482 patients and one RCT including 60 patients with the compound of postoperative pulmonary complication.[2,3,31,32,33,35,37] Three cohort studies and the RCT showed that the sugammadex group had a significantly lower incidence of the compound pulmonary complication compared to the neostigmine group.[2,3,31,37] Two cohort studies reported numerically lower incidence in the sugammadex group,[32,35] and one cohort study reported a numerically higher incidence in the sugammadex group.[33]

Pooled data from cohort studies showed the incidence of the compound postoperative pulmonary complication when reversing NMB with sugammadex was significantly lower than neostigmine (relative risk [RR]: 0.73; 95% CI: 0.60–0.89; $P = 0.002$; $I^2 = 81\%$) [Figure 2]. The risk for publication bias was low for this comparison (Egger's test; $P = 0.498$). The overall GRADE quality of evidence was rated as very low because of the serious risk of bias and high heterogeneity [Supplementary Table 3, http://links.lww.com/CM9/B167]. Meta-analysis was not performed for RCT because only one study was included.

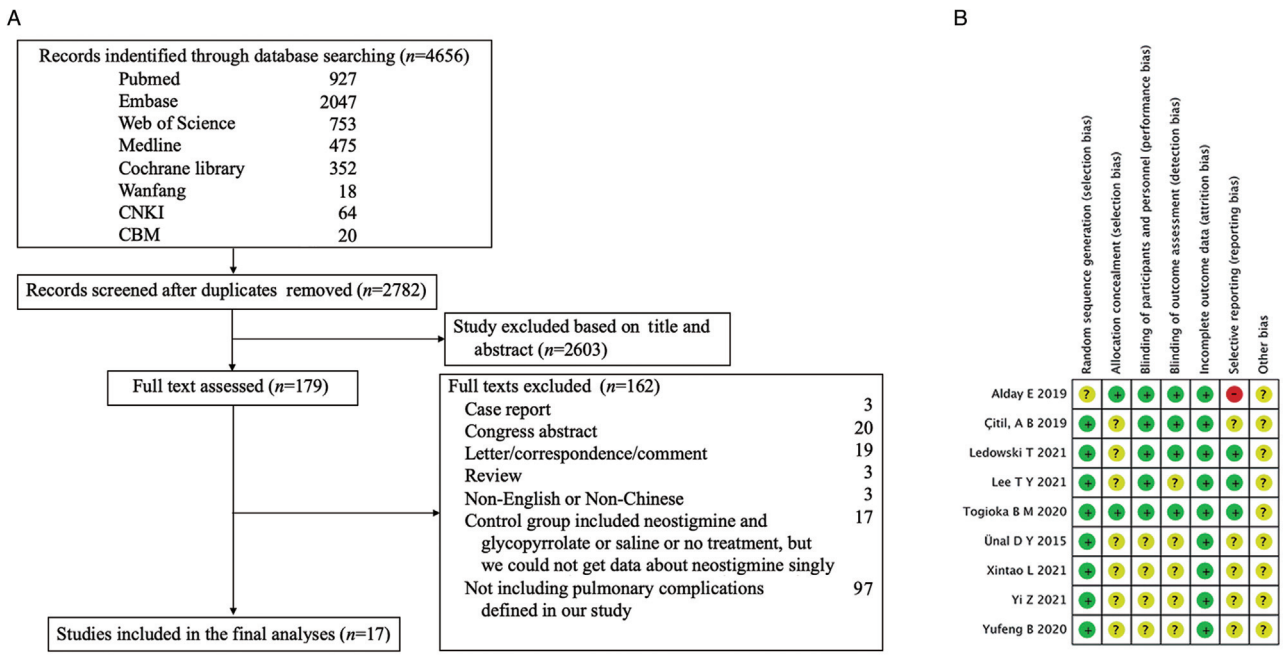

Figure 1: (A) PRISMA flow chart of study selection. (B) Risk of bias for randomized controlled studies. Green indicates low risk of bias; yellow indicates unclear risk of bias; red indicates high risk of bias. PRISMA: Preferred Reporting Items for Systematic Review and Network Meta-analyses; CNKI: China National Knowledge Infrastructure; CBM: Chinese BioMedical Literature Databases.

Table 1: Characteristics of studies included comparing incidence of postoperative pulmonary complications using sugammadex and neostigmine.

Studies	Sample size	Age, years	Study design	Surgery type	Ventilation parameters	Dose of sugammadex	Dose of neostigmine
Togioka *et al*[23]	200	Sugammadex 74.8 ± 4.3, neostigmine 75.1 ± 4.0	RCT	Surgeries with duration ≥ 3 h	Not reported	2 mg/kg	0.07 mg/kg
Ünal *et al*[24]	74	Sugammadex 44.81 ± 9.7, neostigmine 46.62 ± 11.3	RCT	Operation for obstructive sleep apnea	Controlled positive-pressure ventilation with $EtCO_2$ value of 30–36 mmHg	2 mg/kg	0.04 mg/kg
Çitil *et al*[25]	60	Sugammadex 51.0 ± 10.2, neostigmine 52.0 ± 9.6	RCT	Elective pulmonary resection	One-lung ventilation and maintained $EtCO_2$ between 30 mmHg and 35 mmHg.	2 mg/kg	0.05 mg/kg
Lee *et al*[27]	93	Sugammadex 63.8 ± 9.7, neostigmine 65.5 ± 8.6	RCT	Video-assisted thoracoscopic lobectomy	One-lung ventilation, low tidal volume (4–6 mL/kg), positive end-expiratory pressure, and lung recruitment	2 mg/kg	0.05 mg/kg
Alday *et al*[26]	126	Sugammadex 65.9 ± 12.0, neostigmine 69.9 ± 13.0	RCT	Major abdominal surgery (liver resection, pancreatectomy, gastrectomy, or any type of colectomy)	VT (mL/kg): sugammadex 8.1 ± 1.2, neostigmine 8.1 ± 1.2; F_iO_2 (mmHg): sugammadex 0.5 ± 0.9, neostigmine 0.5 ± 0.7; Alveolar recruitment: sugammadex 15 (23.4) neostigmine 27 (43.6)	4 mg/kg	40 μg/kg
Ledowski *et al*[28]	168	Sugammadex 63.8 ± 9.7, neostigmine 65.5 ± 8.6	RCT	Selective and non-cardiothoracic surgery	Not reported	2 mg/kg	0.05 mg/kg
Xintao *et al*[29]	96	Sugammadex 61.1 ± 3.4, neostigmine 62.1 ± 3.9	RCT	Thoracoscopic-laparoscopic radical esophagectomy	VT 6–8 mL/kg; f 12–16/min; I: E 1: 2; FiO_2 60%; maintained PCO_2 35–45 mmHg	2 mg/kg	0.05 mg/kg
Yufeng *et al*[30]	100	Sugammadex 51 ± 8, neostigmine 49 ± 6	RCT	Radical resection of lung cancer under thoracoscope	One-lung ventilation	2 mg/kg	2 mg
Yi *et al*[31]	60	Sugammadex 72 ± 4, neostigmine 72 ± 4	RCT	Laparoscopic radical gastrectomy	VT 6–8 mL/kg; f 12–16/min; $ETCO_2$ 35–45 mmHg	2 mg/kg	0.03 mg/kg
Kirmeier *et al*[3]	8795	55 ± 17	Prospective cohort study	Except cardiac surgery	Not reported	Not reported	Not reported
Martinez-Ubieto *et al*[32]	179	60.85 ± 16.19	Prospective study of cohorts	Except emergency surgery	Volume-controlled ventilation	2–4 mg/kg	0.03–0.05 mg/kg
Kheterpal *et al*[2]	45,712	Sugammadex 56 [47, 68], neostigmine 59 [46, 70]	Retrospective cohort study	Except outpatient procedure; emergency, cardiac, liver, or lung transplantation surgery	Median ventilator driving pressure (cm H_2O), median (interquartile range): sugammadex 15 [12.0, 19.0], neostigmine 15 [12.0, 19.0]	Not reported	Not reported
Ledowski *et al*[33]	90	53 ± 20	Retrospective cohort study	Orthopedic, general plastic and ear nose and throat surgical cases, and other surgical specialties	Not reported	100–400 mg	1.25–5 mg
Ezri *et al*[34]	179	Sugammadex 42 ± 12, neostigmine 42 ± 12	Retrospective cohort study	Laparoscopic sleeve gastrectomy	Not mentioned? reported	1.5–2.0 mg/kg	2.5 mg
Han *et al*[35]	1232	Sugammadex 63.5 ± 11.7, neostigmine 62.9 ± 11.6	Retrospective cohort study	Laparoscopic gastrectomy	Positive end-expiratory pressure (cm H_2O): sugammadex 261 (42.4), neostigmine 250 (40.6); Peak inspiratory pressure (mmHg): sugammadex 18 ± 3.6, neostigmine 18 ± 3.3	2 or 4 mg/kg	20–50 μg/kg
Li *et al*[36]	10,491	Sugammadex 51 ± 17, neostigmine 52 ± 16	Retrospective cohort study	Except transplantation surgeries and surgeries from complications of another diagnostic or surgical procedure within the previous 30 days	Intraoperative tidal volume (mL/kg): sugammadex 7.5 (6.8–8.3), neostigmine 8.3 (7.4–9.4)	Not reported	Not reported
Yu *et al*[37]	474	Sugammadex 66.0 ± 6.7, neostigmine 65.7 ± 7.5	Retrospective cohort study	Robot-assisted laparoscopic prostatectomy	Oxygen concentration: 50%; tidal volume: 6–8 mL/kg; maximum peak airway pressure: no more than 30 cmH_2O; $EtCO_2$: 30–40 mmHg; positive end-expiratory pressure and recruitment maneuvers not performed	Not reported	Not reported

Data are presented as n (%), mean ± standard deviation or median (interquartile range). $EtCO_2$: End tidal carbon dioxide; f: frequency; F_iO_2: Fraction of inspiration O_2; ICU: Intensive care unit; I:E: Inspiratory/expiratory ratio; PACU: Postanesthesia care unit; PCO_2: Partial pressure of CO_2; RCT: Randomized control trial; VT: ventilation volume.

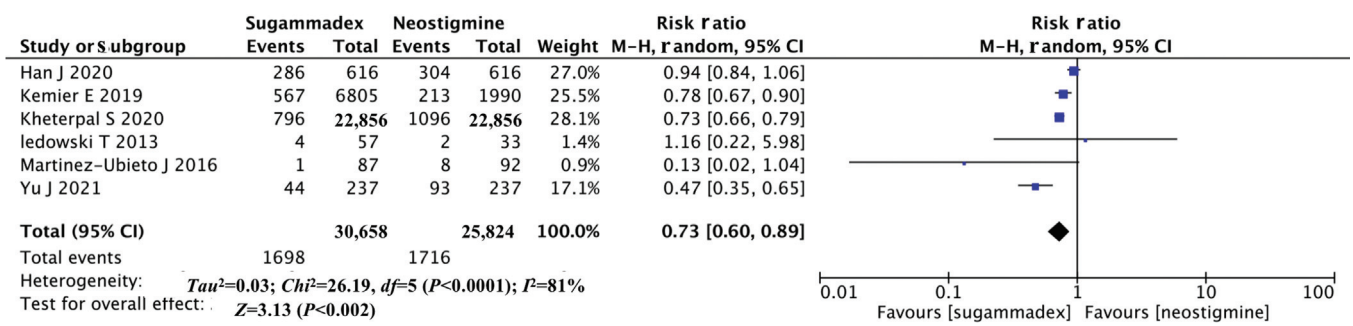

Figure 2: Forest plot of the compound postoperative pulmonary complications. CI: Confidence interval; M-H:Mantel-Haenszel; RCTs: Randomized controlled trials.

Pneumonia

With regard to pneumonia, we included seven RCTs consisting of 817 patients.[23-29] Among them, three studies showed a lower incidence of pneumonia in the sugammadex group than that in the neostigmine group;[27-29] one RCT showed an equal incidence of respiratory infection in two groups;[25] two RCTs found a higher incidence of pneumonia in the sugammadex group than the neostigmine group;[23,26] and one RCT did not found pneumonia occurred in both groups.[24] However, none of the RCTs showed identified significant differences. Pooled data showed no difference between sugammadex and neostigmine (RR: 0.58; 95%CI: 0.24–1.40; $I^2 = 0\%$) [Figure 3]. The risk for publication bias was low (Egger's test; $P = 0.610$). The overall GRADE quality of evidence was rated as moderate due to the serious risk of bias [Supplementary Table 3, http://links.lww.com/CM9/B167].

We also included five cohort studies consisting of 58,088 patients.[2,34-37] Among them, two studies showed that sugammadex significantly reduced postoperative pneumonia.[2,35] Furthermore, two studies showed a numerically lower incidence of pneumonia in sugammadex and one showed a numerically higher incidence of postoperative pneumonia in sugammadex without statistical significance. Pooled data showed a lower incidence of postoperative penumonia in the sugammadex than that in the neostigmine group (RR: 0.64; 95% CI: 0.48–0.86; $I^2 = 42\%$) [Figure 3]. The risk for publication bias was low (Egger's test; $P = 0.609$). The overall GRADE of evidence was rated as very low because of the serious risk of bias [Supplementary Table 3, http://links.lww.com/CM9/B167].

Respiratory failure

We included only one RCT consisting of 100 patients and no respiratory failure occurred in either the sugammadex or the neostigmine group.[30] A total of three cohort studies consisting of 47,418 patients were included.[2,35,37] Two studies showed the sugammadex group had a significantly lower incidence of respiratory failure than the neostigmine group,[2,37] while one study reported an equal incidence of respiratory failure in the two groups.[35] Meta-analysis showed that the incidence of respiratory failure was significantly lower in the sugammadex group compared with the neostigmine group (RR: 0.48, 95% CI: 0.41–0.56, $I^2 = 0\%$) [Figure 3]. The risk for publication bias was low (Egger's test; $P = 0.331$). The overall GRADE quality of evidence was rated as low [Supplementary Table 3, http://links.lww.com/CM9/B167].

Atelectasis

Six RCTs consisting of 640 patients were included,[23-27,29] among which, four RCTs showed a numerically lower incidence of atelectasis in the sugammadex than the neostigmine group without statistical significance;[23,26,27,29] one did not found atelectasis occurred in both groups;[24] one showed an equal incidence of atelectasis in both groups.[25] Pooled data showed sugammadex did not lower the incidence of postoperative atelectasis than neostigmine (RR: 0.85; 95% CI: 0.69–1.05; $I^2 = 0\%$) [Figure 3]. The risk for publication bias was low (Egger's test; $P = 0.205$) and the overall GRADE quality of evidence was rated as moderate due to the serious risk of bias [Supplementary Table 3, http://links.lww.com/CM9/B167].

We included two cohort studies consisting of 1411 patients.[34,35] One study showed lower incidence in the sugammadex group,[34] while another study showed higher incidence in the sugammadex group.[35] However, both studies did not find statistical significance. Pooled data did not show the difference in the incidence of atelectasis between the two groups (RR: 1.01; 95% CI: 0.87–1.18; $I^2 = 0\%$) [Figure 3]. The overall GRADE quality of evidence was rated as very low because of the serious risk of bias [Supplementary Table 3, http://links.lww.com/CM9/B167].

Additional analyses

We performed subgroup analyses for the primary outcome based on patients' average age due to the high heterogeneity [Supplementary Figure 1, http://links.lww.com/CM9/B167]. In patients with age ≥60 years, there is no significant difference between the two groups (RR: 0.58; 95% CI: 0.29–1.16; $I^2 = 90\%$). As for patients younger than 60 years old, the sugammadex group had a lower incidence of the compound pulmonary complication than the neostigmine group (RR: 0.74; 95% CI: 0.69–0.80; $I^2 = 0\%$). Because only one study was included in one of the subgroups divided by gender and the doses of the sugammadex in the included studies varied to a large extent, we did not perform a subgroup analysis of the

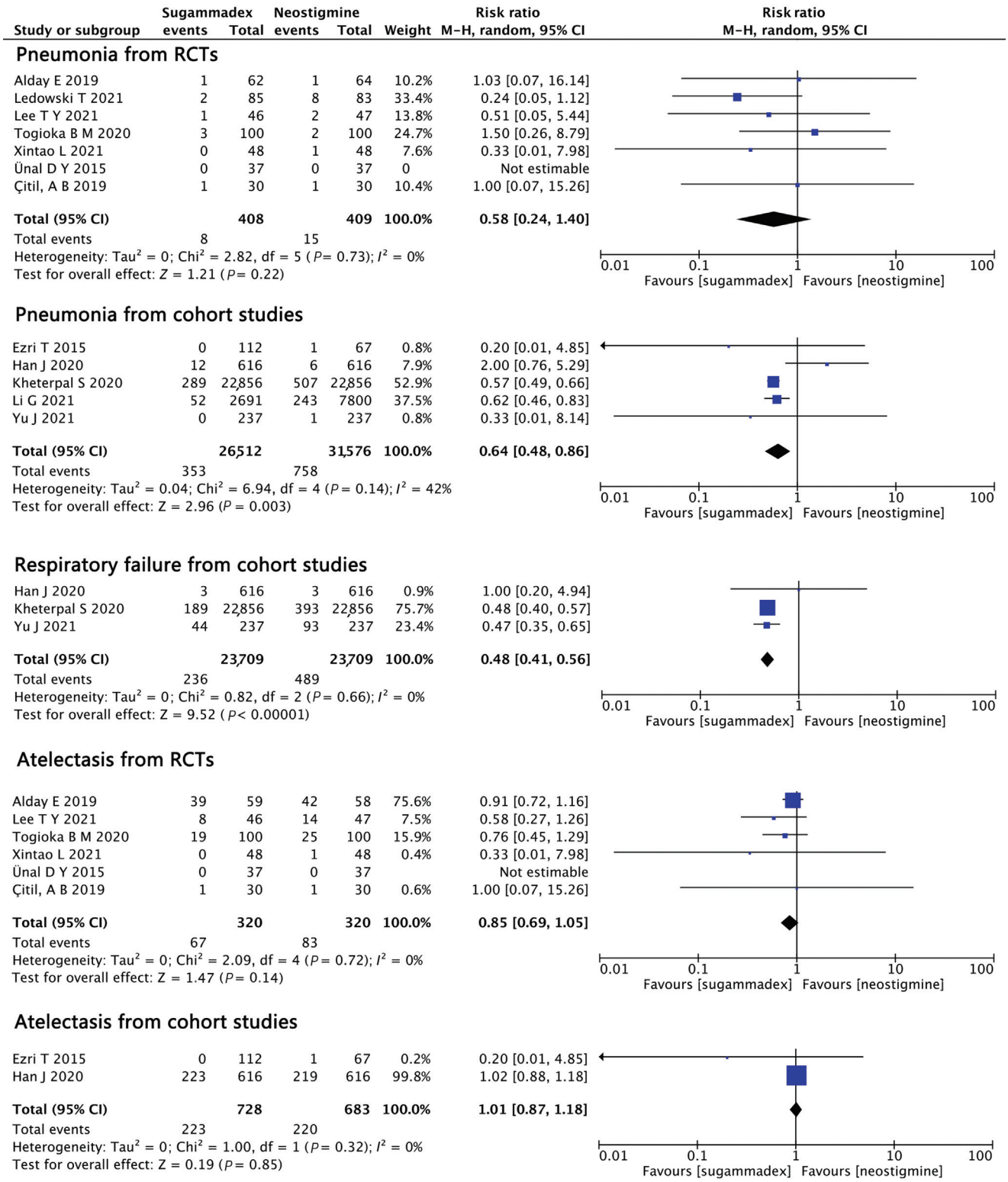

Figure 3: Forest plot of the specific postoperative pulmonary complications. CI: Confidence interval.

primary outcomes based on gender and the treatment regimen. Because the included trials were less than ten, we did not perform meta-regression. Our result of the primary outcome was robust to sensitivity analysis [Supplementary Table 4, http://links.lww.com/CM9/B167].

Discussion

Overall, nine RCTs and eight cohort studies were included for meta-analysis. Pooled data from cohort studies demonstrated that sugammadex as a reversal agent could decrease the incidence of compound pulmonary complication,

pneumonia, and respiratory failure than neostigmine, but it had no benefit in suppressing the occurrence of atelectasis. Only one RCT compared the compound pulmonary complication between sugammadex and neostigmine but had multiple unclear biases. Pooled data from RCTs did not show the superiority of sugammadex in decreasing the incidence of pneumonia, respiratory failure, and atelectasis.

Nearly 40% of patients who receive NMB agents have residual postoperative neuromuscular blockade after being transferred to the postanesthesia care unit.[38] Residual neuromuscular paralysis impairs the diaphragm as well as chest wall strength and reduces the patient's ability to cough and clear secretions, which leads to alveolar collapse, microaspiration, and other pulmonary complications.[39] Furthermore, reversal with sugammadex results in less sputum production.[40] The advantage of sugammadex is more than shortening neuromuscular recovery duration regardless of the degree of the blockade. Both neuromuscular monitoring and clinical signs show residual postoperative curarization happens less frequently with sugammadex than neostigmine,[32,33,9] which indicates sugammadex can reduce postoperative pulmonary complications than neostigmine. The meta-analysis by Abad-Gurumeta *et al*[41] confirmed sugammadex can decrease the incidence of clinical signs of postoperative residual paralysis than neostigmine. The meta-analysis by Hristovska *et al*[9] showed sugammadex can lower the incidence of postoperative desaturation than neostigmine with only two studies included. Our meta-analysis further showed the potential advance of sugammadex in decreasing the compound pulmonary complication.

However, only one RCT was included for the primary outcome, and pooled data derived from RCTs and cohort studies indicated different results for secondary outcomes. Although some cohort studies performed statistical methodologies to adjust for known confounders, perioperative data elements, such as lung-protective ventilation, the use of muscle relaxant monitoring, and fluid management were not measured, and their impact on postoperative pulmonary complications was not assessed. The cohort studies usually include patients from several years ago, but sugammadex was only commonly used in recent years. Therefore, the improvement of perioperative management over time, including the management of ventilation and fluid, may aggregate the pulmonary protective function of sugammadex.[36] Only one RCT reported the comparison of the compound pulmonary complication and obtained the result favoring sugammadex.[31] However, this study included only 60 patients and had multiple unclear biases. The pooled data from RCTs did not show a significant difference in specific pulmonary complications between sugammadex and neostigmine. The overall incidences of the compound pulmonary complication, pneumonia, and respiratory failure were quite low, so most RCTs did not select pulmonary complications as primary outcomes. Therefore, their sample size was calculated according to other outcomes and was inadequate for detecting the difference between sugammadex and neostigmine.

In addition, the primary outcome derived from cohort studies has high heterogeneity with I^2 higher than 75%. After performing the subgroup analysis based on age, heterogeneity decreased in the subgroup of patients with an average age of <60 years ($I^2 = 0\%$), but it remained in those no younger than 60 years old ($I^2 = 88\%$). Studies in the latter subgroup derived from different surgery types, ventilation strategies, gender ratio, treatment regime of sugammadex, and preoperative pulmonary conditions. This implied patients' age may be the source of heterogeneity but not the only one. Due to the limited studies, we did not perform subgroup analysis based on gender and the treatment regime of sugammadex.

Undoubtedly, sugammadex outperformed neostigmine in lowering the risk of postoperative residual neuromuscular blockade, which has been confirmed by many well-designed RCTs and systematic review.[6,9,42] Longer-term outcomes of residual neuromuscular blockade, such as postoperative pulmonary complications, have a greater impact on the clinical choice of NMB reversal. Although pooled data from cohort studies showed the superiority of sugammadex in the compound pulmonary complication, pneumonia, and respiratory failure, the results should be carefully interpreted due to not absolutely controlled confounding factors. At present, RCTs that reported the incidence of pulmonary complications were small in the sample size. Due to the low incidence of pulmonary complications, the sample size was not large enough to detect the benefit of sugammadex on pulmonary protection. Therefore, neither the cohort studies nor RCTs can offer definitive instruction in choosing NMB reversals to reduce postoperative pulmonary complications. Considering this low incidence of pulmonary complications in normal patients, further RCTs with a larger-scale need to be performed on patients with high risk to offer a convincing answer.

There are several limitations for the current study. First, only one RCT was included for the primary outcome. The compound pulmonary complication is a comprehensive outcome, which is more reliable for postoperative pulmonary complications than specific outcomes. Due to the low incidence of pulmonary complications, most RCTs did not select them as primary outcomes. Moreover, the composite outcome was not obtained by directly adding up all the incidence of specific pulmonary complications if not reported and we included studies according to the definition strictly. These factors limited literature inclusion. Second, this primary outcome had significant but unexplained heterogeneity. Pre-planned subgroup analyses based on age had limited success in explaining heterogeneity. Meta-regression and subgroup analyses according to gender and treatment regime of sugammadex could not be performed due to the limited number of studies. Third, the evaluation of pulmonary complications was not performed on a fixed day. Over time, early mobilization and chest physiotherapy may affect pulmonary events and residual paralysis.[43] Fourth, sugammadex dosing in included studies ranged from 1.5 to 4.0 mg/kg, and the use of NMB monitoring was insufficient. In the absence of NMB monitoring, it may be ineffective to exclude residual neuromuscular blockade.[44]

In conclusion, our systematic review provided very low-quality evidence that sugammadex had an advantage in reducing the compound pulmonary complication over

neostigmine. Due to the absence of absolutely controlled confounders in cohort studies and RCTs with small scales, limited evidence suggests an advantage of sugammadex over neostigmine in reducing pneumonia, respiratory failure, and atelectasis. Therefore, well-designed RCTs with larger scales performed in patients with higher risk are needed.

Funding

This study was supported by grants from the Sichuan Science and Technology Program (Nos. 2020YFS0188 and 2020YJ0283).

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How to cite this article: Liu H, Luo R, Cao S, Zheng B, Ye L, Zhang W. Superiority of sugammadex in preventing postoperative pulmonary complications. Chin Med J 2023;136:1551–1559. doi: 10.1097/CM9.0000000000002381