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Respiration and the Airway

Reversal of residual neuromuscular block with neostigmine or sugammadex and postoperative pulmonary complications: a prospective, randomised, double-blind trial in high-risk older patients

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Abstract

Background: Residual neuromuscular block is associated with an increased risk of postoperative pulmonary complications in retrospective studies. The aim of our study was to investigate prospectively the incidence of postoperative pulmonary complications after reversal with either sugammadex (SUG) or neostigmine (NEO) in high-risk older patients.
Methods: We randomly allocated 180 older patients with significant morbidity (ASA physical status 3) ≥75 yr old to reversal of rocuronium with either SUG or NEO. Adverse events in the recovery room and pulmonary complications (defined by a 5-point [0–4; 0=best to 4=worst] outcome score) on postoperative Days 1, 3, and 7 were compared between groups.
Results: Data from 168 patients aged 80 (4) yr were analysed; SUG *vs* NEO resulted in a reduced probability (0.052 *vs* 0.122) of increased pulmonary outcome score (impaired outcome) on postoperative Day 7, but not on Days 1 and 3. More patients in the NEO group were diagnosed with radiographically confirmed pneumonia (9.6% *vs* 2.4%; P=0.046). The NEO group showed a non-significant trend towards longer hospital length of stay across all individual centres (combined 9 *vs* 7.5 days), with a significant difference in Malaysia (6 *vs* 4 days; P=0.011).
Conclusions: Reversal of rocuronium neuromuscular block with SUG resulted in a small, but possibly clinically relevant improvement in pulmonary outcome in a select cohort of high-risk older patients.
Clinical trial registration: ACTRN12614000108617.

Keywords: neostigmine; neuromuscular block; perioperative complications; postoperative pulmonary complications; reversal; sugammadex

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Editor's key points

- Previous retrospective studies have shown an association between residual neuromuscular block with an increased risk of postoperative pulmonary complications.
- This prospective study investigated the incidence of postoperative pulmonary complications after reversal with either sugammadex or neostigmine in high-risk older patients.
- Reversal of rocuronium neuromuscular block with sugammadex resulted in a lower incidence of postoperative pneumonia in a select cohort of high-risk older patients.

Neuromuscular blocking agents (NMBAs) were introduced into clinical anaesthesiology in the form of intocostrin (curare) in 1942 by Griffith.[1] However, soon after the introduction of curare, anaesthesiologists became aware of the dangers of residual curarisation, or residual neuromuscular block.[2] Although the implementation of the pharmacological reversal of residual neuromuscular block with cholinesterase inhibitors such as neostigmine (NEO) in the 1950s was a major step towards the avoidance of residual neuromuscular block,[3] the incidence of the condition has remained unacceptably high (~40%).[4] Even mild residual neuromuscular block is well known to affect respiratory function and the ability to swallow and maintain a patent airway,[5] particularly in older patients.[6] Consequently, higher rates of postoperative pneumonia, aspiration, and atelectasis have been ascribed to residual neuromuscular block.[7,8] Although residual neuromuscular block after NEO reversal has been seen as the gold standard after relaxant general anaesthesia, evidence has emerged showing that under certain circumstances, acetylcholinesterase inhibitors can themselves impair neuromuscular function.[9]

Since its launch in 2008, sugammadex (SUG) has been shown to reverse NMBAs more quickly and reliably compared with NEO.[10] Sonographic and electromyography-based assessment of diaphragmatic and intercostal muscular recovery from residual neuromuscular block is more pronounced after administration of SUG *vs* NEO.[11,12] Several retrospective and prospective observational investigations have reported lower rates of residual neuromuscular block and respiratory complications after reversal with SUG *vs* NEO.[13–17] Recently, Kheterpal and colleagues[17] showed a 47% reduced rate of postoperative pneumonia after reversal with SUG *vs* NEO in a retrospective cohort of 45 712 patients. A randomised prospective investigation involving 200 subjects receiving either SUG or NEO found no differences in pulmonary outcome between the groups of older patients.[18] However, this study included a large proportion of reasonably healthy subjects.

We examined the effects of reversal of residual neuromuscular block with SUG *vs* NEO on postoperative pulmonary complications in a prospective, blinded, and randomised study design involving higher-risk older patients with ASA physical status 3–4. The hypothesis was that reversal with SUG in this cohort of high-risk patients results in a lower incidence of postoperative pulmonary complications within 7 postoperative days.

Methods

The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12614000108617) and approved by the institutional review boards of all participating study centres (Asan Medical Center, Seoul, Republic of South Korea on April 1, 2014; University of Malaya, Kuala Lumpur, Malaysia on May 15, 2014; University of Western Australia [UWA], Crawley, Australia on May 16, 2015; University Debrecen, Debrecen, Hungary on October 15, 2015; and Martini General Hospital, Groningen, the Netherlands on May 12, 2016).

After written informed consent, 180 ASA physical status 3 or 4 patients ≥75 yr of age planned to undergo surgery under general anaesthesia with the use of NMBAs were included between May 2015 and March 2019. Exclusion criteria included emergency surgery; incapacity to consent; pre-existing chest infection, septicaemia, and severe neuromuscular disease; or patients undergoing cardiothoracic surgery. Patients were randomised to receive reversal of a rocuronium-based neuromuscular block with either SUG 2 mg kg^{-1} or NEO 0.05 mg kg^{-1} (up to a maximum dose of 5 mg) with atropine 0.015 mg kg^{-1} at the end of surgery.

Patients received general anaesthesia using either a volatile anaesthetic- or a propofol-based maintenance and opioids per the attending anaesthetists' choice. For ethical considerations, the protocol did not prescribe a specific practice regarding intraoperative neuromuscular monitoring, and all attending anaesthetists were asked to commit to whether or not they would usually apply such monitoring during surgery, and specifically after administration of the reversal agent. Patients in both groups received rocuronium 0.6 mg kg^{-1} on induction of anaesthesia and further bolus doses of 5–20 mg at the discretion of the attending anaesthetist. To achieve a comparable depth of neuromuscular block, quantitative monitoring of the train-of-four (TOF) at the adductor pollicis brevis muscle (via supramaximal stimulation of the ulnar nerve) was used by an (unblinded) attending research assistant (not involved in postoperative data collection) with the TOF kept at two twitches towards the end of surgery and at the point of reversal. At the end of surgery, and solely at the discretion of the attending anaesthetist, the research assistant administered the study drug, leaving the clinician blinded to what reversal drug had been given. Further neuromuscular monitoring (from study drug administration until tracheal extubation) was only undertaken if the attending clinician had stated that this was the standard practice, or in case of urgent clinical requirement. The point of tracheal extubation was solely defined by the attending anaesthetist. After extubation, patients were given oxygen 6 L min^{-1} via a Hudson face mask, and discharged from the operating theatre to either the PACU or ICU. Patients for whom tracheal extubation at the end of surgery was unexpectedly impossible because of clinical requirements were subsequently excluded from further data analysis (see Consolidated Standards of Reporting Trials [CONSORT] flow diagram).

Patients successfully extubated at the end of surgery were observed for acute postoperative complications, such as haemoglobin oxygen desaturation, aspiration, signs of muscle weakness, and postoperative nausea and vomiting (PONV).

Randomisation, masking, and outcomes

Randomisation was achieved via a web-based commercial randomisation service (RANDOMIZE.NET) using randomly

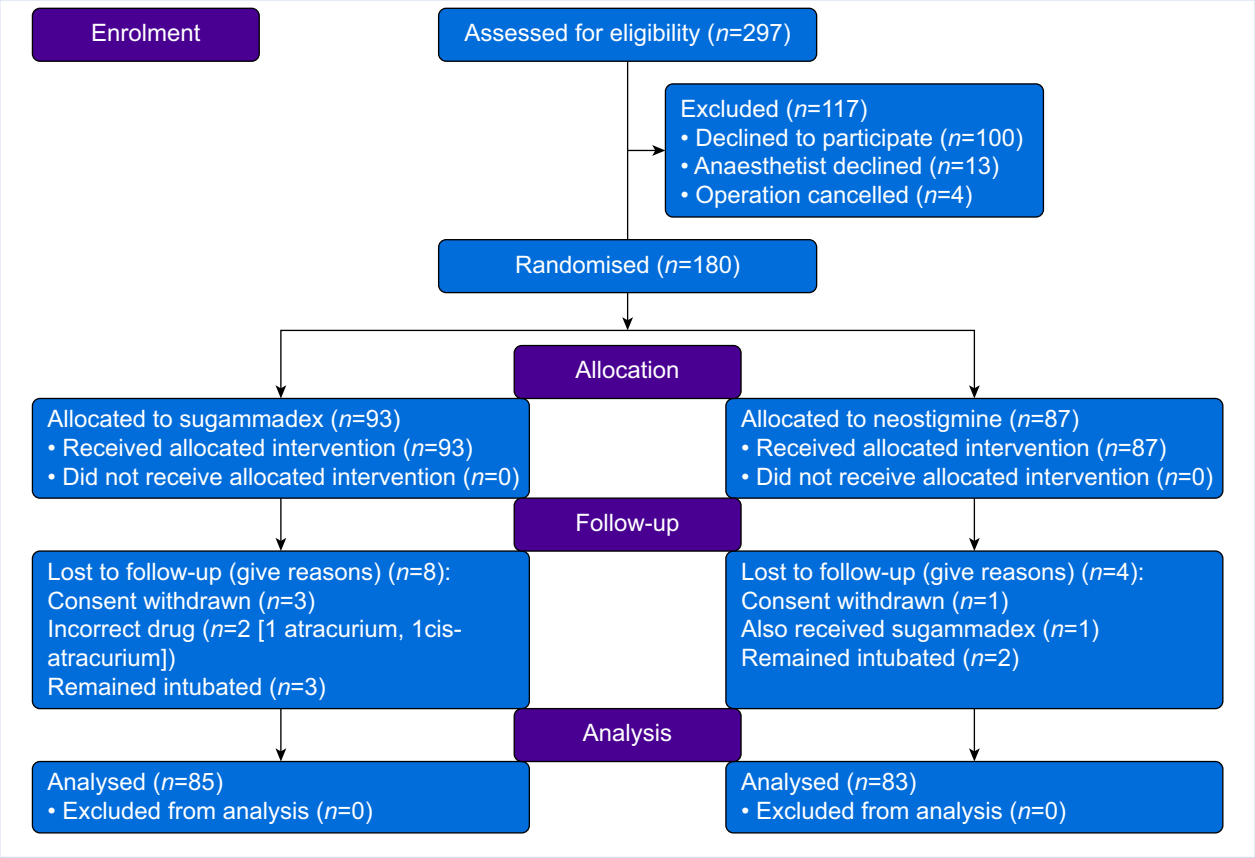

Fig 1. Consolidated Standards of Reporting Trials flow diagram.

permuted blocks (block size 4 or 6; blocking factor 2 or 3) (CONSORT flow chart; Fig. 1). The process of randomisation was performed by a research assistant who also followed the patient into the operating surgery to administer the study drug at the end of surgery, but who was not further concerned with the collection of postoperative data. The study drugs were prepared without this being witnessed by the attending anaesthetist and drawn up with normal saline to 5 ml in an unlabelled 5 ml syringe. The collection of postoperative data and reporting of chest radiographs (if such were performed) were undertaken by a research assistant and radiologist, as appropriate, who were unaware of the study allocation.

During conduct of the study but before unblinding of the treatment allocation, it emerged that six randomisations (study nos. 93, 94, 96, 156, 157, and 160) had erroneously taken place via the online randomisation website without these numbers corresponding to actually consented participants. To account for this error, the decision was made to extend the randomisation from no. 180 to no. 186.

Postoperatively, and after discharge from the PACU, subjects were observed on postoperative Days 1, 3, and 7 (if still in hospital) by a member of the research team blinded to study group allocation. At each visit, a 5-point pulmonary outcome score (details below) was obtained. Furthermore, chest radiographs or computer tomographic images within the first 7 postoperative days were studied for reports of aspiration, atelectasis, or pneumonia (all images requested by clinicians [no prescription by study protocol] and reported by specialist radiologists not related to the study team). Newly prescribed antibiotics because of clinically diagnosed or radiographically proved chest infection within 7 days after surgery were also recorded. All subjects were followed up either in writing or via telephone call to obtain 30 day mortality data.

Pulmonary outcome score

To facilitate the quantitative comparison of postoperative pulmonary complications, a 5-point (0–4; 0=best outcome; 4=worst outcome) outcome score was used. This score has been previously validated using retrospective data from 1444 patients comparing pulmonary complications after different NMBA reversal strategies (score 0/25/50/75/100% used instead of 0–4, but with same parameters used to calculate the score).[13] Scores were obtained preoperatively and on postoperative Days 1, 3, and 7, and comprised four parameters: white cell count >11 000 10^9 ml^{-1}, subjective shortness of breath, body temperature >38°C, and diagnosis of pneumonia by a clinician. The parameter 'physician diagnosis of pneumonia' was defined using the US Centers for Disease Prevention and Control definitions,[19] however, without radiographic confirmation. Clinically diagnosed pneumonia plus radiographic confirmation was logged and compared separately.

Further to recording of outcome score before surgery, patients were also evaluated with regard to known or suspected

Table 1 Subject characteristics and intraoperative parameters in subjects reversed with either sugammadex or neostigmine. SD, standard deviation.

	Sugammadex	Neostigmine	P-value
Age (yr)	75–91	75–88	0.083
BMI (kg m^{-2}), mean (SD)	26 (4)	26 (4)	0.775
Sex, *n* (%)			0.452
Male	31 (36.5)	32 (38.6)	
Female	54 (63.5)	51 (61.4)	
Pre-existing pulmonary comorbidities, *n* (%)	15 (18.1)	15 (18.3)	0.235
Type of surgery, *n* (%)			0.813
General	46 (54.1)	49 (59.0)	
Orthopaedic	24 (28.2)	21 (25.3)	
Other	15 (15.6)	13 (15.7)	
Urgency, *n* (%)			0.596
Elective	77 (90.6)	75 (90.4)	
Urgent	8 (9.4)	8 (9.6)	
Total time of surgery (min), mean (SD)	122 (67)	127 (72)	0.652
Total anaesthesia time (min), mean (SD)	167 (72)	173 (77)	0.579
Total dose of rocuronium (mg), mean (SD)	67 (79)	58 (22)	0.284
Total dose of rocuronium (mg kg^{-1} min surgery $time^{-1}$), mean (SD)	0.58 (0.33)	0.58 (0.37)	0.957
Train-of-four monitoring used, *n* (%)	42 (49)	49 (59)	0.136

risk factors for impaired pulmonary outcome (i.e. smoking, asthma, and chronic obstructive lung disease).

Statistical methods

A repeated-measures power analysis was conducted during the study design, which showed that 150 subjects randomised to two groups were required with at least three observations per subject to allow a minimum difference of 5% on a symptom scale of 0–4 with α=0.05 and power=0.87. A slightly larger sample was recruited to allow for errors in assessment of eligibility.

A planned interim analysis of the postoperative pulmonary outcome score and 30 day mortality was conducted after enrolment of 90 subjects to satisfy concerns that subjects were randomised to the potentially inferior drug NEO. This was conducted by a biostatistician not involved in data collection, and it was concluded that an observed trend towards a better outcome after SUG was not sufficiently strong to recommend early trial termination. No further interim analyses were conducted.

Description of the sample characteristics used frequency and percentage for categorical variables and mean (standard deviation [SD]) for normally distributed continuous variables, and median (inter-quartile range) for skewed continuous variables. For each subject, we determined for Days 1, 3, and 7 whether the score was higher than the preoperative score. The resulting binary variable was analysed using a mixed-effects logistic regression analysis with day interacting with treatment group as fixed effects and patient nested within centre as random effects. The Netherlands centre was removed from this specific analysis, as it had only randomised three patients, all receiving the SUG treatment. Mann–Whitney *U*-test was used to compare treatment groups for equality of length of stay.

Role of funding source

This study was funded by the UWA, Crawley, Australia. The funder provided financial compensation for the study drug SUG and patient insurance. Neither UWA nor any other than the investigators had any influence on the study design, data collection and analysis, and article preparation or submission.

Results

Data from 168 subjects (85 SUG and 83 NEO) were analysed (Fig. 1).

Subject characteristics

The majority of subjects were female (*n*=105 *vs* *n*=63 male); age, mean (SD) [range] 80 (4) [75–91] yr. All patients were ASA physical status 3. No differences between treatment groups were observed for any of the recorded subject characteristics, total dose of intraoperatively administered neuromuscular blocking drug, total anaesthesia and surgery times, or time from skin closure to PACU admission (Table 1). However, the time from study drug administration to tracheal extubation and the incidences of TOF ratio <90 or <80 were significantly lower for SUG *vs* NEO (Table 2).

Acute postoperative complications

No differences were found between the treatment groups with regard to any of the investigated acute complications observed in the PACU: desaturation (peripheral oxygen saturation <95%, <90%, and <85%), feeling weak, diplopia, difficulty swallowing, PONV, airway obstruction, unplanned tracheal re-intubation or ICU admission, bradycardia, or tachycardia (Table 3).

Pulmonary outcome

The postoperative pulmonary outcome score between the two groups showed no significant difference at baseline or on postoperative Days 1, 3, and 7. However, the distribution of outcome scores on the postoperative days showed that in group NEO, more patients still showed higher scores than in group SUG, with all subjects scoring 3 or 4 found in the NEO group on postoperative Days 3 and 7 (Fig. 2).

Table 2 Train-of-four recovery characteristics after sugammadex or neostigmine reversal. Train-of-four was only measured at the time of tracheal extubation in a total of 38 subjects (sugammadex) and 45 (neostigmine), respectively. SD, standard deviation.

	Sugammadex	Neostigmine	P-value
Time reversal to tracheal extubation (min), mean (SD)	8.7 (5.4)	11.1 (6.7)	0.009
Train-of-four ratio at time of tracheal extubation, mean (SD)	90.9 (17.9)	87.2 (14.8)	0.299
Incidence of train-of-four ratio >90%, *n* (%)	36 (86)	29 (60)	0.007
Incidence of train-of-four ratio >80%, *n* (%)	34 (90)	32 (71)	0.035

A generalised mixed-model logistic regression analysis examining the probability of subjects in the two groups for having higher pulmonary outcome scores on postoperative Days 1, 3, and 7 (*vs* preoperative baseline) showed ~50% lower probability for patients in the SUG *vs* NEO group on Day 7. However, these results did not reach statistical significance (Fig. 3).

Corresponding to the observed trend in improved pulmonary outcomes in SUG, this group also showed a significant difference in radiographically diagnosed cases of pneumonia within 7 postoperative days: SUG two cases (2.4%) *vs* NEO eight cases (9.6%); $P=0.046$. Thus, 80% of all confirmed cases of pneumonia were observed after reversal with NEO.

Length of hospital stay

Although a trend towards a shorter LOS in SUG (combined median of 7.5 [5–10] *vs* NEO 9 [6–13] days) was observed across all centres, this effect was only significant in Malaysia (Malaysia SUG 4 [2–6] *vs* NEO 6 [4–9], $P=0.011$; South Korea SUG 8 [6–10] *vs* NEO 8 [6–13], not significant; Hungary SUG 13 [10–18] *vs* NEO 14 [10–16] days, not significant).

Thirty-day mortality

No difference in 30 day postoperative mortality was found between groups.

Table 3 Acute events in the PACU after reversal with either sugammadex or neostigmine. No significant differences were detected for any of the parameters (χ^2 test). PONV, postoperative nausea and vomiting.

	Sugammadex, *n* (%)	Neostigmine, *n* (%)	P-value
SpO_2 <95%	9 (11)	9 (11)	0.577
SpO_2 <90%	3 (4)	2 (2)	0.511
SpO_2 <85%	1 (1)	0 (0)	0.506
Diplopia	0 (0)	3 (4)	0.118
Difficulty swallowing	7 (8)	5 (6)	0.400
Feeling weak	27 (32)	30 (36)	0.331
Shortness of breath	4 (5)	4 (5)	0.627
Airway obstruction	1 (1)	0 (0)	0.506
Tracheal re-intubation	0 (0)	0 (0)	—
Unexpected ICU admission	2 (2)	0 (0)	0.254
PONV	10 (12)	12 (14)	0.387
Severe PONV	6 (7)	8 (10)	0.252
Aspiration	0 (0)	1 (1)	0.494
Tachycardia/bradycardia	7 (8)	13 (16)	0.111

Data availability

All de-identified data are available from the corresponding author upon reasonable request, at the sole discretion of the corresponding author.

Discussion

In this first prospective randomised controlled study investigating pulmonary outcomes after reversal of neuromuscular block with either NEO or SUG in a cohort of high-risk older patients, we report a significantly lower rate of postoperative pneumonia. The not statistically significant reduced probability for having a worse pulmonary outcome score compared with preoperative baseline in SUG-reversed patients suggests that a follow-up study with greater power is necessary. A similar reduction of the risk for postoperative pulmonary complication in older patients was observed in a retrospective investigation in 1440 patients,[13] and in more recent retrospective studies.[16,17]

However, a study by Togioka and colleagues[18] that investigated 200 older patients after longer procedures found no differences in postoperative pulmonary complications between SUG and NEO. One reason for their findings may be the fact that the authors included predominantly healthy patients (ASA physical status 2) and that their length of hospital stay was relatively short. The choice of a relatively healthy cohort may have resulted in a study under-powered to detect differences between the reversal methods. The relatively short hospital length of stay (mean ~4 days) may have further contributed to the lack of differences found during the patients' stay in hospital. Interestingly, the same study reported a three-fold increase in hospital readmission within 30 postoperative days in the NEO group.[18] However, the study did not indicate the reasons for readmission.

The mechanism by which SUG may contribute to a reduction in postoperative pulmonary complication has not yet been definitively proved. However, it appears that residual neuromuscular block contributes to a significant risk of complications, such as atelectasis, aspiration, and pneumonia.[20] Initial postoperative hypoventilation may result in atelectasis. Especially in high-risk older patients, this condition may not spontaneously resolve and could facilitate subsequent pneumonia. In older patients, even a small degree of residual neuromuscular block can significantly impair pharyngeal muscle function, resulting in unsuccessful swallowing, and thus an increased risk of postoperative (micro-)aspiration.[21]

Although the outcome benefit for SUG covered the entire period of 7 postoperative days, we observed a higher risk for impaired pulmonary outcomes in NEO towards the end of the observation period (Day 7). This adds credibility for the hypothesis of an 'initial hit' and subsequent development of

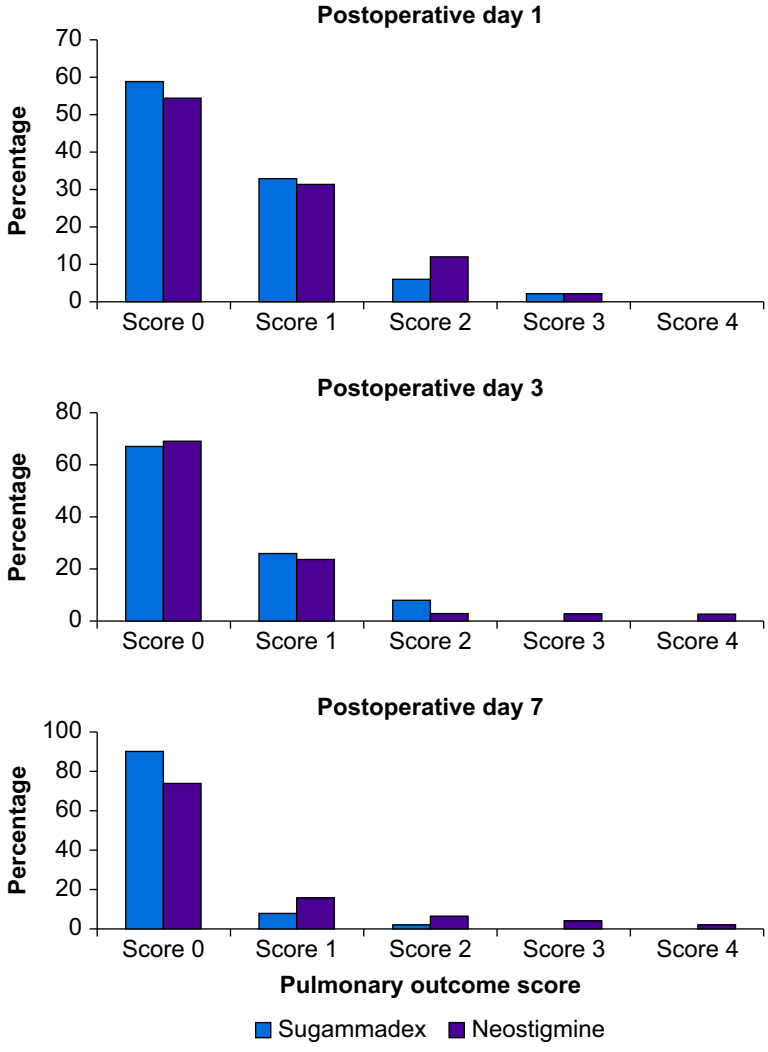

Fig 2. Percentage of subjects in both treatment arms with 0–4 points for the pulmonary outcome score (4=worst outcome) on postoperative Days 1, 3, and 7.

pneumonia. Such an initial hit may have been microaspirations and atelectasis in a specifically vulnerable cohort of patients. Although Alday and colleagues[22] did not find significant differences in postoperative lung function between patients reversed with SUG *vs* NEO, they did not selectively target high-risk older patients, and their results may hence be less valid in such populations. Furthermore, their study compared results within hours after surgery, not over several days.

The risk of radiographically confirmed pneumonia was found to be significantly greater in the NEO group. Retrospectively investigating hospital readmission rates after reversal with SUG or NEO in 1479 patients after major abdominal surgery, Oh and colleagues[23] found that SUG-reversed patients had a 68% lower readmission rate and a 20% reduction of hospital length of stay. Fever and respiratory tract infections were amongst the most prominent reasons for hospital readmission, adding further plausibility to the hypothesis of residual neuromuscular block-associated longer-term pulmonary complications. However, the Post-operative Pulmonary Complications After Use of Muscle Relaxants in Europe (POPULAR) study, a prospective snapshot audit investigating European practice in neuromuscular monitoring, reversal, and postoperative pulmonary complications in 22 803 patients, reported no differences in outcomes when comparing patients reversed with SUG or NEO.[24] There was no evidence for improved outcome when neuromuscular monitoring was used, which is in stark contrast to the general assumption that monitoring does improve patient safety by reducing the rate of residual neuromuscular block. However, in a sub-study of POPULAR, the investigators found a significantly lower risk for postoperative pulmonary complications with greater neuromuscular recovery (TOF ratio >95% *vs* TOF ratio >90%). They also acknowledged that higher doses of SUG were more often associated with TOF ratio >95% and that relative under-dosing of SUG may have explained the lack of positive effects for SUG-based reversal reported in the original POPULAR study.[25]

Our study has some limitations. Firstly, the sample size was calculated based on any detectable change in

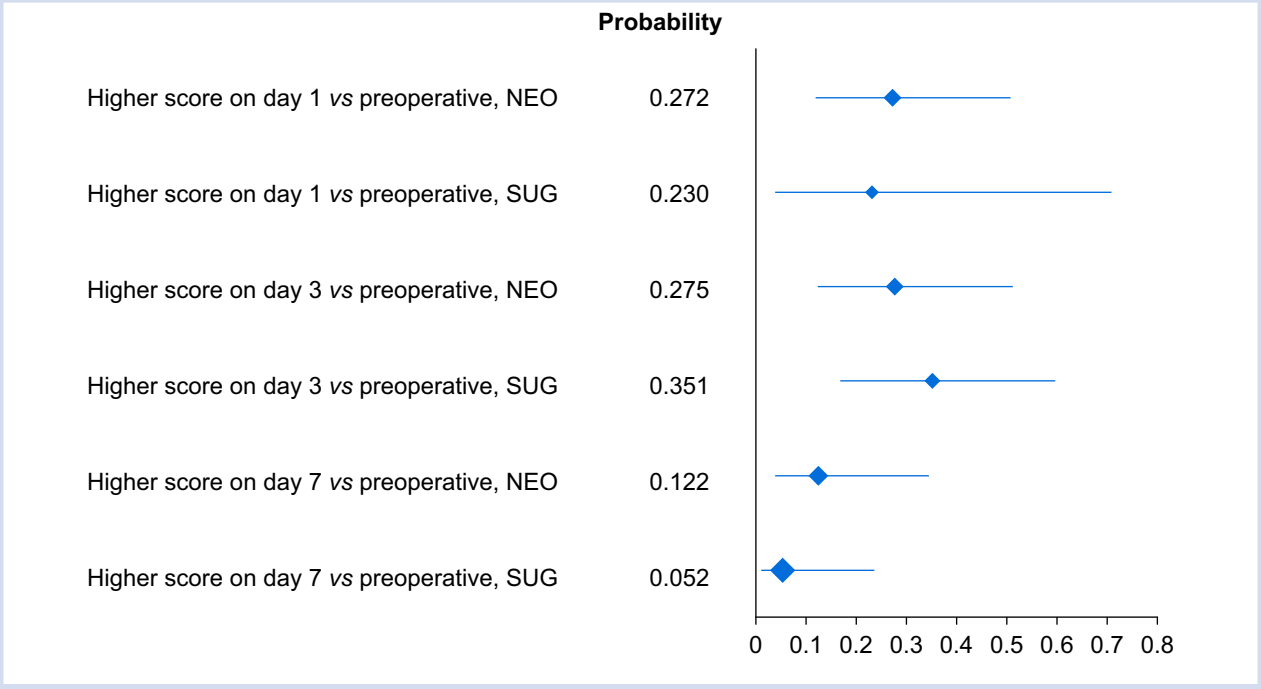

Fig 3. Forest plot for the probability of subjects in each group on each of postoperative Days 1, 3, and 7 to show higher pulmonary outcome scores (worsened outcome) compared with preoperative baseline values. Differences between groups were not statistically significant. NEO, neostigmine; SUG, sugammadex.

postoperative pulmonary outcome measured by a 5-point outcome score, allowing it to be relatively small. Although this facilitated study conduct, it hindered our ability to draw conclusions about several important findings. With the event rate of postoperative pulmonary complications being relatively low and the number of controlled factors high, a study providing a definite answer to the benefits of SUG *vs* NEO would, if all patients rather than a select high-risk cohort were included, require in excess of 10 000 subjects to be recruited, and would make such a study one of the most expensive of all time.[26] Hence, Leslie[26] suggested smaller 'real-life' trials as the most feasible option to investigate the matter. Although our study may well fit into this category, it is certainly not to be viewed as a definite trial, and a larger trial confirming or refuting our findings appears warranted.

A second limitation may be the lack of a specific intraoperative ventilation protocol. Lung-protective ventilation strategies are known to influence the rate of postoperative complications.[27] However, all participating trial centres used lung-protective ventilation strategies with low-to-modest tidal volumes, positive end-expiratory airway pressure of at least 5 cm H_2O, and pressure-controlled ventilation.

Lastly, we decided to utilise a previously described[13] pulmonary outcome score as primary outcome parameter. Although the components of this score largely match the consensus factors for comparisons of postoperative pulmonary complications,[19] it is not identical to the suggested comparators. The problem of different outcome measures has recently been highlighted by Bartels and Hunter.[28] We utilised a validated score to quantify postoperative pulmonary outcome. As the protocol for the study was designed well before the consensus paper on pulmonary outcomes was published, there was little chance to implement it *post hoc*. Although this may limit direct comparisons with other studies, we believe that our results still justify the conclusion. However, to allow close comparisons between studies, we strongly recommend using the definitions of postoperative pulmonary complications and pneumonia described by Abbott and colleagues.[19]

Conclusions

In this prospective, randomised, blinded investigation of 168 ASA physical status 3 older patients, reversal of rocuronium with SUG *vs* NEO, patients receiving SUG had a significantly lower rate of confirmed postoperative pneumonia, with a non-significantly shorter length of hospital stay. We conclude that in a select cohort of higher-risk older patients, reversal with SUG may offer a clinically relevant benefit.

Authors' contributions

Study conception: TL, HDdB, BF
Protocol design: TL
Funding organisation: TL
Data collection: PSL, HSY, HDdB, LA, IIS, ZS-M, LC, BF
Data analysis: TL, BAT
Data interpretation: TL, BF
Statistical analysis: BAT
Writing of paper: all authors

Declarations of interest

TL, PSL, and HDdB have received speaker honoraria and travel grants from Merck (manufacturer of sugammadex). IIS is involved in a Merck-funded study at the University of Malaya.

However, none of the aforementioned declared conflicts have been related to the planning, conduct, analysis, or publication of this study. The other authors have nothing to declare.

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University of Western Australia.

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