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Clinical Investigation

CLINICAL INVESTIGATION

Impact of neuromuscular block monitoring and reversal on postoperative pulmonary complications in thoracic surgery: a Bayesian analysis of the iPROVE-OLV trial

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Abstract

Background: Postoperative pulmonary complications (PPCs) are a significant concern in thoracic surgery. A modifiable factor influencing PPCs is postoperative residual neuromuscular block (NMB), which impairs respiratory muscle function.
Methods: We performed a *post hoc* Bayesian analysis of data from the iPROVE-OLV study, a multicentre randomised controlled trial involving patients undergoing thoracic surgery with one-lung ventilation. We compared participants managed with any neuromuscular monitoring and any reversal *vs* those managed without either. The primary outcome was the occurrence of a composite of PPCs within the first 7 postoperative days.
Results: Of the 698 patients included, 657 received any neuromuscular monitoring and any reversal, while 41 did not. Patients managed with any neuromuscular monitoring and any reversal had a lower incidence of PPCs (20%) compared with those without either (34%). Bayesian random effect logistic regression indicated that the use of any neuromuscular monitoring and any reversal reduced PPCs with an odds ratio (OR) ranging from 0.67 (95% credibility interval, CrI, 0.39–1.11) to 0.84 (95% CrI 0.48–1.37), depending on the prior model used. The probability of benefit (OR <1) was between 77% and 94%. Subgroup analysis indicated that sugammadex was more effective than neostigmine in reducing PPCs, with a high probability of benefit (97%), and both neuromuscular monitoring and reversal reduced PCCs when evaluated separately with a high probability of benefit.
Conclusion: Utilising neuromuscular monitoring and reversal agents significantly reduced the risk of PPCs in thoracic surgery. Sugammadex was more efficacious in reducing PPCs compared with neostigmine. These findings support the combined use of neuromuscular monitoring and reversal drugs.
Clinical trial registration: NCT03182062.

Keywords: neuromuscular block; neuromuscular monitoring; one-lung ventilation; postoperative pulmonary complications; reversal agents; sugammadex; thoracic surgery

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Editor's key points

- Residual neuromuscular block impairs respiratory muscle function and can increase the risk of postoperative pulmonary complications (PPCs), a significant concern in thoracic surgery patients.
- This *post hoc* Bayesian analysis of data for 698 participants from the iPROVE-OLV trial analysed patients undergoing thoracic surgery with one-lung ventilation for the occurrence of a composite of PPCs within 1 week.
- Participants managed with neuromuscular monitoring and reversal of neuromuscular block had reduced incidence of PPCs (20%) compared with those managed without either (37%), and sugammadex was more efficacious compared with neostigmine.
- Use of neuromuscular monitoring and reversal agents significantly reduced the risk of PPCs in thoracic surgery, a modifiable risk factor recommended by current guidelines.

Postoperative complications have been recognised as a major issue in healthcare,[1] and postoperative pulmonary complications (PPCs) are one of the major contributors.[2,3] Patients undergoing thoracic surgery are particularly prone to these complications because of the surgery itself and the potentially injurious ventilation technique during one-lung ventilation (OLV).[4] Thoracic surgery is an independent risk factor in preoperative PPCs scores.[5] A modifiable factor contributing to PPCs is postoperative residual neuromuscular block, in which muscle weakness after the intraoperative use of neuromuscular blocking agents (NMBAs) persists longer than desired.[6] This can impair respiratory muscle function and airway patency, increasing the risk of complications.[7,8]

A recent study of patients undergoing thoracic surgery reported the effect of an individualised ventilation strategy compared with a standard one on the occurrence of PPCs, showing that an individualised strategy reduced PPC risk.[9] The study protocol recommended managing neuromuscular block (NMB) according to local guidelines,[10] but allowed the anaesthesia team to follow providers' preferences. This study compared outcomes between patients managed with or without the use of any neuromuscular monitoring and any neuromuscular reversal agents.

Bayesian statistics combine prior knowledge with new data to update the likelihood of a hypothesis. Unlike traditional *P*-values, which assess the probability of observing data assuming that a null hypothesis is true, Bayesian methods provide a direct measure of how likely a hypothesis is true given the evidence, for example, the probability of treatment of being beneficial is 20%. This enables more actionable, probabilistic statements about treatment effects, making it particularly useful in clinical decision-making.[11–13]

We aimed to evaluate the association between NMB management with any neuromuscular monitoring and any reversal compared with no neuromuscular monitoring and no reversal with regard to occurrence of PPCs. Our objective was to assess if the type of NMB management, defined as either adherence to NMB management guidelines with neuromuscular monitoring and reversal or no neuromuscular monitoring and no reversal was associated with an increased risk of PPC occurrence.

Methods

This was a *post hoc* Bayesian analysis, a method that starts with prior beliefs about the likelihood of different outcomes before observing data. This approach is different from frequentist methods, in which analysis is performed solely based on observed data. Priors represent the initial beliefs about the parameters of a statistical model before any data are observed, and denote the assumptions or guesses about a hypothesis before it is tested; past data can be used as a prior, or mathematical methods can be used to establish priors, for example, based on expert opinions or general principles. Priors can also be set to reflect no initial knowledge and assume that all possibilities are equally likely. They are then updated considering observed data using Bayes' theorem to obtain the posterior distribution, which indicates the updated beliefs after considering the new data. The likelihood function assesses the probability of the observed data under each possible option. The conditional probability obtained by this updating process can be used to make informed estimates or compute ranges of credibility based on a predefined percentage of probability, such as 95% highest density interval (HDI) or credibility interval (CrI). Researchers have recently used this approach to examine data from anaesthesia and critical care studies.[11–13]

We conducted this analysis on the iPROVE-OLV study sample.[9] This was a large multicentre randomised controlled trial (RCT) in patients undergoing thoracic surgery with one-lung ventilation (OLV). Patients were randomised to two groups: (1) iOLA–HFNC (individualised one-lung approach–high-flow nasal cannula): patients received intraoperatively an alveolar recruitment manoeuvre, which involved increasing alveolar pressure up to 40 cm H_2O. After this, individualised positive end-expiratory pressure (PEEP) was titrated to achieve the best compliance of the respiratory system. Postoperatively, patients received individualised high-flow oxygen therapy depending on oxygenation status. (2) STD-O_2 (standard oxygenation): intraoperatively patients received a fixed PEEP of 4 cm H_2O during OLV and conventional oxygen therapy was administered postoperatively without further individualisation based on oxygenation. All patients had a tidal volume of 8 ml kg^{-1} of predicted bodyweight (PBW) during two-lung ventilation and 5–6 ml kg^{-1} PBW during OLV. The trial was registered with ClinicalTrials.gov (NCT03182062); the protocol was published before patient enrolment[14] and followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. The final protocol was approved by the local Institutional Review Board in all participating centres. Study data were collected using the Research Electronic Data Capture (REDCap, Vanderbilt University, Nashville, TN, USA) tools hosted at the Barcelona Clinic Hospital.

Data recording

Full details on data collection are published in the original protocol and RCT report of the iPROVE-OLV study.[9,14] Briefly, the attending physician determined the part of the anaesthetic approach that was unrelated to ventilatory considerations in accordance with each institution's standards.

Intraoperative NMB management was also carried out according to each centre's standard of care but provider preference was allowed, which included the option of using reversal agents or not, and use of any neuromuscular monitoring or not.

Inclusion criteria

For the main analysis, we included patients who received intraoperatively both any neuromuscular monitoring and reversal drugs of any type or those who received neither, thus defining two cohorts. We excluded patients who did not undergo tracheal extubation in the operating room and those who received either any neuromuscular monitoring or any reversal drugs, but not both. The rationale for this choice was that while clinicians were encouraged to follow the recommended NMB management guidelines, formal data on use of quantitative neuromuscular monitoring or train-of-four (TOF) ratio at the time of tracheal extubation were not available.

Outcomes

We used the same primary outcome as the original study, that is, a composite of PPCs in the first 7 postoperative days. The composite included atelectasis requiring bronchoscopy, severe respiratory failure, contralateral pneumothorax, early extubation failure (rescue with continuous positive airway pressure (CPAP), noninvasive ventilation, invasive mechanical ventilation, or reintubation), acute respiratory distress syndrome, pulmonary infection, bronchopleural fistula, or pleural empyema. A detailed description of each of these complications is reported in Table S1 in the Supplementary material.[14]

Primary objective

Our primary objective was to assess the effect of NMB management, defined as a binary variable with either any neuromuscular monitoring and any reversal, or no neuromuscular monitoring and no reversal, on the primary outcome in patients undergoing thoracic surgery.

Statistical analysis

We utilised information from every patient within the iPROVE-OLV database without formally calculating sample size. As the analysis aimed to investigate a physiological hypothesis, we did not define a predetermined effect size. Because of the Bayesian framework, sample size calculation is not as strict as in a classical frequentist approach, where the *a priori* null hypothesis and multiple comparisons have to be considered.

To assess the effect of the NMB management strategy on the occurrence of PPCs, we carried out a Bayesian random effect logistic regression. We introduced the NMB strategy and the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) risk score[5] (intermediate, or 26–44, *vs* high, or ≥44) and randomisation group (ST-O_2 *vs* iOLA–iHFNC) as population effects and the participating centre as a random effect. As previously recommended, we estimated the model with three different priors for the NMB strategy, that is, neutral, pessimistic, and optimistic. We defined the strength of these prior beliefs, that is, the variance setting to establish the shape of the distribution, as moderate for the optimistic and neutral prior, and weak for the pessimistic one. In other words, we set our priors so that we could not rule out an eventual benefit but could mostly rule out large effect sizes for the intervention and acknowledge a nonnegligible chance of the intervention being harmful.[11] This was carried out to reflect different beliefs that various stakeholders may have on the effect of the analysed intervention. As for the covariables, we fitted the model assuming that the intermediate ARISCAT risk score effect is beneficial and that there is a very low chance that it is harmful and a neutral prior to the randomisation group.

In mathematical form, for the NMB strategy priors, the neutral sceptical prior was normally distributed and centred at the absence of effect (OR=1; log[OR]=0) with a standard deviation (SD) of 0.355, such that 0.95 of the probability falls in the range of OR between 0.5 and 2. The pessimistic and optimistic priors were informed by the estimate reported in a recent publication that reported the effect of having a TOF ratio (TOFr) >0.95 at extubation decreased the risk of PPCs (OR=0.72).[15] The optimistic prior SD was defined to retain a 0.15 probability of harm (Pr[OR >1]). The pessimistic prior was initially chosen to retain a 0.30 probability of benefit (Pr[OR <1]).

The region of practical equivalence (ROPE) measures how much of the posterior probability distribution falls between a specific interval of equivalent effect. By assessing how much of the 95% HDI from the posterior distribution falls within the ROPE, we can quantify the probability of the studied intervention having a benefit or harm and if no differences between interventions are credible given the data. We set the ROPE as the interval between 0.9<OR<1.1. In addition, we defined a threshold for severe harm at OR >1.25.

We also assessed the influence of priors on the primary outcome posterior distributions by assessing the heterogeneity of the effect after fitting a conventional meta-analytic model with the aggregate estimates of the different priors models. This was carried out, as postulated in published recommendations,[11] by considering the results given by different priors as a different study to assess how much priors influenced the results. As baseline data are the same, the heterogeneity from this meta-analysis results from the influence of priors on results. For this analysis, we used a sceptical moderate strength prior for the effect size and a DuMouchel prior for heterogeneity.[11]

We performed the following subgroup analyses by fitting the aforementioned model, adding an interaction between the main independent variable, that is, NMB strategy, and the subgroup of interest. We assessed (1) type of surgery, that is, thoracoscopy *vs* open or converted to open surgeries; (2) type of NMB agent, that is, isoquinolinium *vs* aminosteroid, and reported the effect estimated by pairwise contrasts for the NMB strategy in the groups of interest; (3) type of reversal agent, that is, sugammadex *vs* neostigmine, reporting the effect estimated by pairwise contrast for the type of reversal agent in the any neuromuscular monitoring and any reversal cohort. In addition, we performed the following sensitivity analysis as follows. (1) We applied the main analysis model to propensity-score-matched cohorts. The no monitoring–no reversal group was matched to the any neuromuscular monitoring–any reversal group by ARISCAT score and randomisation group in a 1:1 ratio using the nearest neighbour method with calliper of 0.1. (2) We fitted a model with any neuromuscular monitoring and any reversal as separate variables allowing for an interaction between them to assess the effect of each measure separately. This analysis included the entire cohort, including also those patients who received either, but not both, any neuromuscular monitoring or any

reversal; this was fitted with previously described neutral priors for all the included variables. (3) We assessed the impact of misclassification bias through Monte Carlo simulation. Assuming nondifferential misclassification, that is, misclassification is equally likely in both groups, we sampled 10 000 values from uniform distributions with a minimum value of 0.75 and 0.8 and a maximum value of 0.9 and 0.95 for sensitivity and specificity, respectively. In other words, we assumed a range of equally probable values for both parameters and then used them to correct the estimated OR using published formulas.[16,17]

For all models, we drew 4000 samples from the posterior distribution after fitting the models with *brms* Hamiltonian Markov No U-turn sampler using each of the previously defined priors. We determined how much of the probability density lies in the ROPE interval or exceeds the threshold for severe harm. We also determined the expected predicted posterior probabilities of treatment effect using the *emmeans* package for R (v1.8.5). All analyses used the R software (version 4.2.3, Core Team, Vienna, Austria) software.

Results

We included 698 patients in the analyses; 657 received intraoperative neuromuscular monitoring and reversal before tracheal extubation, while 41 received neither (Fig. 1). Baseline characteristics of both groups are reported in Table 1. Preoperative characteristics were similar between groups; however, patients who did not receive either neuromuscular monitoring or reversal underwent longer surgeries (median duration 193 min [25th–75th percentile: 176–248] compared with 170 min [25th–75th percentile:125–222]) and were given isoquinolinium NMB drugs (cisatracurium 43% compared with 23%) and epidural analgesia (83% compared with 63%) more often than patients who received both intraoperative monitoring and reversal. The majority of surgeries were oncologic lobectomies in both groups, while the most used NMB agent–reversal combination in the any neuromuscular monitoring–reversal group was rocuronium–sugammadex.

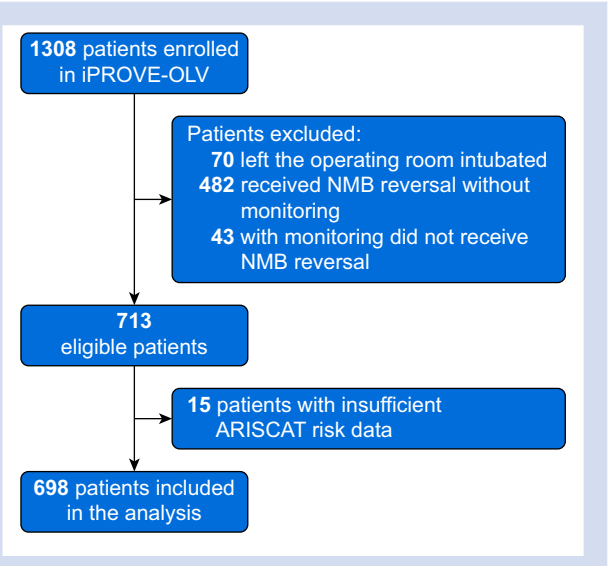

Fig 1. Study analysis flow-chart. ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; NMB, neuromuscular block.

The occurrence of PPCs was 20% in the any neuromuscular monitoring–reversal group and 34% in the no neuromuscular monitoring–no reversal group. The OR of an any neuromuscular monitoring–reversal strategy compared with no neuromuscular monitoring–no reversal strategy on the occurrence of PPCs was 0.84 (95% CrI 0.48–1.37), 0.83 (0.40–1.52), and 0.67 (0.39–1.11) for the model fitted with a neutral, pessimistic, and optimistic prior, respectively. The probability of a beneficial effect, that is, OR <1, was between 77% and 94%, depending on the prior. The probability mass comprised in the ROPE region was between 9% and 22% (Table 2 and Fig. 2). The estimated heterogeneity I^2 parameter from the aggregate estimate meta-analysis was 0.111. Therefore, ~11% of the variance between estimates was caused by the priors (Fig. S1).

Subgroup analysis showed that the OR of sugammadex reversal compared with neostigmine reversal on the occurrence of PPCs in the any neuromuscular monitoring–reversal cohort was 0.53 (95% CrI 0.23–1.04), 0.54 (0.24–1.05), and 0.53 (0.23–1.05) for the model fitted with a neutral, pessimistic, and optimistic prior, respectively, with a high probability of benefit, that is, 97% regardless of prior (Fig. 3 and Table 3). The probability of effect was similar between patients who underwent open or thoracoscopic surgery and patients who received aminosteroid or isoquinolinium NMBAs (Fig. S2 and Table 3). The propensity score returned a balanced cohort of 41 patients in each group (Fig. S3). The analysis fitted on this cohort returned estimates that were similar to the main analysis (Table S2). The model fitted with any neuromuscular monitoring and reversal as separate variables showed that the ORs for the occurrence of PPCs for any neuromuscular monitoring compared with no neuromuscular monitoring and for reversal compared with no reversal were 0.84 (0.51–1.31) and 0.91 (0.50–1.52), respectively, with a probability of a beneficial effect, that is, OR <1, of 68% and 79%, respectively. The interaction effect shows a probability of benefit for reversal of 80% and 36% in the no neuromuscular monitoring and any neuromuscular monitoring groups, respectively (Tables S3 and S4). The misclassification bias analysis returned a median corrected OR estimate of 0.89 (2.5th–97.5th percentile 0.64–1.26), 0.88 (0.63–1.23), and 0.65 (0.45–0.91) for the model fitted with a neutral, pessimistic, and optimistic prior, respectively.

Discussion

We applied a Bayesian analysis framework on a convenience sample from a multicentre thoracic surgery trial to estimate the impact of an intraoperative NMB management strategy, which included neuromuscular monitoring and reversal agents, compared with a strategy without either. The findings can be summarised as: (1) NMB management with any neuromuscular monitoring and any reversal reduced the probability of pulmonary complications occurrence compared with spontaneous, unmonitored recovery; and (2) this reduction was consistent across open or thoracoscopic surgery; and (3) with both aminosteroid or isoquinolinium agents; (4) use of sugammadex, compared with neostigmine, further decreased PPCs when both any neuromuscular monitoring and any reversal agents were used; and (5) while both any neuromuscular monitoring and any reversal are beneficial individually, reversal is more effective in patients without neuromuscular monitoring.

Table 1 Baseline and intraoperative characteristics. Data are reported as median (25th–75th percentile) or *n* (%). ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; COPD, chronic obstructive pulmonary disease; iOLA–iHFNC, perioperative individualised open-lung approach; NMB, neuromuscular block; NMM: neuromuscular monitoring; SpO_2, peripheral oxyhaemoglobin saturation; STD-O_2, standard lung-protective ventilation. *ASA criteria for physical status include a classification for normal health (1), mild systemic disease (2), severe systemic disease (3), severe systemic disease that is a constant threat to life (4), and a moribund person who is not expected to survive without the operation (5). †Defined as haemoglobin <12 g dl^{-1} for females and <13.0 g dl^{-1} for males. ‡ARISCAT score estimates the risk of postoperative pulmonary complications, with scores greater or equal to 45 indicating high risk. ¶Reversal completely separates some categories.

	Overall *n*=698[1]	No NMM–no reversal *n*=41[1]	Any NMM–any reversal *n*=657[1]	Difference[2] (95% CI)[23]
Age, yr (years)	65 (59–72)	68 (59–73)	65 (59–72)	1.6 (−1.8 to 4.9)
Sex (female)	256/696 (37%)	15/41 (37%)	241/655 (37%)	0% (−6% to 15%)
Weight (kg)	72 (64–82)	70 (62–78)	72 (64–82)	−2.1 (−5.8 to 1.5)
Height (cm)	168 (161–173)	166 (162–170)	168 (160–174)	−0.73 (−3.3 to 1.8)
Body mass index (kg m^{-2})	25.7 (23.1–28.9)	26.6 (22.1–29.0)	25.6 (23.2–28.8)	−0.08 (−1.5 to 1.3)
Oncologic surgery (yes)	611/698 (88%)	31/41 (76%)	580/657 (88%)	−13% (−27% to 2%)
ASA physical status*				0.24 (−0.07 to 0.56)
1	11/696 (1.6%)	1/41 (2.4%)	10/655 (1.5%)	
2	321/696 (46%)	15/41 (37%)	306/655 (47%)	
3	360/696 (52%)	25/41 (61%)	335/655 (51%)	
4	4/696 (0.6%)	0/41 (0%)	4/655 (0.6%)	
SpO_2 (%)	97 (96–98)	97 (96–97)	97 (96–98)	−0.29 (−0.95 to 0.38)
Preoperative haemoglobin (g dl^{-1})	13.7 (12.6–14.8)	13.2 (12.3–14.6)	13.7 (12.6–14.8)	−0.27 (−0.84 to 0.30)
Preoperative anaemia† (yes)	156/689 (23%)	10/38 (26%)	146/651 (22%)	3.9% (−12% to 20%)
Charlson comorbidity index	4.0 (2.0–5.0)	4.0 (2.0–6.0)	4.0 (2.0–5.0)	0.24 (−0.58 to 1.1)
Respiratory infection within the past month (yes)	29/698 (4.2%)	2/41 (4.9%)	27/657 (4.1%)	1% (−7% to 8%)
Hypertension (yes)	343/698 (49%)	20/41 (49%)	323/657 (49%)	0% (−17% to 16%)
Coronary artery disease (yes)	66/698 (9.5%)	9/41 (22%)	57/657 (8.7%)	13% (−0.87% to 27%)
Diabetes mellitus type 1 (yes)	12/698 (1.7%)	0/41 (0%)	12/657 (1.8%)	−1.8% (−4% to 0.5%)
Diabetes mellitus type 2 (yes)	122/698 (17%)	11/41 (27%)	111/657 (17%)	9.9% (−5.2% to 25%)
Smoker (yes)	192/698 (28%)	13/41 (32%)	179/657 (27%)	4.5% (−11% to 20%)
Alcohol abuse (yes)	63/698 (9.0%)	4/41 (9.8%)	59/657 (9.0%)	0.8% (−9.3% to 11%)
COPD (yes)	180/698 (26%)	12/41 (29%)	168/657 (26%)	3.7% (−12% to 19%)
Chronic kidney disease (yes)	64/698 (9.2%)	7/41 (17%)	57/657 (8.7%)	8.4% (−4.6% to 21%)
Chronic liver disease (yes)	16/698 (2.3%)	2/41 (4.9%)	14/657 (2.1%)	2.7% (−5.2% to 11%)
Snoring (yes)	216/698 (31%)	12/41 (29%)	204/657 (31%)	−1.8% (−17% to 14%)
Sleep apnoea (yes)	51/698 (7.3%)	5/41 (12%)	46/657 (7.0%)	5.2% (−6.3% to 17%)
Crystalloids administered (ml)	1000 (700–1337)	1000 (700–1500)	1000 (70–1300)	81 (−90 to 252)
Colloids administered (ml)	0.0 (0.0–0.0)	0.0 (0.0–312.5)	0.0 (0.0–0.0)	111 (−105 to 328)
Blood transfusion (yes)	18/698 (2.6%)	2/41 (4.9%)	16/657 (2.4%)	2.4% (−5.6% to 10%)
Blood transfusion (ml)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.33 (−15 to 16)
Estimated blood loss (ml)	200 (100–300)	300 (105–400)	200 (100–300)	98 (−17 to 214)
Surgery duration (min)	175 (125–225)	193 (176–248)	170 (125–222)	32 (2.9–62)
One-lung ventilation duration (min)	149 (110–200)	148 (100–208)	149 (110–200)	20 (−29 to 69)
Vasoactive drugs use (yes)	330/698 (47%)	10/41 (24%)	320/657 (49%)	−24% (−39% to 9.3%)
Hypnotic agent				0.04 (−0.33 to 0.42)
Halogenated volatile	550/685 (80%)	22/28 (79%)	528/657 (80%)	
Intravenous	135/685 (20%)	6/28 (21%)	129/657 (20%)	
Neuromuscular blocking agent				0.53 (0.15–0.90)
Rocuronium	515/684 (75%)	15/28 (54%)	500/656 (76%)	
Cisatracurium	166/684 (24%)	12/28 (43%)	154/656 (23%)	

Continued

Table 1 Continued

	Overall n=698[1]	No NMM–no reversal n=41[1]	Any NMM–any reversal n=657[1]	Difference[2] (95% CI)[23]
Atracurium	2/684 (0.3%)	1/28 (3.6%)	1/656 (0.2%)	
Other	1/684 (0.1%)	0/28 (0%)	1/656 (0.2%)	
Reversal agent				¶
None	41/692 (6%)	41/41 (100%)	0/651 (0%)	
Sugammadex	465/692 (67%)	0/41 (0%)	465/651 (71%)	
Neostigmine	186/692 (27%)	0/41 (0%)	186/651 (29%)	
Neuromuscular blocking agent–reversal agent pairings				¶
Isoquinolinium–no reversal	13/677 (2%)	13/28 (46%)	0/649 (0%)	
Isoquinolinium–sugammadex	0/677 (0%)	0/28 (0%)	0/649 (0%)	
Isoquinolinium–neostigmine	151/677 (22%)	0/28 (0%)	151/649 (23%)	
Rocuronium–no reversal	15/677 (3%)	15/28 (54%)	0/649 (0%)	
Rocuronium–sugammadex	462/677 (68%)	0/28 (0%)	462/649 (71%)	
Rocuronium–neostigmine	33/677 (5%)	0/28 (0%)	33/649 (6%)	
Analgesic agent				0.39 (0.02–0.76)
Remifentanil	139/681 (20%)	10/29 (34%)	129/652 (20%)	
Sufentanil	12/681 (1.8%)	0/29 (0%)	12/652 (1.8%)	
Fentanyl	370/681 (54%)	14/29 (48%)	356/652 (55%)	
Other	160/681 (23%)	5/29 (17%)	155/652 (24%)	
Analgesia administration route				0.47 (0.15–0.79)
Intravenous	253/698 (36%)	7/41 (17%)	246/657 (37%)	
Epidural or paravertebral block	445/698 (64%)	34/41 (83%)	411/657 (63%)	
Nausea/vomiting prophylaxis (yes)	677/685 (99%)	27/29 (93%)	650/656 (99%)	−6.0% (−17% to 5.1%)
ARISCAT score‡ (categories)				0.30 (−0.01 to 0.62)
Intermediate	657/698 (94%)	18/41 (44%)	387/657 (59%)	
High	146/698 (21%)	23/41 (56%)	270/657 (41%)	
Randomisation group				0.21 (−0.11 to 0.52)
STD-O_2	405/698 (58%)	16/41 (39%)	324/657 (49%)	
iOLA–iHFNC	293/698 (42%)	25/41 (61%)	333/657 (51%)	
Type of surgery				0.01 (−0.31 to 0.34)
Thoracoscopy	340/698 (49%)	26/39 (67%)	437/650 (67%)	
Thoracotomy	358/698 (51%)	13/39 (33%)	213/650 (33%)	
Oncologic surgery (yes)	611/698 (88%)	31/41 (76%)	580/657 (88%)	−13% (−27% to 2%)
Surgical indication				0.67 (0.35–0.99)
Segmentectomy	118/698 (17%)	4/41 (10%)	114/657 (17%)	
Lobectomy	420/698 (60%)	26/41 (63%)	394/657 (60%)	
Bilobectomy	25/698 (4%)	1/41 (3%)	24/657 (4%)	
Pneumonectomy	20/698 (3%)	1/41 (3%)	19/657 (3%)	
Other	115/698 (16%)	9/41 (21%)	106/657 (16%)	
Pulmonary complications in the first 7 postoperative days	146/698 (21%)	14/41 (34%)	132/657 (20%)	14% (−2.1% to 30%)

Table 2 Average effect estimates from the main model for the primary outcome. The reference categories for the binary variables were: No NMM–no reversal; ARISCAT score intermediate and STD-O_2 for each of the three variables reported. ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; ARR, absolute risk reduction; iOLA–iHFNC, perioperative individualised open-lung approach; NMM, neuromuscular monitoring; OR, odds ratio; ROPE, region of practical equivalence defined by an OR interval of: 0.9 and 1.1; STD-O_2, standard lung-protective ventilation. *Only one estimate is provided for the effect of high ARISCAT score and iOLA–iHFNC ventilation strategy (study group) as the model was estimated with a single prior for these variables.

Estimates		OR (95% CI)*	ARR (95% CI)	ROPE region probability (%)	Probability of benefit or serious harm (%)		
					OR <1	OR <0.8	OR >1.25
Any NMM–any reversal	Neutral	0.84 (0.48–1.37)	−6 (−17 to 2)	22	79	50	5
	Pessimistic	0.83 (0.40–1.52)	−8 (−22 to 2)	19	77	53	8
	Optimistic	0.67 (0.39–1.11)	−11 (−22 to −1)	9	94	77	1
High ARISCAT score iOLA–HFNC	*	1.72 (1.18–2.41)	12 (6–17)	0	0	0	95
		0.47 (0.32–0.65)	−11 (−16 to −6)	0	100	99	0

The confidence required to change clinical practice based on an intervention depends on its complexity, its potential harms, outcome significance, and patient factors. A higher threshold is needed for invasive or complex interventions. In our case, neuromuscular monitoring and reversal agent use are noninvasive practices that involve minimal side-effects, and carry a high likelihood of benefit. This supports the practicality and advisability of implementing these measures. In the context of our analyses, the usefulness of Bayesian probabilistic reasoning to help decision–making is evident; our results show that using any neuromuscular monitoring and reversal is really likely to protect from PPCs. There is general agreement that the use of quantitative neuromuscular monitoring and reversal can prevent postoperative residual neuromuscular block, which has been linked with an increase in incidence of PPCs.[18] Indeed, current guidelines on NMB management recommend quantitative neuromuscular monitoring and reversal drug administration, if needed, titrated to the NMB depth at the time of reversal.[19,20] However, recently published data show that this practice is not universally followed. A recent large multicentre European observational study reported that only 42.1% of patients receiving NMBAs during surgery underwent neuromuscular monitoring, and only 47.9% of patients received a reversal agent before tracheal extubation.[7] These figures were only marginally higher in a very large analysis assessing anaesthetic practice in the USA,[21] and in a large RCT carried out in the same context as that motivating the current analysis.[22] Both reports showed a proportion of patients undergoing spontaneous recovery of >20%. Suboptimal NMB management is even more consequential to patient safety, as it adds a potentially modifiable risk factor for PPCs to an already high-risk cohort of patients, such as those undergoing thoracic surgery.[23] These patients often present with substantial pulmonary comorbidities, and often require OLV and a deeper level of NMB to ensure diaphragmatic paralysis to facilitate surgery.[24]

We observed that among patients who received NMBA reversal, those who received sugammadex had a lower probability of developing PPCs in line with previous results. A single-centre RCT in patients undergoing thoracic surgery with OLV showed that use of sugammadex led to fewer postoperative hypoxaemic episodes compared with neostigmine.[25] Moreover, a large retrospective study in noncardiac surgery patients found that use of sugammadex was associated with fewer PPCs compared with neostigmine after propensity-score matching,[26] and a secondary analysis that assessed patients at high risk of PPCs confirmed this association, although the percentage of patients undergoing thoracic surgery in the latter analysis was only 11.9%.[27] In a retrospective large two-centre study, the effect of using sugammadex on PPC occurrence was indeterminate, although it is unclear when and how NMB was monitored during surgery, and sugammadex was beneficial in a subgroup analysis of patient with quantitative neuromuscular monitoring.[28]

We carried out the main analysis excluding the cohort of patients who received reversal but no neuromuscular monitoring, because unmonitored administration of reversal agents can lead to under-dosing or over-dosing, which is not recommended and could, therefore, have introduced a misclassification bias. This methodological choice resulted in unequally sized groups. However, logistic regression can fit estimates with precision even in unequally sized groups, albeit with a loss of statistical power compared with a model fitted on equally sized groups.[29] The issue of statistical power in

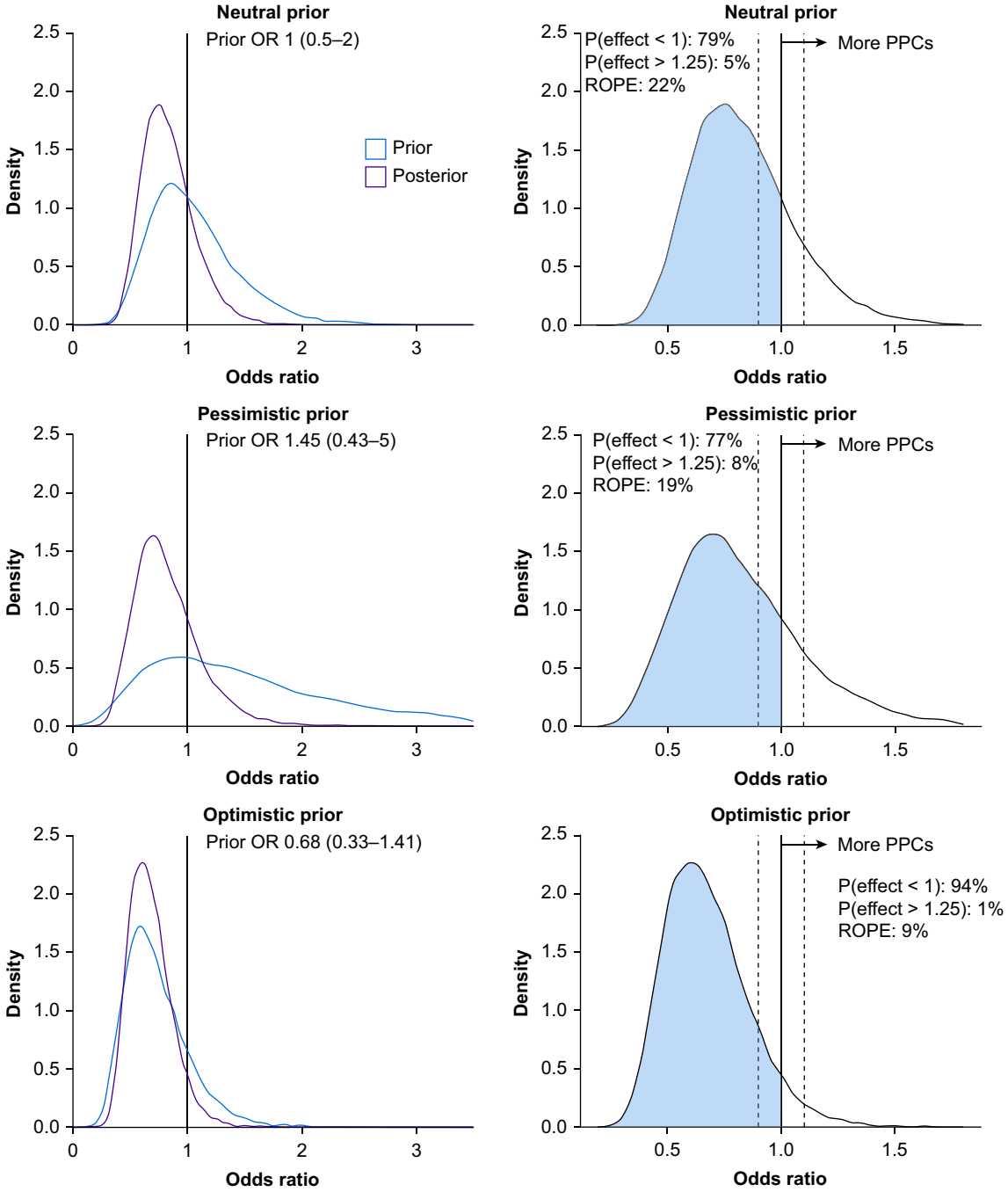

Fig 2. Effect of monitoring and reversal administration shown using the OR scale. Left column panels: graphs show the probability distributions for the effect of monitoring and reversal before and after estimating the model on the data, that is, prior and posterior distributions. Each panel reports the mean (95% CI) of the prior distribution in the OR scale representing different types of beliefs for the treatment effect. Right column panels: the posterior distributions, that is, treatment effect estimates, for how neuromuscular monitoring and reversal agent use affect the chance of developing PPCs. The blue area highlights where the OR suggests a benefit (OR <1), meaning reduced risk of PPCs. CI, confidence interval; OR, odds ratio; PPC, postoperative pulmonary complication; ROPE, region of practical equivalence.

classic frequentist terms, that is, the probability of rejecting the alternative hypothesis when it is true, is not applicable to our analysis as we carried out a Bayesian estimation and estimated posterior probability distribution. Therefore, we can attach actual probabilities to our results. Also, a sensitivity analysis on a matched cohort confirmed the results. Another

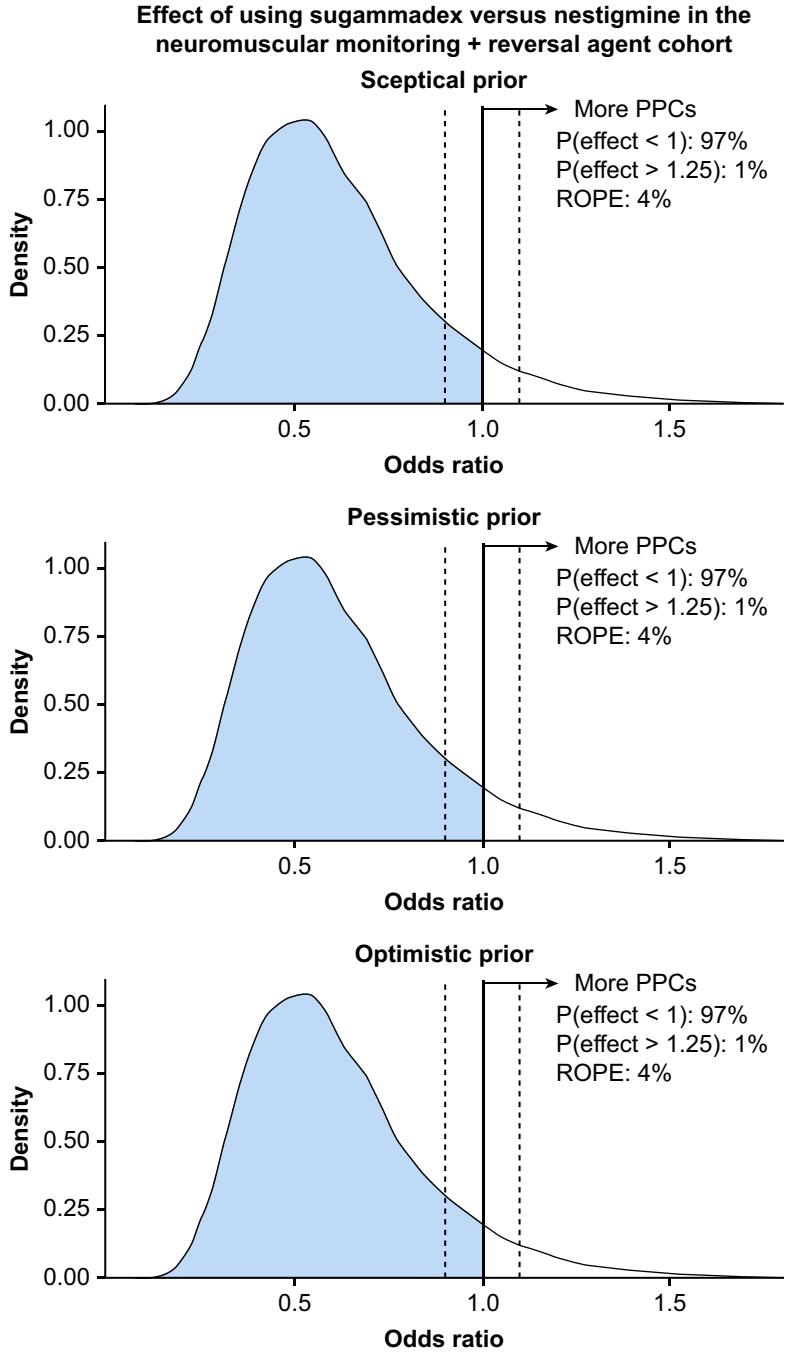

Fig 3. Posterior probability distributions for the conditional effect of sugammadex compared with neostigmine in the any neuromuscular monitoring and any reversal agent group. Light blue area: probability mass for the benefit threshold (OR <1). Black vertical dashed lines: region of practical equivalence boundaries (OR 0.9–1.1). OR, odds ratio; PPC, postoperative pulmonary complication; ROPE, region of practical equivalence.

issue is the potential misclassification embedded in the original study data because of the absence of TOFr data at tracheal extubation; while quantitative neuromuscular monitoring was recommended, it was not mandatory. This might have led to misclassification in either the no NMB–no reversal or NMB–reversal groups, based on guideline adherence. A Monte Carlo simulation showed that reduced classification accuracy could affect the findings. However, the analysis assumed nondifferential misclassification, using a wide range of equally likely sensitivity and specificity values, representing a general scenario because of limited data. Additionally, we assessed the effect of neuromuscular monitoring and reversal separately, finding both to have protective effects against PPCs. The interaction effect showed a higher probability of benefit from

Table 3 Subgroup analysis. CrI, credible interval; N, neutral; NMB, neuromuscular block; NMM, neuromuscular monitoring; O, optimistic; OR, odds ratio; P, pessimistic; ROPE, region of practical equivalence, i.e. the probability distribution between 0.9 and 1.1 OR. † This comparison is carried out in the cohort receiving neuromuscular monitoring and reversal agents as no patient in the no neuromuscular monitoring–no reversal agent cohort received any of these drugs.

Pairwise comparison	Subgroup analyses						
	Subgroup	Prior	OR (95% CrI)	ROPE region probability (%)	Probability of benefit or harm (%)		
					OR <1	OR <0.8	OR>1.25
Any NMM–any reversal *vs* No NMM–no reversal	Open surgery	N	0.80 (0.33–1.68)	15	77	58	11
		P	0.82 (0.31–1.79)	15	75	58	12
		O	0.69 (0.28–1.42)	11	87	72	5
	Thoracoscopy	N	0.88 (0.50–1.47)	25	72	41	8
		P	0.91 (0.42–1.73)	21	68	43	15
		O	0.71 (0.39–1.17)	12	92	72	2
	Aminosteroid	N	0.80 (0.45–1.35)	19	81	55	4
		P	0.77 (0.34–1.53)	15	81	62	7
		O	0.63 (0.33–1.07)	6	96	87	1
	Isoquinolinium	N	0.77 (0.16–2.40)	9	77	66	15
		P	0.73 (0.14–2.33)	8	79	69	13
		O	0.63 (0.13–1.96)	7	85	76	9
Sugammadex *vs* neostigmine	Any NMM–any reversal strategy†	N	0.53 (0.23–1.04)	4	97	90	1
		P	0.54 (0.24–1.05)	4	97	90	1
		O	0.53 (0.23–1.05)	4	97	90	1

reversal in patients without neuromuscular monitoring, suggesting that the effects of reversal vary based on the use of neuromuscular monitoring. The most beneficial intervention was combining both neuromuscular monitoring and reversal.

Our study has several strengths. It features a large sample size, specifically assessing the association between NMB and PPCs in a vulnerable cohort of thoracic surgery patients, unlike prior studies that were smaller[24,25] or only included a subset of thoracic patients.[7,26,27,30] Furthermore, we used a Bayesian statistical approach, which assesses the probability of intervention effect based on the observed data and prior knowledge, and offers a full posterior distribution for both the effect estimate and heterogeneity, also enabling tailored hypotheses testing such as whether the estimate exceeds a prespecified threshold.[31]

Our study also has limitations. Firstly, a TOFr of 0.9 before extubation was not reported, so the incidence of postoperative residual neuromuscular block cannot be calculated. Secondly, the original study did not record if neuromuscular monitoring was quantitative or qualitative, nor the administered doses or times of reversal drug administration; therefore, a certain amount of misclassification bias cannot be ruled out. Nevertheless, if it existed, it would be biased toward the absence of effect for the any neuromuscular monitoring and reversal strategy. Indeed the additional misclassification bias shows how the median estimate can vary considerably depending on how much we allow groups to be a precise reflection of the underlying unobserved categories, that is, NMB management according to or not according to existing neuromuscular monitoring guidelines. In other words, these findings suggest that any neuromuscular monitoring strategies might be suboptimal. Thirdly, rescue administration of reversal agents in the PACU (to treat residual neuromuscular block) was not reported. Finally, subgroup analysis only investigated physiological hypotheses in subgroups of interest and thus should be seen as exploratory.

In conclusion, our results indicate that using both neuromuscular monitoring and reversal agents significantly reduced the likelihood of PPCs compared with unmonitored spontaneous recovery, with consistent benefits across different thoracic procedures and types of NMBAs. Sugammadex was particularly effective in reducing complications compared with neostigmine. Despite some limitations, including incomplete data on specific neuromuscular block monitoring practices, the findings support implementation of these strategies in routine clinical practice in patients undergoing thoracic surgery.

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All authors approved the submitted version and agree to be accountable for all aspects of the work.

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Declaration of interest

The authors declare that they have no conflicts of interest.

Data sharing statement

Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and supplementary material), and the study protocol, statistical analysis plan, and software code, will be available after the publication date to researchers who provide a methodologically sound proposal and to achieve the aim of the approved proposal. Proposals should be directed to the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2024.11.041.

Appendix 1

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