Dose-dependent Association between Intermediate-acting Neuromuscular-blocking Agents and Postoperative Respiratory Complications

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ABSTRACT

Background: Duration of action increases with repeated administration of neuromuscular-blocking agents, and intraoperative use of high doses of neuromuscular-blocking agent may affect respiratory safety.

Methods: In a hospital-based registry study on 48,499 patients who received intermediate-acting neuromuscular-blocking agents, the authors tested the primary hypothesis that neuromuscular-blocking agents are dose dependently associated with the risk of postoperative respiratory complications. In the secondary analysis, the authors evaluated the association between neostigmine dose given for reversal of neuromuscular-blocking agents and respiratory complications. *Post hoc*, the authors evaluated the effects of appropriate neostigmine reversal (neostigmine ≤60 μg/kg after recovery of train-of-four count of 2) on respiratory complications. The authors controlled for patient-, anesthesia-, and surgical complexity–related risk factors.

Results: High doses of neuromuscular-blocking agents were associated with an increased risk of postoperative respiratory complications (n = 644) compared with low doses (n = 205) (odds ratio [OR], 1.28; 95% CI, 1.04 to 1.57). Neostigmine was associated with a dose-dependent increase in the risk of postoperative respiratory complications (OR, 1.51; 95% CI, 1.25 to 1.83). *Post hoc* analysis revealed that appropriate neostigmine reversal eliminated the dose-dependent association between neuromuscular-blocking agents and respiratory complications (for neuromuscular-blocking agent effects with appropriate reversal: OR, 0.98; 95% CI, 0.63 to 1.52).

Conclusions: The use of neuromuscular-blocking agents was dose dependently associated with increased risk of postoperative respiratory complications. Neostigmine reversal was also associated with a dose-dependent increase in the risk of respiratory complications. However, the exploratory data analysis suggests that the proper use of neostigmine guided by neuromuscular transmission monitoring results can help eliminate postoperative respiratory complications associated with the use of neuromuscular-blocking agents. **(ANESTHESIOLOGY 2015; 122:1201-13)**

THE World Health Organization estimates that at least 187 million surgeries requiring general anesthesia are performed each year worldwide.[1] Anesthesiologists often use intermediate-acting neuromuscular-blocking agents (NMBAs) to facilitate tracheal intubation and maintain optimal surgical conditions.[2] However, studies show that NMBAs are associated with postoperative respiratory complications including postextubation hypoxia, respiratory failure, negative pressure–induced pulmonary edema, and atelectasis.[3–5]

Postoperative respiratory complications are the second most common postoperative surgical complications, after wound infection,[6,7] and contribute to a significant financial

What We Already Know about This Topic

- Use of high doses of intermediate-acting neuromuscular blockers may result in residual weakness and compromise patient safety

What This Article Tells Us That Is New

- In an analysis of nearly 50,000 subjects, use of intermediate-acting neuromuscular blockers was associated with a dose-dependent increase in pulmonary complications
- Neostigmine also was associated with a dose-dependent increase in pulmonary complications although exploratory analysis suggested that this reflected lack of neostigmine dose adjustment using neuromuscular transmission monitoring

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burden on hospitals and patients. The average surgical cost is $5,015 for patients without respiratory complications, increasing 12-fold to $62,704 for patients who experience respiratory complications.[6–9]

Anesthesiologists need to balance optimal surgical conditions and associated side effects of medications used to accomplish surgical relaxation. Although deeper levels of neuromuscular blockade may improve surgical conditions, larger doses of NMBAs are more difficult to reverse and put patients at a greater risk of developing residual paralysis.[10]

Repeated administration of NMBAs leads to a prolonged duration of action, as defined by the time between administration of NMBA and recovery to a train-of-four (TOF) ratio greater than or equal to 0.9.[10–12] We, therefore, hypothesized that NMBAs are dose dependently associated with increased risk of postoperative respiratory complications. Our secondary hypothesis was that the acetylcholinesterase inhibitor neostigmine, which is used to reverse the effects of NMBAs at the end of the case, does not ameliorate their harmful effects on postoperative respiratory outcomes.

Materials and Methods

Study Design and Setting

After obtaining the approval from the Partners Institutional Review Board (protocol number: 2014P000420), we performed an observational analysis by using data on adult patients who underwent noncardiac surgery at Massachusetts General Hospital between January 2007 and September 2012. Intraoperative data were retrieved from the anesthesia information management system (AIMS). The AIMS includes the following data elements: comorbidities, operative procedure, physiological data, medications, fluid therapy, and adverse events. In addition, we used billing and demographic data from the Research Patient Data Registry (RPDR). The RPDR is a centralized clinical data registry that gathers data from hospital legacy systems for the purpose of research.

By using similar methodology to previous outcomes-based studies from our group, we validated our data by reabstracting clinical information from the anesthesia record and comparing it with the electronic data on a sample of 100 randomly selected patients.[13,14]

Patient Selection

We included patients aged 18 yr and older who underwent noncardiac surgical procedures, received intermediate-acting NMBAs, and whose tracheas were intubated at the beginning of the case and extubated in the operating room at the end of the case. Cases for which the same patient had additional surgical procedures within the previous 4 weeks were excluded.

Exposure Variables

We defined the use of intermediate-acting NMBAs as any intraoperative dose of atracurium, cisatracurium, rocuronium, or vecuronium. We defined the use of neostigmine for reversal as any intraoperative administration of neostigmine. To define the dose of intermediate-acting NMBAs, we created a composite variable that took into account the dose of all the above medications as multiples of their median dose required per body weight to achieve 95% reduction in maximal twitch response from baseline in 50% of the population (ED95),[15–17] corrected for ideal body weight.[18,19] The NMBA dose was specified in our multivariate models as a categorical variable based on its quintile distribution. Neostigmine dose was corrected for ideal body weight.[19]

Outcome Measures

The primary outcome measure was a composite variable that included the following major postoperative respiratory complications within the first 3 days after extubation: respiratory failure, pulmonary edema, tracheal reintubation, and pneumonia. All study outcomes (respiratory failure, pulmonary edema, tracheal reintubation, and pneumonia) were defined using *International Statistical Classification of Diseases and Related Health Problems, Ninth Revision codes*, and Current Procedural Terminology codes, have been described previously[14] and are listed in appendix 1.

Covariate Data

By using data from the AIMS and RPDR databases, we defined the preoperative characteristics of our study population: sex, age, body mass index, admission type (in-patient/ambulatory), emergent/nonemergent surgery, and American Society of Anesthesiologists physical status classification. We controlled for patient comorbidities by using the Deyo-Charlson Comorbidity Index[20] and for risk of postoperative respiratory complications by using a previously validated score for preoperative prediction of adverse postoperative respiratory outcomes (SPORC) score.[13] The SPORC score is an 11-point weighted score that allows anesthesiologists to preoperatively define a patient's risk of reintubation.[13] We also controlled for anesthesia duration (time between tracheal intubation and extubation), vasopressor use (calculated as a norepinephrine equivalent dose in microgram per hour),[21] opioid dose (calculated as total morphine equivalent dose in milligram),[22] depth of anesthesia (median dose of inhaled anesthetic agents corrected for age),[23] hypotension (number of minutes spent with a mean arterial pressure <50 mmHg), intraoperative fluid volume (the total volume of colloids and crystalloids administered between intubation and extubation, assuming that colloids have double the effective intravascular filling effect of crystalloids), and blood transfusion (number of units of erythrocytes).

By using a previously validated method, we classified surgical body region into 11 distinct groups according to Current Procedural Terminology code mapping[24] and stratified procedural severity using relative value units.[25] Surgical body regions are listed in table 1, and control variables included in each analysis are listed in appendix 2.

Table 1. Characteristics of Study Population

All Cases	Cases (%) without Pulmonary Complications	Cases (%) with Pulmonary Complications
48,499	46,687 (96.26)	1,812 (3.74)
Subgroup	**Cases without Pulmonary Complications**	**Cases (%) with Pulmonary Complications**
NMBA dose as multiples of ED95 (quintiles)		
0.09–2.19	9,883	205 (2.03)
2.20–2.94	9,456	256 (2.64)
2.95–3.80	9,329	310 (3.22)
3.81–5.15	9,104	397 (4.18)
>5.15	8,915	644 (6.74)
Neostigmine dose (μg/kg ideal body weight)		
0	12,273	334 (2.65)
<20	1,369	38 (2.70)
20–40	7,390	233 (3.06)
41–60	11,058	386 (3.37)
61–80	9,216	482 (4.97)
>80	5,381	339 (5.93)
Age (yr)		
18–25	2,668	26 (0.97)
26–35	4,292	54 (1.24)
36–45	6,847	118 (1.69)
46–55	1,088	269 (2.60)
56–65	10,648	444 (4.00)
66–75	7,568	503 (6.23)
>75	4,576	398 (8.00)
Sex		
Male	20,697	912 (4.22)
Female	25,990	900 (3.35)
Body mass index		
<18 (underweight)	571	39 (6.39)
18–24.9 (normal weight)	14,939	560 (3.61)
25–29.9 (overweight)	15,520	556 (3.46)
30–34.9 (obese)	8,679	355 (3.93)
35+ (morbidly obese)	6,978	302 (4.15)
Procedure duration (h)		
<1:00	2,439	41 (1.65)
1:00–2:00	12,877	324 (2.45)
2:01–4:00	20,916	721 (3.33)
4:01–8:00	9,490	626 (6.19)
>8:00	965	100 (9.39)
ASA classification		
1	5,033	23 (0.45)
2	29,021	607 (2.05)
3	12,113	1,075 (8.15)
4	512	107 (17.29)
5	8	0 (0.00)
Charlson Comorbidity Index		
0	24,133	139 (0.57)
1–2	12,398	537 (4.15)
3–4	4,213	406 (8.79)
5–6	1,200	186 (13.42)
>6	4,743	544 (10.29)
SPORC score		
0	24,301	231 (0.94)
1–3	15,341	589 (3.70)
4–6	5,962	720 (10.78)
>6	1,083	272 (20.07)
Depth of anesthesia (median age-corrected minimum alveolar concentration in quintiles)		
<0.75	7,762	473 (5.74)
0.75–0.88	9,545	475 (4.74)
0.89–1.00	9,987	372 (3.59)
1.00–1.12	9,866	268 (2.64)
>1.12	9,527	224 (2.30)
Norepinephrine equivalent dose (μg kg^{-1} h^{-1} quintiles)		
0	20,129	701 (3.37)
0.15–15.49	5,744	308 (5.09)
15.50–27.60	5,761	261 (4.33)
27.61–44.84	5,673	222 (3.77)
44.85–77.5	5,327	192 (3.48)
>77.5	4,053	128 (3.06)
Surgical body region		
Central nervous system	3,411	120 (3.40)
Endocrine	2,408	28 (1.15)
Hemic/lymphatic	538	11 (2.00)
Hernia	1,359	22 (1.59)
Integumentary	4,041	49 (1.20)
Musculoskeletal	11,543	252 (2.14)
Oropharyngeal/ esophagus	918	140 (13.23)
Abdomen (no hernias)	9,133	397 (4.17)
Thoracic	1,775	447 (20.12)
Urology/gynecology	9,412	149 (1.56)
Vascular	2,149	197 (8.40)
Admission type		
In-patient	39,510	1,767 (4.28)
Ambulatory	7,177	45 (0.62)
Emergency surgery status		
Emergent	1,890	140 (6.90)
Nonemergent	44,797	1,672 (3.60)
Units of blood transfused intraoperatively		
0	44,789	1,561 (3.37)
1–2	1,528	189 (11.01)
3–4	300	46 (13.29)
5–6	49	11 (18.33)
>6	21	5 (19.23)
Total fluid resuscitation volume (ml in quintiles)		
<1,000	15,133	440 (2.83)
1,000–1,300	3,286	108 (3.18)
1,301–2,000	12,344	410 (3.21)
2,001–3,000	7,687	273 (3.43)
>3,000	8,237	581 (6.59)

(*Continued*)

Table 1. (*Continued*)

All Cases	Cases (%) without Pulmonary Complications	Cases (%) with Pulmonary Complications
48,499	46,687 (96.26)	1,812 (3.74)
Subgroup	**Cases without Pulmonary Complications**	**Cases (%) with Pulmonary Complications**
Total morphine equivalent dose (mg in quintiles)		
0	10,416	734 (6.58)
<3.25	4,281	150 (3.39)
3.25–6.50	7,750	206 (2.59)
6.51–9.25	8,837	223 (2.46)
9.26–13.25	4,915	156 (3.08)
>13.25	10,488	343 (3.17)
Number of hypotensive minutes		
0	35,991	1,065 (2.87)
1–5	6,659	538 (7.48)
6–10	2,507	111 (4.24)
11–15	688	43 (5.88)
16–20	229	15 (6.15)
21–25	194	14 (6.73)
26–30	125	7 (5.30)
>30	294	19 (6.07)
Use of train-of-four monitoring		
Yes	33,216	1,292 (3.74)
No	13,471	520 (3.72)
Subgroup	**Median (Interquartile Range) Cases without Pulmonary Complications**	**Median (Interquartile range) Cases with Pulmonary Complications**
Surgical procedure relative value units	17.28 (11.35–23.53)	23.53 (17.31–29.40)
Time (min) between last NMBA dose and extubation	85 (58–131)	81 (59–125)

Characterization of the study cohort as defined by all covariates. Values given as frequencies (%) unless stated otherwise.

ASA = American Society of Anesthesiologists; ED95 = median dose required per body weight to achieve 95% reduction in maximal twitch response from baseline in 50% of the population; NMBA = neuromuscular-blocking agent; SPORC score = score for preoperative prediction of adverse postoperative respiratory outcomes.

Statistical Analysis

A hypothesis-driven approach was used to build our regression models, and we included all potential confounders based on *a priori* clinical and pathophysiological knowledge. We performed logistic regression analysis with the use of SPSS version 22 (IBM, USA), STATA version 13 (StataCorp, USA), and SAS version 9.2 (SAS Institute, USA). Results are presented as odds ratios (ORs) with 95% CIs. We considered a two-tailed *P* value of less than 0.05 to be statistically significant.

For our primary analysis, we performed logistic regression analysis to examine the association between dose of intermediate-acting NMBAs and risk of adverse respiratory events (respiratory failure, pulmonary edema, tracheal reintubation, and pneumonia) within the first 3 days after surgery. We calculated a *P* value for trend across intermediate-acting NMBA dosages by using the Wald test. As listed in appendix 2, we included neostigmine dose, age, sex, body mass index, American Society of Anesthesiologists classification, procedure duration, all Charlson Comorbidity Index variables, all SPORC score variables, depth of anesthesia (age-corrected minimum alveolar concentration), norepinephrine equivalent dose per hour, surgical body region, surgical procedure relative value units, admission type (inpatient/ambulatory), emergency surgery status, transfused blood units, total fluid resuscitation volume, morphine equivalent dose, number of hypotensive minutes, and use of TOF monitoring for confounder control in our model. Our dose calculations were based on ideal body weight due to the hydrophilic nature of NMBAs. For clinical applicability, we performed further analysis with categorized NMBA dosages in quintiles by using the same model, enabling us to illustrate the doses that were associated with a high OR for respiratory complications.

To address potential unidentified confounding effects of surgery type, we repeated our primary analysis on a subset of subjects who had laparoscopic cholecystectomies. We chose this common upper abdominal surgical procedure because the incidence of respiratory complications is relatively high.[26] In this logistic regression, we only included neostigmine dose, age, sex, body mass index, American Society of Anesthesiologists classification, and morphine equivalent dose for confounder control to avoid a type II error caused by a lower sample size. To account for the potential confounding effect of multiple surgeries, we repeated our primary analysis after excluding all cases with any repeat surgery within the 5-yr time window that our data was collected by using a logistic regression with the same confounder control model as for the full dataset.

For our secondary analysis, we performed logistic regression analysis to examine the dose-dependent association between the use of neostigmine and risk of postoperative respiratory complications within the first 3 days after surgery. We then examined the risk of postoperative respiratory complications as a function of the dose of reversal agent. For both regressions, we used the same confounder control as for the primary model, including NMBA dose. We calculated a *P* value for trend across neostigmine dose categories by using the Wald test and categorized neostigmine dosages for further analysis and clinical applicability.

All other comparisons were made with an exploratory intention. To identify whether the risk of postoperative respiratory complications is affected by administration according to TOF monitoring, we repeated our primary analysis in a subset of patients who received neostigmine after a minimum TOF count of 2. To identify whether a combination of optimized neostigmine dose, and use of twitch monitoring can eliminate the dose-dependent effects of NMBAs on respiratory complications, we repeated our primary and secondary analyses in a subset of

cases where neostigmine was given after a TOF count of 2 or greater and at doses 60 μg/kg or less. The definition of optimized neostigmine dose was based on the results of a recently published study[27] and our exploratory analysis. We additionally categorized our full patient population to reflect appropriate reversal (neostigmine ≤60 μg/kg given at a TOF count of ≥2), inappropriate reversal (neostigmine >60 μg/kg or neostigmine ≤60 μg/kg given without TOF monitoring indicating recovery of TOF count to 2 before neostigmine administration), and no reversal and ran a logistic regression with the same confounder control as for our primary and secondary analyses.

Results

Table 1 shows the characteristics of our study cohort. Between January 2007 and September 2012, a total of 72,158 surgical cases met the inclusion criteria of this study, and after excluding cases with missing data (n = 23,659), 48,499 cases were included in the analysis. The stepwise exclusion from collected data to our final dataset for analysis is demonstrated in figure 1. Of the intermediate-acting NMBAs administered, 46.0% were benzylisoquinoline NMBAs and 54.0% were aminosteroidal NMBAs. Neostigmine was administered in 74.0% of the cases, and subjective assessment of evoked TOF count in response to TOF stimulation was used in 71.2% of cases. Of the 48,499 cases included in the analysis, 1,812 cases (3.7) experienced postoperative respiratory complications, 1,211 (2.5%) experienced pulmonary edema, 627 (1.3%) experienced respiratory failure, 333 (0.7%) experienced pneumonia, and 123 (0.3%) were reintubated within the first 3 postoperative days. A total of 392 patients (0.8%) had more than one respiratory complication.

Primary Analysis

Logistic regression analysis revealed a higher risk of postoperative respiratory complications with administration of higher doses of intermediate-acting nondepolarizing NMBAs (composite respiratory outcome, highest quintile *vs.* lowest quintile: OR, 1.28; 95% CI, 1.04 to 1.57; $P = 0.02$; fig. 2). Dose–response function across NMBA doses revealed a P value for trend of 0.005 (relative risk increase per ED95 increase: OR, 1.024; 95% CI, 1.007 to 1.041). ORs for individual respiratory outcomes are shown in table 2. All

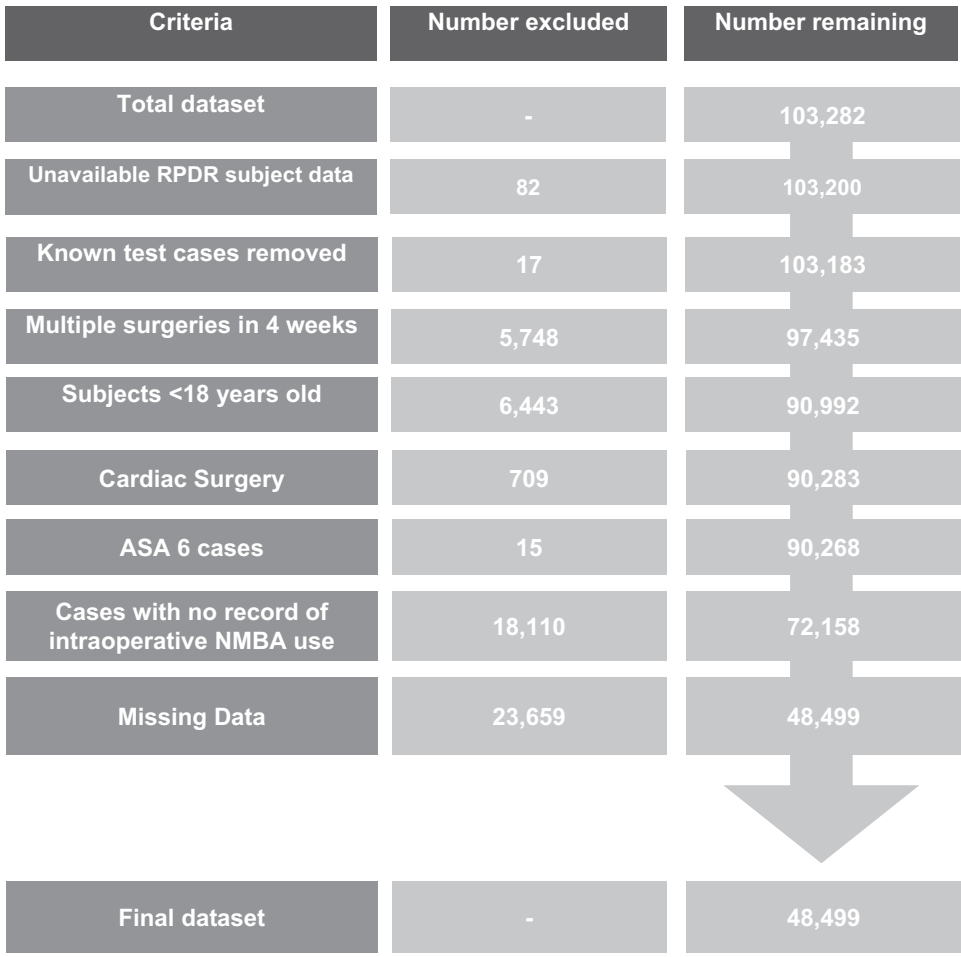

Fig. 1. Stepwise exclusion of data from initial dataset to dataset used for all analyses. ASA = American Society of Anesthesiologists; NMBA = neuromuscular-blocking agent; RPDR = Research Patient Data Registry.

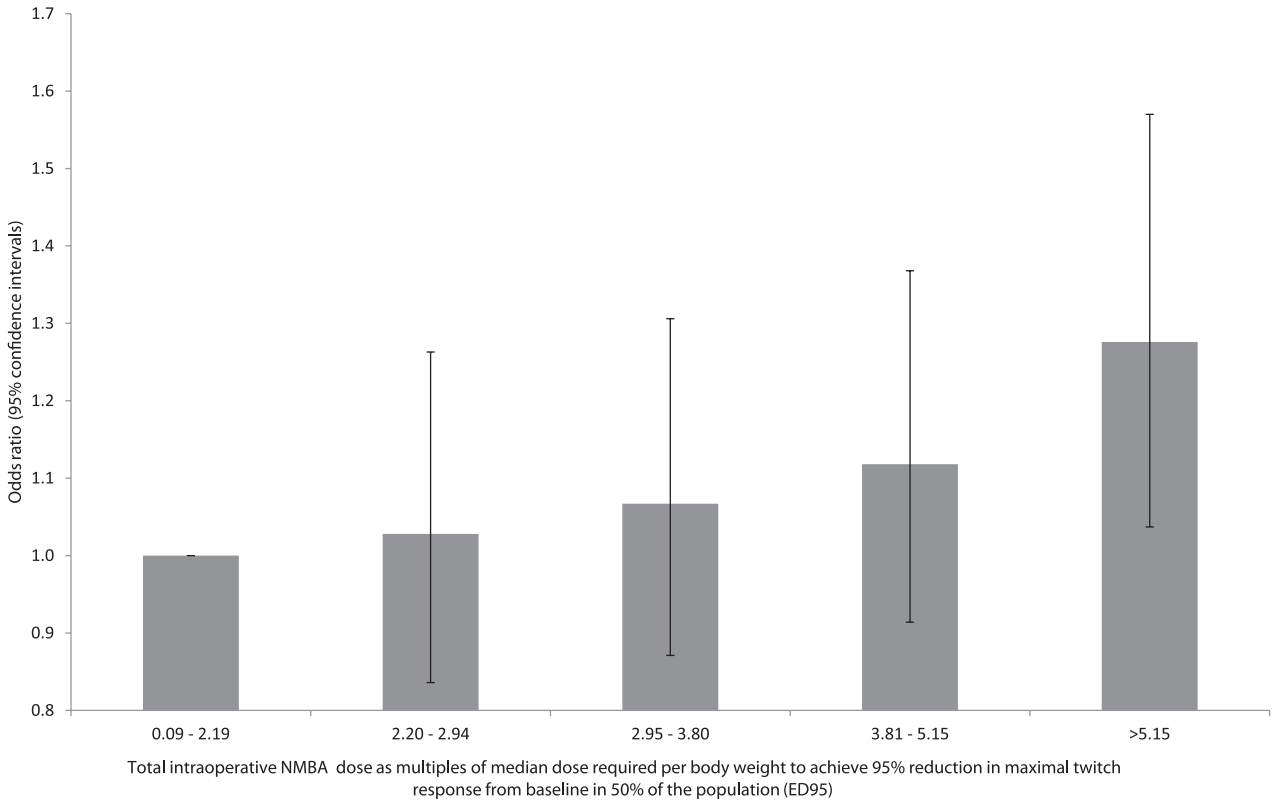

Fig. 2. Association between neuromuscular-blocking agent (NMBA) dose and postoperative respiratory complications. NMBA dose shown as multiples of the median dose required per body weight to achieve 95% reduction in maximal twitch response from baseline in 50% of the population (ED95) categorized by quintile. Effect size displayed as odds ratio with 95% CIs.

variables used in the primary analysis were forced into the regression model and were categorized as shown in table 1.

To control for the potential confounding effect of surgery type, we ran a sensitivity analysis on patients who had a laparoscopic cholecystectomy (n = 1,806). Within this set of cases, the positive association between high-dose intermediate-acting NMBAs and postoperative respiratory complications within 3 days after surgery was significant (highest quintile *vs.* lowest quintile OR, 3.42; 95% CI, 1.01 to 11.57; $P = 0.048$). In our total dataset, 5,748 patients had multiple surgeries within 4 weeks. We removed these cases from the analysis database to minimize the confounding effects. To eliminate the additional confounding effect of multiple surgeries within 5 yr, we performed an additional sensitivity analysis after excluding these cases (n = 9,080). However, NMBA dose was still associated with postoperative respiratory complications (composite

Table 2. Primary Analysis: Association between Use of Intermediate-acting NMBAs and Postoperative Respiratory Complications

NMBA Dose Quintiles as Multiple of ED95	0.09–2.19 (n = 10,088)	2.20–2.94 (n = 9,712)	2.95–3.80 (n = 9,639)	3.81–5.15 (n = 9,501)	>5.15 (n = 9,559)	Odds Ratio Highest *vs.* Lowest Quintiles (95% CIs)
Postoperative respiratory complications	205 (2.0%)	256 (2.6%)	310 (3.2%)	397 (4.2%)	644 (6.7%)	1.28 (1.04–1.57) *P* for trend = 0.005
Breakdown of composite respiratory outcome						
Pulmonary edema	141 (1.4%)	180 (1.9%)	206 (2.1%)	252 (2.7%)	432 (4.5%)	1.20 (0.93–1.54)
Respiratory failure	49 (0.5%)	74 (0.8%)	92 (1.0%)	135 (1.4%)	277 (2.9%)	1.52 (1.06–2.19)
Pneumonia	44 (0.4%)	54 (0.6%)	67 (0.7%)	81 (0.9%)	87 (0.9%)	1.28 (0.82–2.01)
Reintubation	11 (0.1%)	18 (0.2%)	12 (0.1%)	34 (9.4%)	48 (0.5%)	1.29 (0.60–2.75)

Incidences are displayed as frequency (%), and estimated effects are displayed as odds ratios with 95% CIs. For NMBA dose, the value displayed is for the comparison of high dose (fifth quintile) with low dose (first quintile). The following covariates were included in the model: neostigmine dose, age, sex, body mass index, American Society of Anesthesiologists classification, procedure duration, Charlson Comorbidity Index variables, score for prediction of respiratory complications variables, depth of anesthesia (age-corrected minimum alveolar concentration), norepinephrine equivalent dose per hour, surgical body region, surgical procedure relative value units, admission type (in-patient/ambulatory), emergency surgery status, transfused blood units, total fluid resuscitation volume, morphine equivalent dose, number of hypotensive minutes during the case, and documentation of any train-of-four monitoring.

ED95 = median dose required per body weight to achieve 95% reduction in maximal twitch response from baseline in 50% of the population; NMBA = neuromuscular-blocking agent.

respiratory outcome, highest quintile *vs.* lowest quintile OR, 1.38; 95% CI, 1.09 to 1.76; $P = 0.008$).

There was no significant difference in association of benzylisoquinolines on respiratory complications in comparison with aminosteroidal NMBAs (composite respiratory outcome: OR, 1.12; 95% CI, 0.99 to 1.26; $P = 0.08$).

Secondary Analysis

Administration of neostigmine was associated with an increased risk of postoperative respiratory complications (composite respiratory outcome, neostigmine *vs.* no neostigmine: OR, 1.19; 95% CI, 1.03 to 1.37; $P = 0.017$) in a dose-dependent manner (P for trend <0.001). Doses of neostigmine greater than 60 μg/kg were associated with an increased risk of postoperative respiratory complications (composite respiratory outcome: 61 to 80 μg/kg and >80 μg/kg *vs.* <20 μg/kg neostigmine; OR, 1.20; 95% CI, 1.01 to 1.43; $P = 0.034$; and OR, 1.51; 95% CI, 1.25 to 1.83; P <0.001, respectively). Individual results are presented in table 3. When including an interaction term between NMBA dose and neostigmine dose, logistic regression analysis demonstrated a positive interaction effect (OR, 1.70; 95% CI, 1.27 to 2.26; P <0.001), indicating that the association between neostigmine dose and postoperative respiratory complications is stronger in cases where higher doses of NMBAs are administered.

Exploratory Analysis

Appropriate neostigmine reversal has been previously defined as administration after recovery to a TOF count of 2 or greater.[27,28] Based on the results from our secondary analysis, we refined this definition as neostigmine administration at doses 60 μg/kg or less after TOF count of 2 or greater. Appropriate use of neostigmine for NMBA reversal was associated with a decrease in risk for postoperative pulmonary complications (appropriate neostigmine use *vs.* inappropriate neostigmine use: OR, 0.79; 95% CI, 0.69 to 0.92; $P = 0.002$). In the cases with appropriate neostigmine reversal, total NMBA dose given during surgery no longer predicted the risk of postoperative respiratory complications (composite respiratory outcome, highest *vs.* lowest quintile of NMBA dose: OR, 0.98; 95% CIs, 0.63 to 1.52; $P = 0.94$). In cases where the criterion of appropriate neostigmine administration was not met, high NMBA dose remained associated with a dose-dependent increasing risk of postoperative respiratory complications (composite respiratory outcome, highest *vs.* lowest quintile of NMBA dose: OR, 1.41; 95% CI, 1.11 to 1.79; $P = 0.005$; table 4). Of note, in all cases where neostigmine was administrated at a TOF count of 2 or greater (not taking into account neostigmine dose), high NMBA dose remained associated with a dose-dependent increasing risk of postoperative respiratory complications (composite respiratory outcome, highest *vs.* lowest quintile of NMBA dose: OR, 1.70; 95% CI, 1.26 to 2.28; P <0.001).

Table 3. Secondary Analysis: Association between Use of Neostigmine and Postoperative Respiratory Complications

	Patients, No. (%)	Patients with Respiratory Complications, No. (%)	Comparison with No Neostigmine Administration
Patients who received neostigmine	35,897 (74.0%)	1,478 (4.1%)	1.19 (1.03–1.37)
Patients who did not receive neostigmine	12,602 (26.0%)	334 (2.7%)	Not applicable
Dose–response, mg/kg			
<0.02	1,407 (3.9%)	38 (2.7%)	0.97 (0.67–1.40)
0.02–0.04	7,623 (21.2%)	233 (3.1%)	1.05 (0.87–1.27)
0.041–0.06	11,455 (31.9%)	386 (3.4%)	1.09 (0.92–1.30)
0.061–0.08	9,698 (27.0%)	482 (5.0%)	1.20 (1.01–1.42)
>0.08	5,720 (15.9%)	339 (5.9%)	1.51 (1.25–1.83)

Numbers of patients in each category are displayed as frequency (%). Incidences are displayed as frequency (%), and estimated effects are displayed as odds ratios with 95% CIs. The following covariates were included in the model: neuromuscular-blocking agent dose, age, sex, body mass index, American Society of Anesthesiologists classification, procedure duration, Charlson Comorbidity Index variables, score for prediction of respiratory complications variables, depth of anesthesia (age-corrected minimum alveolar concentration), norepinephrine equivalent dose per hour, surgical body region, surgical procedure relative value units, admission type (in-patient/ambulatory), emergency surgery status, transfused blood units, total fluid resuscitation volume, morphine equivalent dose, number of hypotensive minutes during the case, and documentation of any train-of-four monitoring.

Discussion

In this large, single-center study, we show a dose-dependent association between intermediate-acting NMBAs and postoperative respiratory complications. This increased risk in respiratory complications occurs irrespective of the class of NMBA used (benzylisoquinolines or aminosteroidal NMBAs). Neostigmine was associated with a dose-dependent increase in the risk of postoperative respiratory complications. Appropriate neostigmine reversal (doses of ≤60 μg/kg given after recovery of the second TOF twitch) may be sufficient to eliminate the dose-dependent increasing risk of postoperative respiratory outcome, due to NMBAs.

Association between NMBAs and Postoperative Respiratory Complications

Intermediate-acting NMBAs have long been considered to have a safer side effect profile compared with the long-acting NMBA, pancuronium.[29] Despite the transition in clinical practice during the past few decades to the use of intermediate-acting NMBAs, studies continue to show that these drugs are associated with postoperative residual paralysis and associated signs and symptoms of postoperative respiratory failure.[10,14,30–37] The potential causes of postoperative respiratory complications are complex and multifactorial.[13] Underlying comorbidities, intraoperative mechanical ventilation,[38] surgical trauma,[39] fluid resuscitation,[40] and drugs used in anesthesia,[14] all contribute to the risk of respiratory complications.[13] Our data show that high total NMBA doses increase the incidence of postoperative respiratory complications (OR, 1.28; 95% CI, 1.04 to 1.57; $P = 0.02$), probably as a result of residual blockade.[41–46]

Table 4. Exploratory Analysis: Association between NMBA Dose and Risk of Postoperative Respiratory Complications

	Appropriate Reversal (n = 13,799)		Inappropriate Reversal (n = 34,700)	
NMBA Dose (Multiples ED95)	Postoperative Respiratory Complications, n (%)	Effect Size	Postoperative Respiratory Complications, n (%)	Effect Size
0.09–2.19	55 (0.39%)	n/a	150 (0.43%)	Not applicable
2.20–2.94	62 (0.45%)	1.04 (0.69–1.56)	194 (0.56%)	1.03 (0.81–1.31)
2.95–3.80	83 (0.60%)	1.16 (0.77–1.73)	227 (0.65%)	1.06 (0.84–1.34)
3.81–5.15	87 (0.63%)	0.95 (0.62–1.44)	310 (0.89%)	1.20 (0.95–1.52)
>5.15	126 (0.91%)	0.98 (0.63–1.52)	518 (1.49%)	1.41 (1.11–1.79)

Comparison between cases with appropriate (neostigmine ≤60 μg/kg at a minimum of train-of-four count of 2) *vs.* inappropriate (no neostigmine administration or neostigmine administration not guided by train-of-four count or doses >60 μg/kg) reversal of neuromuscular blockade by an NMBA. Incidences are displayed as frequency (%), and estimated effects are displayed as odds ratios with 95% CIs. The following covariates were included in the model: NMBA dose, age, sex, body mass index, American Society of Anesthesiologists classification, procedure duration, Charlson Comorbidity Index variables, score for prediction of respiratory complications variables, depth of anesthesia (age-corrected minimum alveolar concentration), norepinephrine equivalent dose per hour, surgical body region, surgical procedure relative value units, admission type (in-patient/ambulatory), emergency surgery status, transfused blood units, total fluid resuscitation volume, morphine equivalent dose, number of hypotensive minutes during the case, and documentation of any train-of-four monitoring.

ED95 = median dose required per body weight to achieve 95% reduction in maximal twitch response from baseline in 50% of the population; NMBA = neuromuscular-blocking agent.

Repeated administration of NMBAs leads to a prolonged duration of action, as defined by the time between administration of NMBA and recovery to a TOF ratio greater than or equal to 0.9,[10–12] a fact that may not always be taken into account by clinicians. This does not mean that higher individual doses of NMBAs, either by administration of a large individual dose or by repeated administration of smaller dosages, are not safe when clinically indicated, but rather that judicious use of these drugs should be advocated in the interest of patient safety.[47,48]

Neuromuscular Transmission Monitoring and Residual Paralysis

In our cohort, 1,426 providers (2.9%) administered NMBAs during the last 30 min of the case, which probably translates to residual neuromuscular block at the end of the case. Residual paralysis has been reported to occur in 20 to 45% of cases in which NMBAs are used.[10] Objective quantitative monitoring of neuromuscular transmission is the only reliable method to exclude residual neuromuscular blockade; however, qualitative, visual, or tactile TOF monitoring is more widespread.[28,49] Despite the growing body of literature to support the use of neuromuscular transmission monitoring, this practice is not consistently used by anesthesia providers.[49,50] Two recent surveys of anesthesiologists reported that neuromuscular transmission monitoring was only used routinely by 17 to 50% of anesthesia providers.[51,52] In our department, 34,508 of 48,499 anesthesia providers (71.15%) used subjective assessment of the evoked TOF count in response to TOF stimulation. Our data show that the documentation of a TOF count alone does not decrease the dose-dependent risk of respiratory complications associated with NMBAs.

Desirable Patterns of Neostigmine Reversal to Increase Respiratory Safety

Post hoc, we defined, based on our data and a previous report,[27,28] appropriate neostigmine use as neostigmine administration at a visual or tactile evaluated TOF count of 2 or greater at doses less than 60 μg/kg. When neostigmine was administered at a TOF count of 2 or greater and at doses 60 μg/kg or less, NMBA dose was not a significant predictor of respiratory complications (highest *vs.* lowest NMBA dose: OR, 0.98; 95% CI, 0.63 to 1.52; $P = 0.94$). These exploratory findings suggest that the use of TOF monitoring in tandem with neostigmine administration at doses 60 μg/kg or less is a viable strategy to decrease the incidence of NMBA-induced respiratory complications.

In our study, high doses of the acetylcholinesterase inhibitor neostigmine (>60 μg/kg), intended to reverse the effects of NMBAs, increased the risk of respiratory complications independent of NMBA effects. These doses are in the upper range of recommended neostigmine dosing.[53] We speculate based on our data that neostigmine-induced partial neuromuscular transmission block may explain adverse respiratory outcomes in patients who received high-dose neostigmine after recovery of neuromuscular transmission. Based on our results, we believe that anesthesia providers at our institution administer higher doses of neostigmine in an attempt to reverse deeper neuromuscular blockade. We observed a positive interaction effect between total NMBA dose and total neostigmine dose (OR, 1.70; 95% CI, 1.27 to 2.26; $P < 0.001$), indicating that the relation between neostigmine dose and postoperative respiratory complications becomes stronger in cases where higher total doses of NMBAs are given. Our data complement the findings of a recently published observational study, which demonstrated that high-dose neostigmine (>60 μg/kg) resulted in longer time to discharge from the postanesthesia care unit and longer postoperative hospital length of stay.[28] Neostigmine does not reverse deep neuromuscular blockade[10,54–56] and should not be given to patients who present with deep neuromuscular blockade[55–57] because it can result in incomplete reversal. Furthermore, it may lead to anesthesia providers falsely believing their patients to have safe return of muscular function.

Benzylisoquinoline versus *Aminosteroidal NMBAs*

Previous data indicate reduced variability in the time to recovery with benzylisoquinoline NMBAs compared with aminosteroidal NMBAs.[10] Therefore, we evaluated the differential effects of benzylisoquinoline *versus* aminosteroidal NMBAs on our primary outcome measure. We did not find any significant difference between the use of either pharmacological groups and the risk of postoperative respiratory outcomes, despite lower variability in duration of action of benzylisoquinolines compared with steroids.[10]

Clinical Implications

Our data support the view that all patients receiving neuromuscular-blocking drugs should have assessment of the block intensity during the intraoperative period and particularly before tracheal extubation. Clinical signs (*e.g.*, head lift, hand grip, *etc.*) have been shown to be very insensitive indicators of residual block and are not applicable in the anesthetized patient. Intraoperative neuromuscular function should be evaluated by observing the mechanical response to peripheral nerve stimulation whenever a nondepolarizing relaxant is administered. At a minimum, this requires qualitative assessment of the TOF and/or posttetanic count (*e.g.*, visual and tactile observations) in all subjects. However, subjective evaluation of the TOF fade is subject to considerable error. Thus, quantitative monitoring of the depth of neuromuscular block is the preferred method of evaluating residual block.[48]

Our data also support the view that neostigmine dose should be selected based on twitch monitoring results, and we have published a regimen describing on how to titrate neostigmine based on TOF monitoring results.[58]

Limitations

Despite our thorough confounder control, residual confounding is possible as our data are observational. To minimize the confounding effects of surgical complexity, we performed the same analyses on the subgroup of patients undergoing laparoscopic cholecystectomy. In this homogenous subset of patients undergoing similar perioperative course and interventions, we found that our results were reproducible with NMBAs being associated with an increased risk of postoperative respiratory complications (OR, 3.42; 95% CI, 1.01 to 11.57; $P = 0.048$). We also assessed whether removing subjects who had multiple surgeries within the past 5 yr would affect our results. In this sensitivity analysis, an association remained between NMBA dose and postoperative respiratory complications (highest quintile *vs.* lowest quintile: OR, 1.38; 95% CI, 1.09 to 1.76; $P = 0.008$). To identify patients with endotracheal reintubation within the first 3 days after surgery, we included only patients whose tracheas were extubated in the operating room. This may have introduced a selection bias.

The use of NMBAs was dose dependently associated with increased risk of postoperative respiratory complications. Neostigmine reversal was also associated with a dose-dependent increase in the risk of respiratory complications. However, our exploratory data analysis suggests that the proper use of neostigmine guided by neuromuscular transmission monitoring results can help eliminate postoperative respiratory complications associated with the use of NMBAs.

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Competing Interests

Dr. Eikermann received funding for investigator-initiated research from Merck, Whitehouse Station, New Jersey, and from Massimo, Irvine, California. Dr. Eikermann has filed a patent application for a new drug to reverse the effects of neuromuscular-blocking agents. The other authors declare no competing interests.

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Appendix 1.

ICD-9 and CPT Codes Used to Define Pulmonary Outcomes

Pulmonary Outcome	Description	ICD-9/CPT (American Medical Association, USA)	Code
Respiratory failure	Pulmonary insufficiency after trauma and surgery	ICD-9	518.5
	Acute respiratory failure after trauma and surgery	ICD-9	518.51
	Other pulmonary insufficiency, not elsewhere classified, after trauma and surgery	ICD-9	518.52
	Respiratory failure	ICD-9	518.81
	Other pulmonary insufficiency, not elsewhere classified	ICD-9	518.82
	Acute and chronic respiratory failure	ICD-9	518.84
Pulmonary edema	Pulmonary congestion and hypostasis	ICD-9	514
	Acute edema of lung, unspecified	ICD-9	518.4
	Congestive heart failure	ICD-9	428.0
	Fluid overload	ICD-9	276.6
	Other fluid overload	ICD-9	276.69
Tracheal reintubation	Intubation, endotracheal, emergency procedure	CPT (AMA, Chicago, IL)	31500
	Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing; hospital inpatient/observation, initial day	CPT (AMA, Chicago, IL)	94002
Pneumonia	Pneumococcal pneumonia (*Streptococcus pneumoniae* pneumonia)	ICD-9	481
	Pneumonia due to *Klebsiella pneumonia*	ICD-9	482.0
	Pneumonia due to *Pseudomonas*	ICD-9	482.1
	Pneumonia due to *Streptococcus*, unspecified	ICD-9	482.30
	Pneumonia due to *Staphylococcus*, unspecified	ICD-9	482.40
	Pneumonia due to *Staphylococcus aureus*	ICD-9	482.41
	Methicillin-resistant pneumonia due to *Staphylococcus aureus*	ICD-9	482.42
	Pneumonia due to *Escherichia coli*	ICD-9	482.82
	Pneumonia due to other Gram-negative bacteria	ICD-9	482.83
	Pneumonia due to other specified bacteria	ICD-9	482.89
	Bacterial pneumonia, unspecified	ICD-9	482.9
	Pneumonia, organism unspecified	ICD-9	486
	Pneumonia due to other specified organism	ICD-9	483.8
	Pneumonia in aspergillosis	ICD-9	484.6
	Bronchopneumonia, organism unspecified	ICD-9	485
	Pneumonitis due to inhalation of food or vomitus	ICD-9	507.0

AMA = American Medical Association; CPT = Current Procedural Terminology; ICD-9 = *International Classification of Diseases, Ninth Revision*.

Appendix 2.

Control Variables Included in Regression Analyses

Variables	Primary Analysis	Secondary Analysis	Laparoscopic Cholecystectomies	Multiple Surgeries Excluded	Appropriate Neostigmine Analysis
NMBA dose as multiples of ED95	X				
NMBA dose as multiples of ED95 (quintiles)		X	X	X	X
Neostigmine dose (mg/kg ideal body weight)	X	X	X	X	X
Age	X	X	X	X	X
Sex	X	X	X	X	X
Body mass index	X	X	X	X	X
ASA classification	X	X	X	X	X
Procedure duration	X	X		X	X
Charlson Comorbidity Index	X	X		X	X
SPORC score	X	X		X	X
Depth of anesthesia (age-corrected MAC in quintiles)	X	X		X	X
Norepinephrine equivalent dose per hour (quintiles)	X	X		X	X
Surgical body region	X	X		X	X
Surgical procedure relative value units	X	X		X	X
Admission type (in-patient/ambulatory)	X	X		X	X
Emergency surgery status	X	X		X	X
Units of blood transfused	X	X		X	X
Total fluid resuscitation volume (quintiles)	X	X		X	X
Morphine equivalent dose (quintiles)	X	X	X	X	X
Number of hypotensive minutes	X	X		X	X
Use of train-of-four monitoring	X	X		X	X

ASA = American Society of Anesthesiologist; ED95 = median dose required per body weight to achieve 95% reduction in maximal twitch response from baseline in 50% of the population; MAC = minimum alveolar concentration; NMBA = neuromuscular-blocking agent; SPORC = score for preoperative prediction of adverse postoperative respiratory outcomes.