

# Residual Neuromuscular Blockade and Critical Respiratory Events in the Postanesthesia Care Unit

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**BACKGROUND:** Incomplete recovery of neuromuscular function may impair pulmonary and upper airway function and contribute to adverse respiratory events in the postanesthesia care unit (PACU). The aim of this investigation was to assess and quantify the severity of neuromuscular blockade in patients with signs or symptoms of critical respiratory events (CREs) in the PACU.

**METHODS:** We collected data over a 1-yr period. PACU nurses identified patients with evidence of a predefined CRE during the first 15 min of PACU admission. Train-of-four (TOF) ratios were immediately quantified in these patients using acceleromyography (cases). TOF data were also collected in a control group that consisted of patients undergoing a general anesthetic during the same period who were matched with the cases by age, sex, and surgical procedure.

**RESULTS:** A total of 7459 patients received a general anesthetic during the 1-yr period, of whom 61 developed a CRE. Forty-two of these cases were matched with controls and constituted the study group for statistical analysis. The most common CREs among matched cases were severe hypoxemia (22 of 42 patients; 52.4%) and upper airway obstruction (15 of 42 patients; 35.7%). There were no significant differences between the cases and matched controls in any measured preoperative or intraoperative variables. Mean ( $\pm$ SD) TOF ratios were 0.62 ( $\pm$ 0.20) in the cases, with 73.8% of the cases having TOF ratios  $<0.70$ . In contrast, TOF values in the controls were 0.98 ( $\pm$ 0.07) (a difference of  $-0.36$  with a 95% confidence interval of  $-0.43$  to  $-0.30$ ,  $P < 0.0001$ ), and no control patients were observed to have TOF values  $<0.70$  (the 95% confidence interval of the difference was 59%–85%,  $P < 0.0001$ ).

**CONCLUSIONS:** A high incidence of severe residual blockade was observed in patients with CREs, which was absent in control patients without CREs. These findings suggest that incomplete neuromuscular recovery is an important contributing factor in the development of adverse respiratory events in the PACU.

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Residual neuromuscular blockade is commonly observed in the postanesthesia care unit (PACU) when neuromuscular blocking drugs (NMBDs) are administered intraoperatively. Despite the application of techniques proven to limit the degree of residual paralysis (i.e., use of intermediate-acting NMBDs and pharmacological reversal), up to 33%–64% of patients have evidence of inadequate neuromuscular recovery on arrival to the PACU.<sup>1–3</sup> The clinical significance of residual neuromuscular blockade is less well documented. Studies in volunteers have demonstrated that train-of-four (TOF) fade ratios  $<0.70$ – $0.90$  are associated with upper airway obstruction,<sup>4</sup> inadequate recovery of pulmonary function,<sup>4</sup> reduced pharyngeal

muscle coordination, an increased risk for aspiration,<sup>5,6</sup> and an impaired hypoxic ventilatory response.<sup>7,8</sup> Although the adverse physiological effects of small degrees of residual paresis have been established clearly in the laboratory, the impact of incomplete neuromuscular recovery on adverse outcomes in the postoperative setting has been poorly defined. In the only randomized large-scale study assessing the risks of residual blockade, Berg et al. observed that patients with TOF ratios  $<0.7$  in the PACU after the use of pancuronium had a significantly increased risk of postoperative respiratory complications.<sup>9</sup>

Critical respiratory events (CREs) during early recovery from general anesthesia are not uncommon and large prospective observational studies have noted an incidence of adverse respiratory events of 1.3%–6.9% during the PACU admission.<sup>10–12</sup> Although numerous anesthetic management factors play a primary role in the development of early postoperative CREs,<sup>11–14</sup> the specific role of residual paralysis in the development of postoperative respiratory morbidity is uncertain. As stated in one editorial, “There are no outcome data to substantiate the position that patients who arrive in the in the postanesthesia care unit with TOF ratios of 0.5

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experience more adverse events than did those who have recovered to values  $>0.80-0.90$ .<sup>15</sup>

Acceleromyography monitoring, which allows clinicians to accurately quantify small degrees of residual blockade, has been used as a routine monitor to assess patients for evidence of incomplete neuromuscular recovery in the PACU.<sup>16</sup> The aim of this investigation was to determine the incidence of CREs in the PACU after general anesthesia and to examine the association between CREs and residual neuromuscular blockade. We hypothesized that the patients with evidence of severe respiratory impairment in the PACU (cases) would exhibit a higher incidence of severe residual neuromuscular blockade (TOF ratio  $<0.70$ ) than similar matched patients without CREs in the PACU (controls).

## METHODS

This protocol was conducted as a quality assurance project and considered to be part of routine clinical care at that time. Therefore, the study was reviewed and approved as a quality assurance project by the Evanston Northwestern Healthcare IRB and informed consent was not required.

*Study population and data collection:* Given the relatively infrequent occurrence of CREs in the PACU, a case-control study design with prospectively defined cases was performed. All cases during the study period with the outcome of interest (CREs) were identified and then matched with selected control patients for comparison. Cases were identified by collecting data on all consecutive patients arriving in the PACU between the hours of 7:00 AM and 7:00 PM, Monday through Friday, over a 1-yr period (June 10, 2005 to June 10, 2006). Controls were identified among PACU patients at the same times over the same period.

The cases consisted of all patients who received a general anesthetic and who exhibited signs or symptoms of a CRE during the first 15 min of PACU admission. All CREs were identified by the PACU nursing staff. PACU nurses were provided with a series of lectures about the objectives of the quality assurance project and the respiratory outcomes of interest to be identified. Lectures were provided in a group setting and with each nurse before commencing data collection. In addition, weekly meetings with the PACU nursing supervisor were performed to review data collection. A color coded, standardized data collection sheet using a check-box format with the patients' age, sex, type of surgical procedure, and type of CRE was completed for each patient receiving an anesthetic. This quality assessment form was included with each anesthetic record and was considered mandatory documentation by anesthesia providers and PACU nurses. Each CRE was defined on the data collection sheet using the following criteria:

1. Upper airway obstruction requiring an intervention (jaw thrust, oral airway, or nasal airway);

2. Mild-moderate hypoxemia [ $\text{O}_2$  saturations ( $\text{SpO}_2$ ) of 93%–90%] on 3 L nasal cannula  $\text{O}_2$  that was not improved after active interventions (increasing  $\text{O}_2$  flows to  $>3$  L/min, application of high-flow face mask  $\text{O}_2$ , verbal requests to breathe deeply, tactile stimulation);
3. Severe hypoxemia ( $\text{SpO}_2 <90\%$ ) on 3 L nasal cannula  $\text{O}_2$  that was not improved after active interventions (increasing  $\text{O}_2$  flows to  $>3$  L/min, application of high-flow facemask  $\text{O}_2$ , verbal requests to breathe deeply, tactile stimulation);
4. Signs of respiratory distress or impending ventilatory failure (respiratory rate  $>20$  breaths per minute, accessory muscle use, tracheal tug);
5. Inability to breathe deeply when requested to by the PACU nurse;
6. Patient complaining of symptoms of respiratory or upper airway muscle weakness (difficulty breathing, swallowing, or speaking);
7. Patient requiring reintubation in the PACU; and
8. Clinical evidence or suspicion of pulmonary aspiration after tracheal extubation (gastric contents observed in the oropharynx and hypoxemia).

PACU nurses were instructed to review the checklist on each patient during the first 15 min of the PACU admission and to contact a study investigator without delay if a CRE was observed. One of three study investigators then examined the patient to confirm that the patient met at least one of the criteria for a CRE. If signs or symptoms of a CRE were verified and a review of the anesthesia record established that the patient had received a general anesthetic, TOF fade ratios were immediately measured.

TOF ratios were quantified using acceleromyography (TOF-Watch SX<sup>®</sup>; Organon, Roseland, NJ). Two surface electrodes were placed on cleaned skin over the ulnar nerve at the wrist. The acceleration transducer was attached to the volar aspect of the distal phalanx of the thumb via a hand adapter that also applied a constant preload to the thumb (TOF-Watch Handadapter<sup>®</sup>; Organon). The evoked response of the thumb was measured after TOF stimulation (4 pulses of 0.2 ms duration over 2 s at a frequency of 2 Hz). The current intensity was 50 mA in all subjects. Two consecutive TOF measurements (separated by 15 s) were obtained, and the average of the 2 values recorded. If measurements differed by more than 10%, additional TOF measurements were obtained (up to 4 TOF values), and the closest 2 ratios were averaged. TOF values were measured before any narcotics were administered in the PACU and recorded on the data collection sheet.

Patients were categorized into 1 of 3 groups on the basis of TOF data; TOF ratios  $>0.9$  were assessed as acceptable neuromuscular recovery, TOF ratios between 0.9 and 0.7 were considered mild to moderate blockade, and TOF ratios  $<0.7$  were classified as severe neuromuscular blockade (postoperative TOF

ratio associated with an increased risk of respiratory complications).<sup>9</sup> All TOF measurements were obtained by investigators with more than two years of experience with acceleromyography monitoring.

To have a comparison group of cases that underwent general anesthesia but did not develop a CRE in the PACU, each case with a CRE was matched with a control patient. The controls consisted of patients undergoing a general anesthetic with NMBDs during the same period as the cases who were matched with the cases by age, sex, and surgical procedure. As soon as a case was identified, the patient's age, sex, and surgical procedure were entered into a database. Operating room schedules were reviewed at 6:15 AM each morning by one of two primary investigators to identify potential control patients by comparing the age, sex, and procedure of patients undergoing surgery that day with cases entered into the database. TOF data were collected on the first patient identified as a control beginning on the day after identification of each case.

Once a control was identified, PACU nurses were instructed to contact one of the investigators as soon as the patient arrived in the PACU. Anesthesia care providers were not notified that the patient was involved in the study (i.e., anesthesia care providers were blinded to the patient selection as a matched control). Within the first 15 min of the PACU admission, the control patient was examined by the PACU nurse and an investigator for the presence or absence of a CRE. TOF values were measured on each of the control patients as described for the cases and the values recorded on the data collection sheet.

Anesthesia records and preoperative anesthesia evaluations were copied on all study and control patients. Patient demographic data that were recorded included age, sex, height, weight, ASA physical status, preexisting medical conditions, and preoperative medications. Details of the intraoperative anesthetic management included type of surgical procedure, duration of anesthesia, administration of blood products and crystalloids, doses of opioids provided intraoperatively, dosing and timing of administration of NMBDs, and core temperature on arrival to the PACU. All data collection forms were reviewed weekly by one of the investigators to ensure completeness.

Nominal data are presented as the number and percent of subjects in each category. Statistical analysis of the nominal data was performed using the NCSS software (Number Cruncher Statistical System, Kaysville, UT, 2006). Nominal case and control data were compared using McNemar's test. The 95% confidence intervals for the pairwise differences in percentages were calculated using the Nam restricted maximum likelihood estimation score.

Ordinal and continuous data found not to be normally distributed based on the Kolmogorov-Smirnov test for normality of the underlying population are presented as median and range. Statistical analysis of

the ordinal data and continuous data found not to be normally distributed was performed using the Stats Direct software (Stats Direct, Cheshire, United Kingdom, 2007). Ordinal data and non-normally distributed continuous data were compared using Wilcoxon's signed rank test. The 95% confidence intervals for the differences between the population medians were calculated from all pairwise data.

Normally distributed continuous data are presented as mean and standard deviation. Statistical analysis of the normally distributed continuous data was performed using the NCSS software. Normally distributed continuous data were compared using the paired *t*-test. The 95% confidence intervals for the differences between the population means were calculated from all pairwise data.

Given the large number of comparisons being made, the criterion for rejection of the null hypothesis was set at  $P < 0.01$ .

The relationship between variables found to differ between cases and controls to adverse events observed in the cases but not in the controls was sought by simple logistic regression analysis using NCSS 2001 (Number Cruncher Statistical System).

## RESULTS

Data were collected on 7459 patients receiving a general anesthetic admitted to the PACU during the one-year study period (Monday through Friday, 7:00 AM to 7:00 PM). CREs during the first 15 min of the PACU admission were identified in 61 of the general anesthesia patients (incidence of 0.8%). Only one of the 61 patients with a CRE did not receive a NMBD during the intraoperative period (general anesthetic with a laryngeal mask airway). CREs were observed most frequently in patients undergoing general surgical (nonabdominal) (24.6%), orthopedic (18.0%), and thoracic (18.0%) procedures. The most frequently observed CREs in these cases were severe hypoxemia (59.0%), upper airway obstruction (34.4%), and mild hypoxemia (19.7%). Other CREs observed included inability to breathe deeply (11.5%), symptoms of respiratory muscle weakness (9.0%), signs of respiratory distress (8.2%), and reintubation (6.2%). Multiple CREs (e.g., signs of respiratory distress and severe hypoxemia occurring simultaneously in a patient) were observed in 34.4% of the cases. Eight patients required reintubation during the study period; 3 of the 8 patients were urgently reintubated before TOF data could be measured.

Only 42 of these cases were matched with controls; the results of these 42 cases and their matched controls will be presented below. The most common CREs among matched cases were severe hypoxemia (22 cases, 52.4%), upper airway obstruction (15 cases, 35.7%), and mild hypoxemia (10 cases, 23.8%). The incidence of the other CREs in these cases was <10%. No CREs were observed in any of the preoperatively identified control patients.

**Table 1.** Patient Characteristics Used in Matching

	Critical respiratory event group	Control group
No.	42	42
Sex (male:female)	18 (42.9):24 (57.1)	18 (42.9):24 (57.1)
Age (yr)	63.7 ± 14.2	63.7 ± 14.2
Operative procedures		
General	10 (23.8)	10 (23.8)
General abdominal	3 (7.1)	3 (7.1)
Orthopedic	9 (21.4)	9 (21.4)
Vascular	3 (7.1)	3 (7.1)
Neurologic	5 (11.9)	5 (11.9)
Urologic	1 (2.4)	1 (2.4)
Ear Nose Throat	1 (2.4)	1 (2.4)
Gynecologic	4 (9.5)	4 (9.5)
Thoracic	6 (14.3)	6 (14.3)

All values inside parentheses indicate percentages.

The patient characteristics used in matching cases and controls, age, sex, and operative procedures are listed in Table 1. Other patient characteristics are presented in Table 2. Cases did not differ from controls in height, weight, incidence of morbid obesity, smoking or alcohol history, ASA physical status, or preexisting medical conditions.

Twenty-two anesthesia attendings and 40 anesthesia trainees cared for the 42 patients in the critical respiratory event group (cases) and 19 anesthesia attendings and 40 anesthesia trainees cared for the 42 control patients. All attendings caring for the control patients also cared for the cases but only 6 of 74 anesthesia trainees cared for both cases and controls. No anesthesia attending cared for more than 4 cases or more than 4 controls and no anesthesia trainee cared for more than 2 cases or 2 controls. Because of the large number of different anesthesia providers for both cases and controls and the overlap of attendings in both groups, the anesthesia provider was not considered to be a variable in our analysis.

Data collected in the operating room and PACU are presented in Table 3. The duration of the surgical procedures for cases and controls was similar, as was the administration and output of fluids and blood. All patients received a balanced anesthetic consisting of a volatile anesthetic and an opioid. The type of volatile anesthetic used (isoflurane, sevoflurane, or desflurane) and intraoperative dosing of opioids (fentanyl and hydromorphone) were similar for both cases and controls. Management of neuromuscular blockade was also similar for both cases and controls, with no differences noted in type of NMBD, dosing of NMBDs, timing of NMBD administration, or dosing of neostigmine. In all cases and controls, TOF peripheral nerve monitoring was used intraoperatively (ulnar and facial nerve sites used) and neuromuscular blockade was reversed (neostigmine and glycopyrrolate) at the conclusion of the surgical procedure. Quantitative neuromuscular monitoring (TOF-Watch SX<sup>®</sup>; Organon) was not used intraoperatively. Minimal neuromuscular criteria

for tracheal extubation (5-s head lift and no observed fade on TOF stimulation) was documented on all subjects. Core temperatures on arrival to the PACU were not different between cases and controls and hand temperature was >32°C in all subjects.

Acceleromyographic TOF values are presented in Table 3. Significant residual block (mean ± SD, TOF ratio values of 0.62 ± 0.20) was observed in the majority of cases. In contrast, nearly complete neuromuscular recovery was noted in the control group (mean ± SD, TOF ratio values of 0.98 ± 0.07; a difference of -0.36 with a 95% confidence interval of -0.43 to -0.30, *P* < 0.0001). Acceptable neuromuscular recovery (TOF ratio >0.90) was present in only 9.5% of cases versus 90.5% of controls (difference -81.0%, the 95% confidence interval of the difference -90% to -66%, *P* < 0.0001). Severe residual blockade (TOF ratios <0.70) was measured in 31 of the 42 cases (73.8%), whereas severe blockade was noted in none of the controls (difference 73.8%, the 95% confidence interval of the difference 59%–85%, *P* < 0.0001).

The probabilities of upper airway obstruction, severe hypoxemia, and any hypoxemia were found to be related to residual neuromuscular blockade, whether it is expressed as TOF ratio or as degree of residual neuromuscular blockade (Table 4). The sensitivity (i.e., the ability to correctly classify patients with the outcome of interest, in this case any hypoxemia) of the best logistic model, that relating the degree of residual neuromuscular blockade to the probability of any hypoxemia, was 72% while its specificity (i.e., ability to correctly classify patients without the outcome of interest, in this case any hypoxemia) was 85%. Adding the presence or absence of chronic renal insufficiency, the only patient characteristic to approach a statistically significant difference between cases and controls (Table 2), to a multiple logistic regression model with either TOF ratio or degree of residual neuromuscular blockade did not improve the model, so was not included in the final model. It is, however, interesting to note that that both patients requiring re-intubation had chronic renal insufficiency.

## DISCUSSION

The reported incidence of adverse respiratory events in the PACU varies widely, with observational studies noting an incidence of 1.3%–6.9%.<sup>10,11,17</sup> Rose et al. examined the frequency of CREs (defined as hypoxemia, inadequate ventilation, or upper airway obstruction requiring active intervention) in the PACU in 24,157 consecutive patients receiving a general anesthetic.<sup>12</sup> The overall incidence of CREs was 1.3%, although only 0.1% of patients required reintubation in the PACU. The incidence of CREs in the present investigation was 0.8% (61/7459), which is comparable to the findings of Rose et al. and is likely due to a similar study design and method of defining CREs.

**Table 2.** Patient Characteristics Not Used in Matching

	Critical respiratory event group	Control group	Difference (95% CI)	P
No.	42	42	—	—
Weight (kg)	82.3 ± 21.7	84.8 ± 16.2	-2.5 (-10 to 5)	0.515*
Height (cm)	165.6 ± 10.5	168.8 ± 9.9	-3.2 (-6 to -1)	0.023*
ASA physical status				
I	1 (2.4)	3 (7.1)	-4.8% (-17 to 6)	0.317†
II	18 (42.9)	23 (54.8)	-11.9% (-32 to 10)	0.275†
III	22 (52.4)	15 (35.7)	16.7% (-5 to 37)	0.127†
IV	1 (2.4)	1 (2.4)	0% (-10 to 10)	1.000†
CAD	4 (9.5)	4 (9.5)	0% (-13 to 13)	1.000†
Previous MI	1 (2.4)	2 (4.8)	-2.4% (-14 to 8)	0.564†
Previous CHF	2 (4.8)	2 (4.8)	0% (-12 to 12)	1.000†
Arrhythmias	3 (7.1)	3 (7.1)	0% (-13 to 13)	1.000†
Hypertension	19 (45.2)	17 (40.5)	4.8% (-15 to 25)	0.637†
COPD	3 (7.1)	4 (9.5)	-2.4% (-17 to 12)	0.706†
Asthma	4 (9.5)	6 (14.3)	-4.8 (-18 to 8)	0.414†
Sleep apnea	3 (7.1)	3 (7.1)	0% (-13 to 13)	1.000†
Liver disease	0 (0)	0 (0)	—	—
Hepatitis	1 (2.4)	0 (0)	2.4% (-6 to 12)	0.317†
CRI	6 (14.3)	0 (0)	14.3% (5 to 28)	0.014†
ESRD	0 (0)	0 (0)	—	—
Thyroid	7 (16.7)	5 (11.9)	4.8% (-11 to 21)	0.527†
Diabetes	9 (21.4)	6 (14.3)	7.1% (-10 to 24)	0.405†
CVA	1 (2.4)	1 (2.4)	0% (-10 to 10)	1.000†
TIA	1 (2.4)	2 (4.8)	-2.4% (-14 to 8)	0.564†
Morbid obesity	4 (9.5)	4 (9.5)	0% (-13 to 13)	1.000†
Cancer	10 (23.8)	13 (31.0)	-7.1% (-25 to 11)	0.439†
Smoking history	13 (31.0)	11 (26.2)	4.8% (-12 to 22)	0.564†
Drinking history	21 (50.0)	23 (54.8)	-4.8% (-25 to 15)	0.637†

Data are mean ± SD or number of patients (%).

ASA physical status = American Society of Anesthesiologists Physical Status; CAD = coronary artery disease; MI = myocardial infarction; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CRI = chronic renal insufficiency; ESRD = end-stage renal disease; CVA = cerebrovascular accident; TIA = transient ischemic attack.

\* The 95% confidence interval for the difference between the population means was calculated from all pairwise data. The P value given is the probability determined by the two-sided paired t-test for the difference between means.

† The 95% confidence interval for the difference was calculated using the Nam restricted maximum likelihood estimation (RMLE) score. The P value given is the probability determined by McNemar's two-sided hypothesis test about the difference.

The etiology of CREs in the PACU is multifactorial. Patient, surgical, and anesthetic factors all play a role in the development of adverse respiratory events. Previously identified patient risk factors include advanced age, male sex, chronic obstructive pulmonary disease, diabetes, and obesity.<sup>10,12,13</sup> Surgical risk factors for CREs in the PACU include abdominal or orthopedic surgery, emergency operations, and long duration of surgery.<sup>10,12,13</sup> Anesthetic variables associated with postoperative CREs include the use of general anesthesia, opioids, and NMBDs.<sup>10,12</sup> In the present investigation, cases and controls did not significantly differ in patient risk factors for CREs, types of surgical procedures, duration of surgery, and anesthetic management. The principle difference identified between the cases and controls was the presence of neuromuscular blockade in the PACU; 90.5% of the cases had TOF ratios less than or equal to 0.90 while only 9.5% of the controls had TOF ratios less than or equal to 0.90. This suggests that unrecognized residual paresis is an important contributing factor to postoperative CREs.

The most common CRE occurring during the first 15 min of the PACU admission was severe hypoxemia, which was recorded in 0.5% (36 of 7459) of patients in

the entire study population and 36 of the 61 (59.0%) of the cases (matched and unmatched). Mean ± SD TOF ratios of 0.61 ± 0.25 were measured in all cases with SpO<sub>2</sub> <90%. Two previous investigations have noted an association between residual neuromuscular blockade and postoperative hypoxemia. In a study of 83 surgical patients, hypoxemia and hypercarbia occurred more often in patients receiving pancuronium with TOF ratios <0.70 (60%) compared with patients with TOF ratios >0.70 (10%, P < 0.05).<sup>18</sup> An association between TOF ratios <0.90 and hypoxemia (SpO<sub>2</sub> <93%) was also observed in a study of 70 patients undergoing major orthopedic surgery with rocuronium or pancuronium.<sup>19</sup>

Residual neuromuscular blockade may produce postoperative hypoxemia by several mechanisms. Studies in healthy, nonanesthetized subjects administered vecuronium have demonstrated a marked attenuation of the hypoxic ventilatory response at a TOF ratio of 0.70.<sup>7,8</sup> Upper airway obstruction occurs frequently in awake volunteers at TOF ratios of 0.80.<sup>4</sup> Volunteer studies have also demonstrated pharyngeal dysfunction with aspiration at TOF ratios <0.90%.<sup>5,6</sup> In addition, respiratory muscle strength can be impaired at greater levels of residual paresis (TOF

**Table 3. Perioperative Variables**

	Critical respiratory event group	Control group	Difference (95% CI)	P
No.	42	42	—	—
<b>Intraoperative</b>				
Potent volatile anesthetic				
Sevoflurane	29 (69.1%)	26 (61.9%)	7.1% (−14 to 28)	0.513*
Desflurane	4 (9.5%)	7 (16.7%)	−7.1% (−23 to 9)	0.366*
Isoflurane	9 (21.4%)	9 (21.4%)	0% (−17 to 17)	1.000*
Dose fentanyl (μg)	200 (0–800)	200 (0–400)	−25 (−50 to 25)	0.357†
Hydromorphone (No. pts.)	7 (16.7%)	4 (9.5%)	7.1% (−8 to 22)	0.317*
Total OR time (min)	159 ± 81	157 ± 90	2 (−29 to 33)	0.903‡
Estimated blood loss (mL)	50 (0–840)	50 (0–700)	50 (−15 to 150)	0.111†
PRBCs (No. pts.)	3 (7.1%)	3 (7.1%)	0% (−13 to 13)	1.000*
Fluid (L)	1.50 (0.40–6.20)	1.55 (0–4.90)	0.10 (−0.35 to 0.63)	0.666†
Urine output (mL)	177.5 (0–1140)	100 (0–1100)	75 (0 to 150)	0.224†
<b>NM blockade-related data</b>				
Receiving rocuronium (No. pts.)	41 (97.6%)	41 (97.6%)	0 (−10 to 10)	
Dose rocuronium (mg)	58.4 ± 27.1	64.4 ± 33.1	−6.0 (−18.8 to 6.9)	0.354‡
Redosed (No. pts.)	27 (64.3%)	23 (54.8%)	9.5% (−8 to 27)	0.285*
No. redoses	1 (0–4)	1 (0–14)	0 (−0.5 to 0)	0.442†
Last dose to end (min)	80 ± 37	82 ± 31	−2 (−16 to 12)	0.746‡
<b>Other NMBDs used</b>				
Succinylcholine <sup>a</sup>	11 (26.2%)	10 (23.8%)	2.4% (−18 to 23)	0.819*
Cisatracurium	1 (2.4%)	1 (2.4%)	0% (−10 to 10)	1.000*
Dose neostigmine (mg)	4.0 (2.5–5.0)	4.0 (2.0–5.0)	0.25 (−0.25 to 0.5)	0.499†
<b>Postanesthesia care unit</b>				
PACU temperature (°C)	36.34 ± 0.50	36.26 ± 0.37	0.08 (−0.10 to 0.27)	0.377‡
Morphine sulfate equivalent dose (mg)	5 (0–20)	8.75 (0–40)	−2.5 (−5 to 0)	0.048†
Train-of-four ratio	0.62 ± 0.20	0.98 ± 0.07	−0.36 (−0.43 to −0.30)	<0.0001‡
<b>Degree of NM blockade<sup>b</sup></b>				
Acceptable	4 (9.5%)	38 (90.5%)	−81.0% (−90 to −66)	<0.0001*
Mild-to-moderate	7 (16.7%)	4 (9.5%)	7.1% (−9 to 24)	0.366*
Severe	31 (73.8%)	0 (0%)	73.8% (59 to 85)	<0.0001*

Data are mean ± SD, median (range), or number of patients (%).

OR = operating room; PRBCs = packed red blood cell transfusions; Last dose to end = last dose of NMBD to the end of the procedure; NM = neuromuscular; NMBD = neuromuscular blocking drug; PACU = postanesthesia care unit.

\* The 95% confidence interval for the difference was calculated using the Nam restricted maximum likelihood estimation (RMLE) score. The P value given is the probability determined by McNemar's two-sided hypothesis test about the difference.

† The 95% confidence interval for the difference between the population medians was calculated from all pairwise data. The P value given is the probability determined by the two-sided Wilcoxon's signed ranks test.

‡ The 95% confidence interval for the difference between the population means was calculated from all pairwise data. The P value given is the probability determined by the two-sided paired t-test for the difference between means.

<sup>a</sup> All patients administered succinylcholine subsequently received a nondepolarizing NMBD.

<sup>b</sup> Degree of residual NM blockade classified as acceptable neuromuscular recovery = 0 (TOF ratio >0.90), mild-to-moderate = 1 (0.70 ≤ TOF ratio ≤ 0.90), or severe = 2 (TOF ratio <0.70).

<0.6).<sup>20</sup> Although residual neuromuscular blockade was detected in the majority of patients with SpO<sub>2</sub> <90% in the current study, the mechanisms by which the blockade might have resulted in hypoxemia were not established. Impairment of the hypoxic ventilatory response and of respiratory muscle strength are likely important causes of postoperative hypoxemia, but cannot be assessed on routine clinical examinations. Upper airway obstruction was also present in 10 of the 32 (31.3%) of the cases with SpO<sub>2</sub> <90% and was likely an important contributing factor to postoperative hypoxemia. No clinical evidence of aspiration was observed in the operating room or PACU in any of the cases.

Airway obstruction was the second most common CRE in the PACU and occurred in 0.3% (21 of 7459) of patients in the entire study population and 21 of the 61 (34.4%) cases (matched and unmatched). Upper airway obstruction requiring an intervention is a primary cause of early respiratory morbidity and previous

investigations have reported an incidence of this complication of 0.2%–8.5%.<sup>11–13</sup> Although opioids and inhaled anesthetics can induce upper airway dysfunction, partial neuromuscular blockade may also play an important role in postoperative airway obstruction. Using tests of pulmonary and pharyngeal function, Eikermann et al. detected upper airway obstruction in 8 of 12 volunteers at a TOF ratio of 0.50 and 4 of 12 volunteers at a TOF ratio of 0.83.<sup>4</sup> Other investigators have demonstrated significant pharyngeal muscle dysfunction in healthy volunteers at TOF ratios <0.90.<sup>5,6</sup> In contrast to these studies in awake volunteers, postoperative patients may be at greater risk from the adverse effects of mild blockade on upper airway tone due to the residual effects of opioids and inhaled anesthetics. We observed a high incidence (14 of 15, 93.3%) of residual blockade (TOF <0.90) in the 15 matched cases with airway obstruction in the PACU. Their mean ± SD TOF ratios were 0.63 ± 0.17.

**Table 4.** Simple Logistic Regression Models Analyzing the Relationship Between Various Measures of Residual Neuromuscular Blockade and the Presence or Absence of Upper Airway Obstruction or Hypoxemia

Outcome	Variable	Regression coefficient	Standard error	Wald statistic	P	Odds ratio	95% CI
Upper airway obstruction	Intercept	1.220	0.910	—	—	—	—
	Train-of-four ratio	-0.037	0.013	-2.963	0.003	0.96	0.94 to 0.99
Upper airway obstruction	Intercept	-3.831	0.939	—	—	—	—
	Degree of NM blockade*	1.745	0.517	3.371	0.001	5.73	2.08 to 15.80
Severe hypoxemia	Intercept	2.509	0.939	—	—	—	—
	Train-of-four ratio	-0.047	0.012	-3.768	0.0002	0.95	0.93 to 0.98
Severe hypoxemia	Intercept	-2.487	0.539	—	—	—	—
	Degree of NM blockade*	1.290	0.335	3.855	0.0001	3.63	1.88 to 7.00
Any hypoxemia	Intercept	4.431	1.129	—	—	—	—
	Train-of-four ratio	-0.062	0.014	-4.463	<0.0001	0.94	0.91 to 0.97
Any hypoxemia	Intercept	-2.265	0.491	—	—	—	—
	Degree of NM blockade*	1.744	0.339	5.151	<0.0001	5.72	2.95 to 11.11

\* Degree of residual NM blockade classified as acceptable neuromuscular recovery = 0 (TOF ratio >0.90), mild-to-moderate = 1 (0.70 ≤ TOF ratio ≤ 0.90), or severe = 2 (TOF ratio <0.70).

This suggests that residual neuromuscular blockade is a primary contributing factor to this common adverse event in the PACU.

The incidence of emergent reintubation in the PACU for respiratory insufficiency after extubation in the operating room was 0.1% (8 of 7459), which is similar to previous estimates of 0.1%–0.2% noted in studies of postoperative respiratory complications.<sup>11–13</sup> In a study of the etiology of emergent tracheal intubation in the PACU, Mathew et al. identified persistent sedative and muscle relaxant effects as a primary cause of this complication.<sup>13</sup> TOF ratios were measured in 5 of the 8 patients prior to re-intubation; 3 patients were intubated in the PACU before TOF ratios could be assessed, however. Mean ± SD. TOF ratios were 0.36 ± 0.17 in this group, which suggests that residual neuromuscular block was an important cause of ventilatory failure in the PACU.

There are several limitations of the present investigation. First, in a prospective observational trial associations may be identified but causality not definitively established. Although the cases and controls appeared similar, unknown clinical variables that were not accounted for in our analysis may have influenced the development of CREs. Second, investigators measuring TOF ratios in the PACU were not blinded to whether subjects were cases or controls. Such blinding was not possible due to the obvious presence or absence of signs of respiratory distress. However, objective end-points (TOF ratios) were measured in duplicate in all subjects to reduce potential bias. Third, we were unable to match all of the 61 cases with a control subject ( $n = 42$ ) during the one-year data collection period. Extending the length of the quality assurance project may have allowed for more complete matching of groups. Fourth, the clinical agreement between two

isolated acceleromyographic TOF measurements in patients recovering from anesthesia has been questioned by Baillard et al.<sup>21</sup> In contrast to the study by Baillard et al., we used higher stimulating currents (50 mA), which may have increased the accuracy of TOF measurements.<sup>22</sup> However, even 50 mA currents may not be supramaximal in some subjects. Although supramaximal currents can be painful in awake volunteers,<sup>23</sup> we have previously reported that 50 mA TOF stimulating currents were not perceived as painful in patients recovering from anesthesia,<sup>24</sup> and no patients reported discomfort from TOF measurements in the current study. Fifth, the results obtained at our institution (an academic center with a large number of anesthesia care providers with varying levels of experience) may not be applicable to other practice settings. Finally, patients were only followed until discharge from the PACU. The long-term consequences of residual neuromuscular blockage were not assessed in the investigation.

In conclusion, we observed evidence of incomplete neuromuscular recovery in the majority of patients with CREs in the PACU. Our findings suggest that the residual effects of NMBDs can contribute to adverse respiratory events after general anesthesia. Recent data suggest that clinicians lack knowledge relating to clinical assessment of neuromuscular recovery and infrequently monitor the degree of blockade in the perioperative period.<sup>25,26</sup> Cautious management of intraoperative neuromuscular blockade (minimizing the administration of NMBDs, early reversal of blockade, use of quantitative neuromuscular monitoring (acceleromyography)) may reduce the incidence of residual paresis and CREs in the early postoperative recovery period.

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