Postoperative Residual Neuromuscular Blockade Is Associated with Impaired Clinical Recovery

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BACKGROUND: In this investigation, we sought to determine the association between objective evidence of residual neuromuscular blockade (train-of-four [TOF] ratio <0.9) and the type, incidence, and severity of subjective symptoms of muscle weakness in the postanesthesia care unit (PACU).
METHODS: TOF ratios of 149 patients were quantified with acceleromyography on arrival to the PACU. Patients were stratified into 2 cohorts: a TOF <0.9 group (n = 48) or a TOF ≥0.9 (control) group (n = 101). A standardized examination determined the presence or absence of 16 symptoms and 11 signs of muscle weakness on arrival to the PACU and 20, 40, and 60 minutes after admission.
RESULTS: The incidence of symptoms of muscle weakness was significantly higher in the TOF <0.9 group at all times (P < 0.001), as was the median (range) number of symptoms from PACU arrival (7 [3–6] TOF <0.9 group vs 2 [0–11] control group; difference 5, 99% confidence interval of the difference 4–6) until 60 minutes after admission (2 [0–12] TOF <0.9 group vs 0 [0–11] control group; difference 2, 99% confidence interval of the difference 1–2) (all P < 0.0001).
CONCLUSION: The incidence and severity of symptoms of muscle weakness were increased in the PACU in patients with a TOF <0.9. (Anesth Analg 2013;117:133–41)

Residual neuromuscular blockade, defined as a train-of-four (TOF) ratio <0.9 with quantitative neuromuscular monitoring, is a common occurrence in the postanesthesia care unit (PACU). Approximately 40% of patients receiving intermediate-acting neuromuscular blocking drugs (NMBDs) in the operating room present to the PACU with a TOF ratio <0.9.[1] Although most patients recover from small degrees of muscle weakness without obvious complications, some at-risk patient populations may experience adverse postoperative events when neuromuscular recovery is incomplete.[2] A large number of clinical and laboratory investigations have established that residual paresis can produce adverse effects on the respiratory system.[2–6] Several studies have also demonstrated that residual neuromuscular blockade is associated with other undesirable effects that may impair clinical recovery. In particular, symptoms of muscle weakness and prolonged PACU length of stay have been reported in postoperative patients with TOF ratios <0.9.[7–9]

Traditionally, recovery during the early postoperative period has been evaluated by quantifying readily measured indices, such as time to awakening, hemodynamic stability, length of PACU stay, and complications including nausea, vomiting, and pain. However, a variety of other complications attributable to anesthesia and surgery that are not typically assessed by clinicians may occur in the PACU. Standard scoring systems of PACU recovery (i.e., Aldrete scores) do not specifically evaluate patients for unpleasant symptoms of muscle weakness potentially related to residual neuromuscular blockade. In previous studies, we have observed that patients with TOF ratios <0.9 in the PACU often describe symptoms of "feeling weak" or "difficulty seeing and speaking."[2,10] Furthermore, in a recent investigation, we determined that patients randomized to receive acceleromyography (AMG) monitoring had significantly fewer symptoms of residual paresis during the first 60 minutes of the PACU stay compared with patients assessed with conventional qualitative devices (peripheral nerve stimulators).[11] Although a general association between residual neuromuscular blockade and symptoms of muscle weakness was suggested, a detailed analysis of this relationship was not conducted.[11] The aim of the present investigation was to perform a secondary analysis of these data to determine the incidence and severity of symptoms of muscle weakness in patients with (defined as a TOF ratio <0.9) and without (defined as a TOF ratio ≥0.9) residual neuromuscular blockade. A threshold of 0.9 was selected based on data demonstrating an association between AMG-measured TOF ratios <0.9 on admission to the PACU and adverse postoperative events (hypoxemia, prolonged PACU length of stay).[9,12] We also sought to determine the most common symptoms associated with incomplete neuromuscular recovery and whether quality of recovery (QoR) scores were decreased in patients with residual neuromuscular blockade.

METHODS

Patients and Anesthesia

Between October 2009 and October 2010, 155 ASA physical status I to III patients undergoing elective surgical

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procedures requiring neuromuscular blockade, with an anticipated duration of at least 60 minutes, were enrolled in a randomized clinical trial. The NorthShore University HealthSystem IRB approved this investigation, and written informed consent was obtained from all subjects. In brief, the aim of the original study was to determine the effect of AMG monitoring on the incidence of signs and symptoms of residual muscle weakness during the first 60 minutes of PACU stay.[11] The study protocol had several predetermined objectives, including a secondary analysis to determine the association between residual neuromuscular blockade and impaired clinical recovery in the PACU. This secondary analysis is the aim of the present study.

Baseline measures for quality of life before surgery were assessed using the QoR-9 scoring system in the preoperative holding area. Patients were randomly allocated to an AMG group or a control group (qualitative neuromuscular monitoring, standard peripheral nerve stimulator) using a computer-generated randomization code. Individual group assignments were concealed in opaque envelopes until patient entry into the operating room. Anesthetic and neuromuscular management were standardized in both study groups. Anesthesia was induced with propofol (1.5–2.5 mg/kg) and maintained with sevoflurane (titrated to a Bispectral index value of 40–60 and a mean arterial blood pressure within 20% of baseline measures) and fentanyl (approximately 1–2 $\mu g \cdot kg^{-1} \cdot h^{-1}$). All patients received rocuronium 0.6 to 0.8 mg/kg at induction of anesthesia. Neuromuscular blockade was maintained with rocuronium (5- to 10-mg boluses), and additional doses were administered to maintain a visual TOF count of 2 to 3. Neuromuscular blockade was reversed with neostigmine 50 μg/kg and glycopyrrolate 10 μg/kg at the conclusion of surgery.

Neuromuscular Monitoring

Neuromuscular monitoring was conducted as described previously.[11] In summary, the TOF-Watch SX® (Blue Star Enterprises, Chanhassen, MN) was applied to both study groups. A TOF count of 2 to 3 was maintained in all patients during portions of the surgery requiring neuromuscular blockade. However, TOF ratio data could be used in the AMG group to guide NMBD dosing during the last 45 to 60 minutes of the anesthetic when surgical relaxation was no longer required. In the AMG group, tracheal extubation was performed when standard criteria were met (5-second head-lift or hand grip, following commands, stable ventilatory pattern) and a TOF ratio >0.8 was displayed on the panel of the TOF-Watch SX (quantitative neuromuscular monitoring). In the control group, the display panel of the TOF-Watch SX was covered with an opaque piece of cardboard and the device used as a qualitative neuromuscular monitor (no access to TOF ratio data). Tracheal extubation was performed when the same clinical criteria for extubation were achieved as for the AMG group and no fade was visually detected with TOF stimulation (qualitative neuromuscular monitoring). Immediately on arrival to the PACU, uncalibrated TOF ratios were quantified in both groups using the TOF-Watch SX. Residual neuromuscular blockade was defined as a TOF ratio <0.9. In the present investigation, patients were stratified to 1 of 2 cohorts for analysis on the basis of this measurement: a TOF <0.9 group or a TOF ≥0.9 group.

Data Collection

Patients were assessed for signs and symptoms of muscle weakness on arrival to the PACU and 20, 40, and 60 minutes after admission. A standardized examination was performed by a research assistant blinded to TOF ratio data; all tests were conducted in the same order in each subject. Testing for objective evidence of muscle weakness (signs) was immediately followed by an examination for subjective evidence of residual paresis (symptoms, subjective difficulty performing the 11 tests, and 5 specific questions related to muscle weakness). Each patient was assessed for 16 symptoms and 11 signs of muscle weakness at each testing time. Patients either passed (negative response) or failed (positive response) each test. The incidence of symptoms and the incidence of signs of muscle weakness were defined as the presence of ≥1 symptoms or signs, respectively, at each of the 4 testing times in the TOF <0.9 and TOF ≥0.9 cohorts. To quantify severity of weakness in each of the cohorts, the number of symptoms (0–16) and signs (0–11) at PACU arrival and 20, 40, and 60 minutes after admission was calculated to determine a number of symptoms and a number of signs score. As an additional method of assessing severity of muscle weakness in the 2 groups, patients were asked to quantify overall muscle weakness on an 11-point verbal rating scale (0 = no muscle weakness, 10 = most severe muscle weakness ever experienced) at each of the 4 testing times. Patients were assessed every 10 minutes using an Aldrete scoring system (ability to move 4 extremities, ability to breathe, circulation, consciousness, color) for readiness for discharge by PACU nurses blinded to group assignment and TOF data. Other standard recovery data were recorded on a PACU data collection sheet, including the times required to meet discharge criteria and achieve discharge. At the time of PACU discharge, global QoR was measured using the QoR-9 scoring system. Recovery was assessed with the QoR-9 in 9 dimensions, with scores ranging from 0 (extremely poor QoR) to 18 (extremely high QoR).

Statistical Analysis

The sample size of the present, secondary data analysis was determined by the hypothesis that was tested in the primary analysis of these data.[11] In that study, we expected the control rate of symptoms of weakness at a TOF of 0.8 would be similar to the 58% in awake volunteers reported by Eikermann et al.[13] and thought a 50% reduction in that rate would be clinically significant. Therefore, we hypothesized that AMG monitoring could reduce the incidence of symptoms of residual paresis by 50% and estimated that we would need group sample sizes of 52 each to have sufficient power to detect such a difference with sufficient confidence. We enrolled 155 patients in the original study to ensure an acceptable response rate. The study was conducted as planned; data were not incrementally evaluated and the study was not stopped on the basis of incremental evaluation.

Discrete data were compared using Fisher exact test (NCSS, Kaysville, UT). The 99% confidence intervals for the differences in percentages were calculated using the Miettinen and Nurminen method, which was shown by Newcombe to perform well when it was compared with 10 other methods.[14,15] Ordinal data and continuous data that

Table 1. Patient Characteristics

	Train-of-four <0.9	Train-of-four ≥0.9	Difference (99% CI)	*P* value
No.	48	101		
Acceleromyography group	11 (23%)	64 (63%)	−40% (−58% to −18%)	<0.0001
Sex (male/female)	24 (50%)/24 (50%)	57 (56%)/44 (44%)	6% (−16% to 28%)	0.486
Age (y)	56 ± 14	51 ± 16	5 (−2 to 12)	0.042
Weight (kg)	86 ± 22	84 ± 21	3 (−7 to 12)	0.498
Height (cm)	169 ± 11	173 ± 10	−3 (8–2)	0.076
ASA physical status	II (I–III)	II (I–III)	0 (0–I)	0.019

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

were not normally distributed (except times; see below), as determined by the omnibus normality test developed by D'Agostino et al.[16] and identified as such in the tables, are presented as median and range. These data were compared between groups using the Mann-Whitney *U* test (StatsDirect, Cheshire, UK). The median differences and their 99% confidence intervals were calculated using the Hodges-Lehmann approach for shift for which the test of shift can be a difference of median.[17] All times (anesthesia duration, time neostigmine to extubation, time neostigmine to PACU admission, and time PACU admission to meeting discharge criteria) are reported as mean and SD. Because time data such as these, which are used as a surrogate for cost, are often skewed, they were compared with the Aspin-Welch modification of the 2-sample *t* test for data with unequal variance (NCSS), and the mean differences and their 99% confidence intervals were calculated on the basis of that procedure.[18] Normally distributed continuous data are presented as mean and standard deviation. These data were compared using the unpaired *t* test (NCSS). Mean differences and their 99% confidence intervals were calculated.

Given the large number of comparisons being made, the criterion for rejection of the null hypothesis was a 2-tailed $P < 0.01$ to help minimize the chance of a type I error.

RESULTS

Five patients were excluded from analysis because of protocol violations, and TOF measurements were absent in 1 patient. TOF data were recorded in 149 patients; 48 had TOF ratios <0.9 (TOF <0.9 group) and 101 had TOF ratios ≥0.9 (TOF ≥0.9 group). Patient demographic data are presented in Table 1. Patients in the 2 groups differed in the use of intraoperative AMG monitoring; 63% of the patients in the TOF ≥0.9 group had intraoperative AMG monitoring and only 23% of the patients in the TOF <0.9 group had such monitoring (< 0.0001). There were no significant differences between the TOF <0.9 and TOF ≥0.9 groups in age, height, weight, ASA physical status, or preexisting medical conditions (although a higher incidence of hypertension was observed in the TOF <0.9 group [54%] compared with the TOF ≥0.9 group [31%, = 0.007]). Furthermore, the 2 cohorts were similar in types of surgery performed (data not shown). Intraoperative and neuromuscular management data are presented in Table 2. There were no differences between groups in blood loss, crystalloid administration, temperature at the end of the procedure and on arrival to the PACU (data not shown), or intraoperative fentanyl dose. Although the total dose of rocuronium did not differ between groups, 25% of patients in the TOF <0.9 group received rocuronium during the last 45 minutes of the case whereas only 7% of the patients in the TOF ≥0.9 group received rocuronium at this time (= 0.003). Patients in the TOF <0.9 cohort had a lower TOF count at the time of reversal (3 vs 4 in the TOF ≥0.9 group, < 0.0001). On admission to the PACU, the median (range) TOF ratio measured with AMG was 0.75 (0.33–0.87)

Table 2. Perioperative and Neuromuscular Management Data

	Train-of-four <0.9	Train-of-four ≥0.9	Difference (99% CI)	*P* value
No.	48	101		
Anesthesia duration (min)	172 ± 68	166 ± 73	6 (−26 to 38)	0.609
Total fentanyl dose (μg)[a]	200 (50–300)	200 (0–300)	0 (0–50)	0.412
Total rocuronium dose (mg)[a]	60 (30–160)	60 (20–160)	0 (−10 to 10)	0.363
No. of rocuronium redoses[a]	2 (0–11)	1 (0–10)	0 (0–1)	0.201
Patients receiving rocuronium redoses within the last 45 min	12 (25%)	7 (7%)	18% (3%–37%)	0.003
Train-of-four count at reversal[a]	3 (1–4)	4 (0–4)	−1 (−1 to 0)	<0.0001
Time neostigmine to extubation (min)	11 ± 8	13 ± 9	−2 (−6 to 2)	0.196
Time neostigmine to PACU admission (min)	17 ± 9	20 ± 9	−2 (−6 to 2)	0.137
Train-of-four ratio in PACU[a]	0.75 (0.33–0.87)	1.01 (0.90–1.28)	−0.31 (−0.38 to −0.24)	<0.0001
0.7 < train-of-four ratio < 0.9	31 (65%)	0 (0%)	65% (46%–80%)	<0.0001
Train-of-four ratio <0.7	17 (35%)	0 (0%)	35% (20%–54%)	<0.0001
PACU QoR-9, global scores	13 (5–16)	14 (9–16)	−1 (−2 to 0)	<0.001
PACU QoR-9, general well-being dimension	1 (0–2)	2 (1–2)	−1 (−1 to 0)	<0.0001
PACU QoR-9, breathe easily dimension	2 (0–2)	2 (0–2)	0 (0–0)	<0.0001

Data are mean ± SD, median (range), or number of patients (%).
CI = confidence interval; QoR = quality of recovery; PACU = postanesthesia care unit.
The QoR-9 scoring system was used to assess quality of recovery at the time of discharge from the PACU. However, the QoR-9 has not been validated in this setting. Statistically significant differences were noted in global scores and in 2 of the 9 dimensions (listed above).
[a] Continuous data found to not be normally distributed.

in the TOF <0.9 group and 1.01 (0.90–1.28) in the TOF ≥0.9 group (< 0.0001).

Table 3 presents the incidence of symptoms and signs of muscle weakness (presence of ≥1 of the 16 symptoms or 11 signs) during the PACU stay. A high incidence of symptoms was observed in both groups at PACU admission (100% in the TOF <0.9 group compared with 80% in the TOF ≥0.9 group; = 0.0004). However, 60 minutes after PACU arrival, only 26% of the patients in the TOF ≥0.9 cohort had any symptoms of residual paresis whereas 83% of the patients in the TOF <0.9 cohort had such symptoms (< 0.0001). Signs of muscle weakness were observed less frequently than symptoms. At PACU arrival, the incidence of any sign was 43% in the TOF <0.9 cohort compared with 6% in the TOF ≥0.9 cohort (< 0.0001). However, within 20 minutes of PACU admission, none of patients in the TOF ≥0.9 group had any signs of residual paresis whereas 25% of the patients in the TOF <0.9 group had such signs (< 0.0001).

Data relating to severity of muscle weakness are presented in Table 4. Overall weakness, measured on a 0 to10 scale, was significantly greater in the TOF <0.9 cohort during the entire 60-minute measurement period in the PACU (< 0.0001 compared with TOF ≥0.9 cohort). At PACU admission, the median total number of symptoms score (from 0 to 16) was 7 in the TOF <0.9 group and 2 in the TOF ≥0.9 group (< 0.0001). After 40 minutes in the PACU, the number of symptoms score decreased to 0 in the TOF ≥0.9 group, whereas symptom scores were 3 (40 minutes) and 2 (60 minutes) in the TOF <0.9 group (all < 0.0001). In contrast, the median number of signs score (from 0 to 11) was 0 in both groups during the entire 60-minute PACU stay (although statistical differences were noted between groups at all 4 times).

The specific symptoms of residual paresis observed in the TOF <0.9 and TOF ≥0.9 groups during the PACU stay are presented in Table 5 (in descending order of frequency in the TOF <0.9 group). At PACU arrival, symptoms of general weakness, subjective difficulty performing eye-opening and head-lift, subjective difficulty tracking object with eyes, blurry vision, subjective difficulty speaking, and facial weakness were observe in more than half of patients in the

Table 3. Incidence of Symptoms and Signs of Muscle Weakness from PACU Admission to 60 Minutes Thereafter

	PACU admission	20 min after PACU admission	40 min after PACU admission	60 min after PACU admission
Any symptoms				
Train-of-four <0.9	46 (100%)	48 (100%)	43 (90%)	40 (83%)
Train-of-four ≥0.9	80 (80%)	65 (64%)	46 (46%)	26 (26%)
Difference (99% CI)	20% (7%–32%)	36% (22%–49%)	44% (24%–59%)	58% (37%–72%)
P value	0.0004	<0.0001	<0.0001	<0.0001
Any signs				
Train-of-four <0.9	20 (43%)	12 (25%)	6 (13%)	4 (8%)
Train-of-four ≥0.9	6 (6%)	0 (0%)	0 (0%)	0 (0%)
Difference (99% CI)	37% (19 to 57%)	25% (13%–43%)	13% (5%–30%)	8% (2%–24%)
P value	<0.0001	<0.0001	<0.001	0.003

Data are *n* (%).
PACU = postanesthesia care unit; CI = confidence interval.
Train-of-four <0.9 *n* = 48 at all times except at PACU admission when *n* = 46. Train-of-four ≥0.9 *n* = 101 at all times except at PACU admission when *n* = 100.

Table 4. Severity of Symptoms and Signs of Muscle Weakness from PACU Admission to 60 Minutes Thereafter

	PACU admission	20 min after PACU admission	40 min after PACU admission	60 min after PACU admission
Overall weakness				
Train-of-four <0.9	7 (3–10)	7 (2–10)	5.5 (2–10)	5 (0–10)
Train-of-four ≥0.9	4 (0–9)	3 (0–8)	3 (0–8)	2 (0–8)
Difference (99% CI)	3 (2–4)	4 (3–5)	3 (2–4)	3 (2–4)
P value	<0.0001	<0.0001	<0.0001	<0.0001
No. of symptoms score				
Train-of-four <0.9	7 (3–16)	5 (1–13)	3 (0–11)	2 (0–12)
Train-of-four ≥0.9	2 (0–11)	1 (0–13)	0 (0–12)	0 (0–11)
Difference (99% CI)	5 (4–6)	4 (3–5)	3 (2–3)	2 (1–2)
P value	<0.0001	<0.0001	<0.0001	<0.0001
No. of signs score				
Train-of-four <0.9	0 (0–5)	0 (0–2)	0 (0–7)	0 (0–4)
Train-of-four ≥0.9	0 (0–2)	0 (0–0)	0 (0–0)	0 (0–0)
Difference (99% CI)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
P value	<0.0001	<0.0001	0.0003	0.003

Data are median (range).
PACU = postanesthesia care unit; CI = confidence interval.
Overall weakness evaluated on a 11-point verbal rating scale (0 = no muscle weakness, 10 = most severe muscle weakness ever experienced). Number of symptoms score ranges from 0 (no symptoms) to 16 (all 16 symptoms). Number of signs score ranges from 0 (no signs) to 11 (all 11 signs).
Train-of-four <0.9 *n* = 48 at all times except at PACU admission when *n* = 46. Train-of-four ≥0.9 *n* = 101 at all times except at PACU admission when *n* = 100.

Table 5. Symptoms of Muscle Weakness in the PACU

	Train-of-four <0.9	Train-of-four ≥0.9	Difference (99% CI)	*P* value
General weakness				
PACU arrival	42 (91%)	45 (45%)	46% (36%–61%)	<0.0001
20 min	43 (90.0%)	42 (42%)	48% (28%–63%)	<0.0001
40 min	38 (79%)	30 (30%)	50% (28%–66%)	<0.0001
60 min	35 (73%)	19 (19%)	54% (33%–70%)	<0.0001
5-s eye opening				
PACU arrival	41 (89%)	36 (36%)	53% (32%–68%)	<0.0001
20 min	36 (75%)	25 (25%)	50% (29%–67%)	<0.0001
40 min	27 (56%)	18 (18%)	38% (17%–58%)	<0.0001
60 min	14 (29%)	9 (9%)	20% (4%–40%)	0.003
5-s head-lift				
PACU arrival	34 (74%)	15 (15%)	59% (37%–75%)	<0.0001
20 min	28 (58%)	9 (9%)	49% (29%–67%)	<0.0001
40 min	15 (31%)	7 (7%)	24% (8%–44%)	<0.001
60 min	6 (13%)	3 (3%)	10% (−1% to 27%)	0.032
Track object with eyes				
PACU arrival	29 (63%)	34 (34%)	29% (6%–49%)	0.001
20 min	21 (44%)	9 (9%)	35% (16%–54%)	<0.0001
40 min	13 (27%)	6 (6%)	21% (6%–40%)	<0.001
60 min	9 (19%)	2 (2%)	17% (5%–35%)	<0.001
Blurry vision				
PACU arrival	29 (63%)	32 (32%)	31% (8%–51%)	<0.001
20 min	27 (56%)	21 (21%)	35% (14%–55%)	<0.0001
40 min	12 (25%)	9 (9%)	16% (0%–36%)	0.012
60 min	11 (23%)	2 (2%)	21% (8%–40%)	0.0001
Ability to speak				
PACU arrival	28 (61%)	25 (25%)	36% (14%–55%)	<0.0001
20 min	25 (52%)	13 (13%)	39% (19%–58%)	<0.0001
40 min	16 (33%)	8 (8%)	25% (8%–45%)	<0.001
60 min	9 (19%)	3 (3%)	16% (3%–34%)	0.002
Facial weakness				
PACU arrival	25 (54%)	9 (9%)	45% (25%–64%)	<0.0001
20 min	13 (27%)	5 (5%)	22% (7%–41%)	<0.001
40 min	10 (21%)	3 (3%)	18% (5%–36%)	<0.001
60 min	6 (13%)	1 (1%)	12% (2%–29%)	0.005
Ability to cough				
PACU arrival	23 (50%)	12 (12%)	38% (18%–57%)	<0.0001
20 min	18 (38%)	2 (2%)	36% (19%–54%)	<0.0001
40 min	13 (27%)	2 (2%)	25% (11%–44%)	<0.0001
60 min	7 (15%)	2 (2%)	13% (2%–30%)	0.005
Ability to smile				
PACU arrival	19 (41%)	9 (9%)	32% (13%–52%)	<0.0001
20 min	9 (19%)	5 (5%)	14% (1%–32%)	0.013
40 min	6 (13%)	2 (2%)	11% (0%–28%)	0.014
60 min	3 (6%)	1 (1%)	5% (−3% to 21%)	0.099
Ability to swallow				
PACU arrival	17 (37%)	7 (7%)	30% (12%–50%)	<0.0001
20 min	14 (29%)	5 (5%)	24% (9%–26%)	<0.001
40 min	9 (19%)	2 (2%)	17% (5%–35%)	<0.001
60 min	4 (8%)	1 (1%)	7% (−1% to 23%)	0.037
5-s hand grip				
PACU arrival	15 (33%)	6 (6%)	27% (10%–46%)	0.0001
20 min	10 (21%)	1 (1%)	20% (8%–38%)	<0.0001
40 min	3 (6%)	1 (1%)	5% (−3% to 21%)	0.099
60 min	2 (4%)	1 (1%)	3% (−4% to 18%)	0.243
Facial numbness				
PACU arrival	14 (30%)	8 (8%)	22% (6%–42%)	<0.001
20 min	10 (21%)	5 (5%)	16% (2%–35%)	0.006
40 min	3 (6%)	2 (2%)	4% (−4% to 20%)	0.329
60 min	5 (10%)	1 (1%)	9% (1%–26%)	0.014
Ability to breathe deeply				
PACU arrival	13 (28%)	6 (6%)	22% (6%–42%)	<0.001
20 min	9 (19%)	1 (1%)	18% (7%–36%)	<0.001
40 min	7 (15%)	1 (1%)	14% (4%–31%)	0.002
60 min	3 (6%)	1 (1%)	5% (−3% to 21%)	0.099

(Continued)

Table 5. (*Continued*)

	Train-of-four <0.9	Train-of-four ≥0.9	Difference (99% CI)	*P* value
Double vision				
PACU arrival	12 (26%)	10 (10%)	16% (0%–36%)	0.023
20 min	11 (23%)	6 (6%)	17% (2%–36%)	0.005
40 min	8 (17%)	4 (4%)	13% (0%–31%)	0.019
60 min	5 (10%)	1 (1%)	9% (1%–26%)	0.014
5-s protrude tongue				
PACU arrival	12 (26%)	4 (4%)	22% (7%–41%)	<0.001
20 min	9 (19%)	5 (5%)	14% (1%–32%)	0.013
40 min	5 (10%)	1 (1%)	9% (1%–26%)	0.014
60 min	2 (4%)	1 (1%)	3% (−4% to 18%)	0.243
Tongue depressor test				
PACU arrival	6 (13%)	3 (3%)	10% (−1% to 28%)	0.028
20 min	4 (8%)	2 (2%)	6% (−3% to 23%)	0.085
40 min	1 (2%)	3 (3%)	−1% (−9% to 13%)	0.754
60 min	0 (0%)	1 (1%)	−1% (−8% to 11%)	1.000

Data are number of patients (%).

PACU = postanesthesia care unit; CI is confidence interval.

Symptoms = subjective difficulty performing 11 tests of muscle strength and 5 specific questions about muscle weakness. Symptoms are presented in descending order of frequency in the TOF <0.9 group.

Train-of-four <0.9 n = 48 at all times except at PACU admission when n = 46. Train-of-four ≥0.9 n = 101 at all times except at PACU admission when n = 100.

TOF <0.9 group (91%–54% of patients). In contrast, only 9% to 45% of patients in the TOF ≥0.9 group had these same symptoms of muscle weakness in the PACU (all = 0.001 or less compared with the TOF <0.9 group). Statistically significant differences between groups (lower incidence in the TOF ≥0.9 cohort) were noted in 14 of the 16 symptoms at PACU arrival and 7 of the 16 symptoms 60 minutes after admission (all < 0.01).

Requirements for pain medication in the PACU did not differ between groups. The time from PACU admission until meeting discharge criteria did not differ between the TOF ≥0.9 group (73 ± 40 minutes) and the TOF <0.9 group (81 ± 30 minutes) (difference 8 minutes, 99% confidence interval of the difference −7 minutes to 24 minutes; = 0.160). Results of the QoR-9 testing at the time of discharge from the PACU are presented in Table 2.

DISCUSSION

In previous decades, the issue of a patient's perception of muscle weakness after anesthesia and surgery was not a primary concern of clinicians.[19] The more recent practice of using short-acting anesthetic drugs allows for a rapid return of consciousness in the PACU. In this setting, the problem of residual paresis is of greater concern to patients and may adversely affect the recovery process.[19] There are several potential causes of muscle weakness in the early postoperative period. Skeletal muscle strength can be impaired by residual effects of inhaled anesthetics, hypothermia, electrolyte disturbances due to hemodilution, prolonged immobility, or the inflammatory response to perioperative stressors.[20–22] The findings from the present investigation demonstrate that incomplete neuromuscular recovery is a primary risk factor for unpleasant symptoms of postoperative weakness. As expected, the incidence and severity of muscle weakness were significantly greater in patients with TOF ratios <0.9 during the first 60 minutes of the PACU stay. The most common symptoms observed throughout the study included general weakness, visual symptoms, and weakness of facial and perioral muscles. Furthermore, patients with TOF ratios <0.9 on arrival to the PACU had lower QoR.

Assessing the incidence and severity of muscle weakness attributable to residual neuromuscular blockade is difficult in postoperative patients because of the confounding effects of intraoperative anesthetic drugs, pain, hypothermia and shivering, and postoperative analgesics. For this investigation, a standardized examination for symptoms and signs of muscle weakness was developed based on data collected in volunteers by Kopman et al.[23] To reduce any potential sources of bias, the examination was performed by a blinded assessor in an identical manner at 20-minute intervals during the first 60 minutes of the PACU stay. Severity of residual paresis was evaluated by measuring overall weakness on a 0 to 10 scale and recording the total number of symptoms at each measurement time. Not surprisingly, a high incidence of symptoms (at least 1 symptom) was observed at PACU admission in both the TOF <0.9 group (100%) and the TOF ≥0.9 group (80%). This observation was likely attributable to the lingering effects of volatile anesthetics and a small degree of residual neuromuscular blockade present in both groups (see below). However, overall weakness at this time on a 0 to 10 scale was significantly less in the TOF ≥0.9 group (4 vs 7 in the TOF <0.9 group), as was the median total number of symptoms (2 vs 7 in the TOF <0.9 group). After 60 minutes in the PACU, resolution of several potential contributory causes of muscle weakness (residual anesthetic drugs, hypothermia, and pain) would be expected. However, significant muscle weakness was observed in the TOF <0.9 group at this time; 83% of these patients had at least 1 symptom, the median number of symptoms score was 2, and overall weakness was 5 on a scale of 0 to 10. In contrast, only 26% of patients in the TOF ≥0.9 group had any symptoms at 60 minutes, and the median number of symptoms score had decreased to 0 by 40 minutes. Because our 2 cohorts appeared similar in all perioperative characteristics with the exception of degree of neuromuscular recovery, our findings

Table 6. Signs of Muscle Weakness in the PACU

	Train-of-four <0.9	Train-of-four ≥0.9	Difference (99% CI)	*P* value
Track object with eyes				
PACU arrival	16 (35%)	5 (5%)	30% (13%–49%)	<0.0001
20 min	8 (17%)	0 (0%)	17% (7%–34%)	<0.001
40 min	2 (4%)	0 (0%)	4% (–2% to 19%)	0.102
60 min	1 (2%)	0 (0%)	2% (–4% to 16%)	0.322
Ability to cough				
PACU arrival	7 (15%)	1 (1%)	14% (4%–32%)	0.001
20 min	3 (6%)	0 (0%)	6% (0%–22%)	0.032
40 min	4 (8%)	0 (0%)	8% (18%–24%)	<0.01
60 min	2 (4%)	0 (0%)	4% (–2% to 19%)	0.102
5-s eye opening				
PACU arrival	5 (11%)	1 (1%)	10% (1%–27%)	0.012
20 min	0 (0%)	0 (0%)	0% (–6% to 12%)	
40 min	2 (4%)	0 (0%)	4% (–2% to 19%)	0.102
60 min	2 (4%)	0 (0%)	4% (–2% to 19%)	0.102
5-s head-lift				
PACU arrival	4 (9%)	1 (1%)	8% (–1% to 24%)	0.034
20 min	3 (6%)	0 (0%)	6% (0%–22%)	0.032
40 min	2 (4%)	0 (0%)	4% (–2% to 19%)	0.102
60 min	1 (2%)	0 (0%)	2% (–4% to 16%)	0.322
5-s hand grip				
PACU arrival	4 (9%)	0 (0%)	9% (2%–25%)	0.009
20 min	0 (0%)	0 (0%)	0% (–6% to 12%)	
40 min	0 (0%)	0 (0%)	0% (–6% to 12%)	
60 min	0 (0%)	0 (0%)	0% (–6% to 12%)	
Ability to swallow				
PACU arrival	3 (7%)	0 (0%)	7% (0%–22%)	0.030
20 min	0 (0%)	0 (0%)	0% (–6% to 12%)	
40 min	1 (2%)	0 (0%)	2% (–4% to 16%)	0.322
60 min	0 (0%)	0 (0%)	0% (–6% to 12%)	
Ability to smile				
PACU arrival	2 (4%)	0 (0%)	4% (–2% to 19%)	0.098
20 min	0 (0%)	0 (0%)	0% (–6% to 12%)	
40 min	0 (0%)	0 (0%)	0% (–6% to 12%)	
60 min	0 (0%)	0 (0%)	0% (–6% to 12%)	
Ability to speak				
PACU arrival	2 (4%)	0 (0%)	4% (–2% to 19%)	0.099
20 min	1 (2%)	0 (0%)	2% (–4% to 16%)	0.322
40 min	1 (2%)	0 (0%)	2% (–4% to 16%)	0.322
60 min	1 (2%)	0 (0%)	2% (–4% to 16%)	0.322
Ability to breathe deeply				
PACU arrival	1 (2%)	1 (1%)	1% (–6% to 15%)	0.532
20 min	0 (0%)	0 (0%)	0% (–6% to 12%)	
40 min	2 (4%)	0 (0%)	4% (–2% to 19%)	0.102
60 min	1 (2%)	0 (0%)	2% (–4% to 16%)	0.322
Tongue depressor test				
PACU arrival	1 (2%)	0 (0%)	2% (–4% to 16%)	0.322
20 min	0 (0%)	0 (0%)	0% (–6% to 12%)	
40 min	1 (2%)	0 (0%)	2% (–4% to 16%)	0.322
60 min	0 (0%)	0 (0%)	0% (–6% to 12%)	
5-s protrude tongue				
PACU arrival	0 (0%)	0 (0%)	0% (–6% to 12%)	
20 min	0 (0%)	0 (0%)	0% (–6% to 12%)	
40 min	1 (2%)	0 (0%)	2% (–4% to 16%)	0.322
60 min	0 (0%)	0 (0%)	0% (–6% to 12%)	

Data are number of patients (%).
PACU = postanesthesia care unit; CI = confidence interval.
Signs are presented in descending order of frequency in the TOF <0.9 group.
Train-of-four <0.9 *n* = 48 at all times except at PACU admission when *n* = 46. Train-of-four ≥0.9 *n* = 101 at all times except at PACU admission when *n* = 100.

suggest that residual blockade is a primary cause of muscle weakness in the early recovery period.

General weakness was the most common symptom reported in the TOF <0.9 group at PACU arrival (91% of patients) through 60 minutes after admission (73% of patients). Furthermore, severity of general weakness (overall weakness) was high in these patients on arrival to the PACU (7 on a scale of 0 to 10) until the 60-minute measurement time (5 on a scale of 0 to 10). These finding are consistent with previous studies. In patients undergoing cardiac and orthopedic surgery, the most common symptom of residual paresis observed in the first 30 minutes after extubation was

general weakness.[12,24] Awake volunteers who received only a mivacurium infusion complained of generalized fatigue at a TOF ratio 0.85 to 0.9.[23] We hypothesize that incomplete neuromuscular recovery generates adverse effects on a variety of different muscle groups, resulting in the subjective experience of generalized/overall weakness or fatigue.

Visual symptoms (subjective difficulty completing 5-second eye-opening, subjective difficulty tracking object with eyes, blurry vision) were also frequently noted by patients in the TOF <0.9 cohort during the PACU admission. Ocular muscles seem to be particularly sensitive to NMBDs. In awake volunteer studies, all subjects noted significant visual disturbances at a TOF ratio of 0.9.[23,25] A high incidence of visual symptoms (blurred vision and difficulty focusing the eyes) has also been reported in postoperative surgical patients at risk for residual neuromuscular blockade.[8,24] In addition, weakness of facial and perioral muscles (subjective difficulty speaking and smiling, facial weakness) was experienced by a high percentage of patients in the TOF <0.9 cohort. Kopman et al.[23] reported a prominence of symptoms related to paralysis of facial muscles (subjective difficulty speaking and sipping water through a straw and a "flat expression") in awake volunteers at a TOF ratio of 0.75, which was the median TOF ratio measured in our TOF <0.9 group.

Signs of muscle weakness were observed less frequently than symptoms (Table 6). These findings are not surprising, because significant neuromuscular blockade (typically TOF ratios <0.5) must be present before patients are unable to perform standard tests of neuromuscular recovery.[26] At PACU arrival, only 9% of the TOF <0.9 cohort were unable to complete a 5-second head-lift test (the most common test used to assess residual weakness).[27] During the entire PACU stay, the median number of signs of muscle weakness was 0 in both groups. In patients who did have signs of residual paresis, ability to track objects with eyes was the most common test failed during the PACU stay; 35% of patients in the TOF <0.9 group failed this test at PACU arrival. These findings again suggest a sensitivity of ocular muscles to NMBDs. Inability to cough was the second most common sign of muscle weakness observed in patients with TOF ratios <0.9 (15% failure at PACU admission). Coughing requires the coordinated activity of several muscle groups, including the diaphragm, intercostal and abdominal muscles, and the glottis. Weakness in any of these muscles may impair the ability to cough. Our findings confirm previous studies that signs or tests of muscle weakness are poorly predictive of smaller degrees of residual blockade.[26]

There are limitations to the present investigation. First, the etiology of muscle weakness in the PACU is multifactorial. Although the study cohorts appeared similar in perioperative characteristics, it is possible that unmeasured variables may have accounted for differences in symptoms of muscle weakness and QoR between groups. In addition, hypertension was present in more patients in the TOF<0.9 group; it is possible that this condition could alter the pharmacokinetics or pharmacodynamics of rocuronium or neostigmine. Second, TOF measurements that were obtained in the PACU were recorded without baseline normalization or calibration. Therefore, the degree of neuromuscular blockade in both study cohorts was likely underestimated.[28,29] Because baseline control values with AMG average 1.15 (vs 0.96 with mechanomyography [MMG]), the isolated TOF measurements recorded in the PACU likely exceeded the "true" (MMG) TOF value by 10% to 15%.[30] An AMG TOF ratio of 0.9 measured in the PACU without baseline normalization may actually represent a MMG TOF ratio of 0.78 (i.e., 0.9/1.15)[30]; some of the patients in the TOF ≥0.9 cohort may have been assigned to the TOF <0.9 with normalization. This observation may account for the relatively frequent incidence of symptoms that were noted in the TOF ≥0.9 group on admission to the PACU. In addition, quantification of residual block with AMG can be difficult and potentially inaccurate in awake postoperative patients.[31] Third, assessments for signs and symptoms of muscle weakness were only conducted for the first 60 minutes of the PACU stay. We did not determine the time course until complete neuromuscular recovery. Fourth, tracheal extubation was performed in the AMG group when TOF ratios of at least 0.8 were achieved; most data suggest that this threshold should be at least 0.9 to 1.0 to ensure patient safety.

Compared with patients with objective evidence of more complete neuromuscular recovery (TOF ratios ≥0.9), patients with TOF ratios <0.9 in the PACU had a higher incidence and greater severity of symptoms of muscle weakness. ■

DISCLOSURES

Name: Glenn S. Murphy, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Glenn S. Murphy has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Conflicts of Interest: Glenn S. Murphy consulted for Merck and reported a conflict of interest with Merck Advisory Board.
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Attestation: Joseph W. Szokol approved the final manuscript.
Conflicts of Interest: The author has no conflicts of interest to declare.
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Residual Neuromuscular Block Should, and Can, Be a "Never Event"

To the Editor:

In their recent study, Murphy et al.[1] reported about one-third of patients arrived to the postanesthesia care unit (PACU) with a train-of-four ratio (TOFR) <0.9; however, this is not a new finding. In their classic article investigating the causes of death associated with anesthesia and surgery, Beecher and Todd[2] described increased mortality in patients receiving curare as "curare deaths." Although they did not specifically attribute the increased mortality to residual neuromuscular block (RNMB), it seems inescapable that, in fact, Beecher and Todd[2] were describing one of the earliest outcome studies, drawing attention to postoperative RNMB. In the late 1970s, Viby-Mogensen et al.[3]found the incidence of patients arriving to the PACU with a TOFR <0.7 to be 42%. The incidence of RNMB has, since then, been persistently high despite the use of intermediate duration neuromuscular blockers.[4] Addressing this long-neglected problem should be a priority safety concern because it may lead to serious clinical consequences in the PACU.[1]

We therefore urge universal adoption of objective (quantitative) monitoring of neuromuscular transmission as a standard guiding tracheal extubation (TE) decision.[5,6] It is ironic that RNMB is defined in terms of a TOFR, but TE is still performed without a device that measures and displays the TOFR.

We also recommend that both clinical and evoked responses to different patterns of nerve stimulation (not only TOFR) should be used to ascertain adequate neuromuscular recovery before TE.[6,7] Unfortunately, a wide discrepancy exists currently between anesthesiologists' perception of the occurrence of the problem and the actual incidence of >30%. In a recent survey, 80% of the respondents reported that they never encountered a single clinically significant RNMB, and 60% thought the incidence to be <1%.[8] Obviously, this false perception needs to be addressed, and practitioners should become more aware of the problem.

In view of the multiple accumulating reports, including that by Murphy et al.,[1] demonstrating the persisting high incidence of RNMB, we ask all anesthesia societies (national and international) to urgently create practice guidelines/standards governing the clinical management and monitoring of neuromuscular blockade. Until such guidelines are published and implemented, the incidence of adverse events related to RNMB in the PACU will continue to surpass all other PACU anesthetic-related morbidities.

A new culture of considering RNMB as one of the "never events"[9] should prevail, and anesthesia societies should encourage practitioners to achieve a goal of zero incidents.

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Use of Transesophageal Echocardiography to Avoid a Never Event

To the Editor

Two articles in a recent issue of *Anesthesia & Analgesia* emphasize the importance of an intraoperative procedural change we have instituted to enhance patient safety. The first article discussed "never" events,[1] while the second recounted aborting a cardiac surgical procedure before incision.[2] In response to our cardiac surgical program experiencing a similar "near miss" described in the latter article as well as internal review of our program revealing a similar episode in the past, we formally incorporated into our immediate preincision time out[3] for structural cardiac surgery cases the following item: "transesophageal echocardiographic (TEE) confirmation of cardiac surgical pathology." To satisfy this part of the time-out process, the staff anesthesiologist must display the surgical pathology on the TEE monitor and the staff cardiac surgeon must verbally acknowledge observing the appropriate pathology. Both the anesthesiologist and surgeon must then agree and document that the cardiac surgical pathology (as assessed by TEE) warrants surgical intervention. In the event of uncertainty by either physician, no incision is made until further review and discussion resolves any disagreement. If needed, additional consultation is obtained.