

The Train-of-Four Ratio in Patients Fulfilling Clinical Criteria for Extubation

Thavat Chanchayanon, M.D., Supawan Pongsiriwan, M.D.,
Sasikaan Nimmaanrat, M.D., M.Med (Pain Mgt), Chanatthee Kitsiripant, M.D.,
Natsana Wittayanupakorn, R.N., Anongluk Samakkee, R.N.

Department of Anesthesiology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.

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Abstract:

Objective: Neuromuscular blocking agents are commonly used in patients undergoing general anesthesia with an endotracheal tube. This can result in residual neuromuscular blockade and respiratory complications. The decision to extubate is usually based on clinical criteria assessment. This study aimed to investigate the train-of-four (TOF) ratio in patients having fulfilled the clinical criteria before extubation.

Material and Methods: This prospective observational study recruited 294 elective adult patients, with American Society of Anesthesiologists classification I–III, having undergone general anesthesia using muscle relaxants. The baseline TOF ratio was measured before surgery. Once the surgery was finished, the endotracheal tube would be removed if the patient fulfilled the clinical criteria for extubation. The TOF was immediately measured before extubation, and upon postanesthesia care unit (PACU) arrival. The TOF ratio was normalized by dividing it with the baseline TOF ratio.

Results: The overall median interquartile range (IQR) for the normalized TOF (nTOF) outcomes before extubation was 0.87 (0.74, 0.98). Of the 294 patients, 162 (55%) and 132 (45%) had a nTOF ratio of <0.9 and ≥ 0.9 , respectively. On PACU arrival, the overall median IQR TOF ratio was 0.9 (0.8, 0.98), with 51% and 49% of them having had an nTOF ratio of <0.9 or ≥ 0.9 , respectively.

Conclusion: In patients fulfilling the clinical criteria for extubation, approximately half of them demonstrated residual neuromuscular blockade (nTOF <0.9) immediately before extubation and upon PACU arrival. Close observation and monitoring of patients receiving muscle relaxants should be warranted.

Keywords: extubation, extubation criteria, TOF

Contact: Sasikaan Nimmaanrat, M.D., M.Med (Pain Mgt)
Department of Anesthesiology, Faculty of Medicine,
Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.
E-mail: snimmaanrat@yahoo.com.au

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Introduction

Muscle relaxants are frequently utilized in operating rooms to facilitate endotracheal intubation. This is performed to prevent damage to the respiratory tract and relax the muscles, thus improving the success of surgeries, such as thoracic or abdominal procedures. They are also utilized to prevent patient movement during surgery, and ensure cooperation with the ventilator, and so forth.

Generally, muscle relaxants work by inhibiting muscular contraction at the neuromuscular junction, leading to decreased skeletal muscle tone. However, this can result in residual neuromuscular blockade and increase the risk of respiratory complications^{1,2}, such as upper airway obstruction, hypoxia, respiratory failure, or reintubation, causing additional illnesses, disabilities, and fatalities.

Several methods can be used to prevent residual neuromuscular blockade, such as using short-acting or intermediate-acting muscle relaxants instead of long-acting drugs^{3,4}, administering reversal drugs after surgery⁵, and implementing appropriate assessment of the effects. For example, the patient can observe indicative signs and symptoms of drug recovery or use a nerve stimulator to measure muscle twitching to assess the degree of residual neuromuscular blockade before extubation⁶.

A literature review has shown that several studies exist on the removal of endotracheal tubes, using various assessment methods; including clinical criteria and nerve stimulation, both in the operating room and in the recovery room. Murphy et al. evaluated a train-of-four (TOF ratio) immediately before extubation and on postanesthesia care unit (PACU) arrival. The results showed that 88% and 32% of the subjects had TOF <0.9 immediately before extubation and upon PACU arrival, respectively⁷.

Previous studies have also compared residual neuromuscular blockade during endotracheal extubation using clinical assessment and nerve stimulation. The results showed a difference between the two methods, with some providing quantitative ratio data and others providing qualitative data, with no decrease in muscle twitching. The results of signs and symptoms of muscle weakness were significantly different between the quantitative and qualitative groups⁸. Similarly, the evaluation of endotracheal extubation, using both clinical assessment and nerve stimulator assessment, showed a significant difference in the occurrence of respiratory complications⁹.

Regarding TOF ratio assessment in the recovery room, a study by Yip et al. found that 29 out of 94 patients had a TOF ratio <0.9; accounting for 31%, and they had an average recovery time of 55 minutes¹⁰. Similarly, a study by Inervizzi et al. found that 28% of patients who received muscle relaxants during surgery and arrived in the recovery room within 15 minutes had a TOF <0.9¹¹.

Despite what has been mentioned previously, residual neuromuscular blockade assessment before extubation is usually performed by observing symptoms and clinical signs rather than using a nerve stimulator. This is the same practice in our operating room. We postulated that the incidence of residual neuromuscular blockade in the PACU is approximately 30%. Therefore, this study aimed to investigate the prevalence of TOF ratio <0.9 in patients who completed the clinical criteria for extubation.

Material and Methods

Study design

This prospective observational study was approved by the institutional Ethics Committee of the Faculty of Medicine, Prince of Songkla University (REC. 64-183-8-1) and has the Clinicaltrial.gov number TCTR20230130004.

Study setting and population

Data were collected from August 2021 to August 2022 at Songklanagarind Hospital in Thailand, including 301 patients aged between 20 to 60 years with American Society of Anesthesiologists (ASA) classification I–III undergoing non-emergency surgery via general anesthesia and muscle relaxants. Exclusion criteria included: informed refusal, neuromuscular diseases (e.g. Myasthenia Gravis, Guillain-Barré syndrome, Duchenne-Becker muscular dystrophy), requirement for deep block surgery, patients receiving drugs that affect muscle relaxants (e.g. aminoglycosides, magnesium sulfate, lithium, antiepileptic drugs), respiratory tract surgery (e.g. nose, throat, mouth), pregnancy, and participation in other studies.

During the study, subjective withdrawal criteria were considered when the pre-extubation clinical assessment did not meet all of its indications, when patients remained intubated, or when they had not received the reversal agent.

Study protocol

Patients meeting the inclusion criteria were selected and informed as per the study's scope. Their consent to participate was obtained after they had the opportunity to ask questions.

On the day of surgery, all participants had their vital signs monitored, including pulse oximetry, non-invasive blood pressure, and electrocardiography. The TOF ratio was measured using the TOF-Watch SX by placing 2 surface electrodes over the ulnar nerve, with the negative electrode near the wrist and the positive electrode 3 cm proximally. The sensor was placed at the thumb. The baseline TOF ratio was measured before induction. Balanced general anesthesia was maintained via an inhalation agent (sevoflurane or desflurane in mixed air/oxygen), opioids, and muscle relaxants. At the completion of the surgery, anticholinesterase (neostigmine 0.05 mg/kg and atropine 0.6–1.2 mg) was administered.

The staff anesthesiologists, anesthesia residents or nurse anesthetists evaluated the clinical signs and

symptoms¹⁴ before extubation; including: 1) spontaneous breathing with appropriate tidal volume (5 ml/kg), with no rapid shallow breathing or paradoxical breathing, 2) normal pulse oximetry (>97%) and capnography (35–40 mmHg), 3) sustained head lift for 5 seconds, leg lift for 10 seconds or hand grip, 4) no swelling of the airway, 5) no signs of shock (SBP >90 mmHg), and 6) the ability to follow a simple command; such as opening the eyes as instructed, combined with the TOF-Watch SX test before extubation by the research assistant. Additionally, the TOF outcome was not revealed to the staff anesthesiologists, anesthesia residents, or nurse anesthetists. After the tracheal tube was removed and the patient was transferred to the recovery room, the TOF was measured upon immediate PACU arrival. The TOF would be measured again if there were any respiratory complications, including desaturation <92%, stridor/upper airway obstruction, requirement for oxygen supplement, or reintubation. The reported TOF ratio values were normalized by dividing them by the baseline TOF ratio measured before induction^{15–17}.

If there were any respiratory complications; such as desaturation <92%, stridor/upper airway obstruction, postoperative oxygen requirement, reintubation or others, the research assistant or anesthetist nurse in the recovery room would use the TOF-Watch SX to evaluate and record the TOF ratio as the complications occurred.

The TOF ratios reported were normalized by dividing them with the baseline TOF ratio^{15–17}.

Sample size calculation

The sample size was calculated using the formula for precision of an estimated population^{18,19}. The estimated prevalence of a TOF ratio <0.9 is 0.3. Based on previous data, the prevalence of a TOF ratio <0.9 in the PACU was 32%⁷, 31%¹⁰, and 28%¹¹.

The required population size was 224 patients, with error (d)=0.06, alpha (α)=0.05, and Z (0.975)=1.96. After accounting for 20% of incomplete data, the final population size was calculated to be 280 patients.

Statistical analysis

Data analysis was performed using R program version 4.1.2. Categorical data were analyzed using Fisher’s exact test or the chi-squared test and presented as numbers and percentages. Continuous data between groups were analyzed using Student’s t-test or the Wilcoxon rank sum test and presented as the mean and standard deviation (S.D.) or median and interquartile range (IQR). A p-value<0.05 was considered statistically significant.

Results

From August 2021 to August 2022, 4,014 patients met the inclusion criteria. Of these, 847 were excluded; 3,167 were eligible, and 301 were enrolled in this study and gave informed consent. However, 7 patients withdrew from the study because they did not complete the clinical criteria assessment before extubation. Finally, 294 patients were analyzed, as shown in Figure 1.

Table 1 shows the characteristics of 294 patients. The median age was 44.5 years (IQR 38–51), with 10.5% (31 patients) classified as ASA physical status class I, 76.5% (225 patients) classified as class II, and 12.9% (38 patients) classified as class III. Out of the 294 patients, 151 had comorbidities, while 143 had none. Most of the patients were female and had an ASA physical status of class II.

Before extubation: The overall median IQR of the normalized TOF (nTOF) ratio was found to be 0.87 (0.74, 0.98), with 162 out of 294 patients (55.1%) having a nTOF ratio <0.9 and 132 out of 294 patients (44.89%) having a nTOF ratio greater than or equal to 0.9. On arrival at the PACU: the median IQR of the nTOF ratio was 0.9 (0.8, 0.98). 49.32% of patients had a nTOF ratio <0.9, and 50.68% had a nTOF ratio greater than or equal to 0.9 (Figures 2A and 2B).

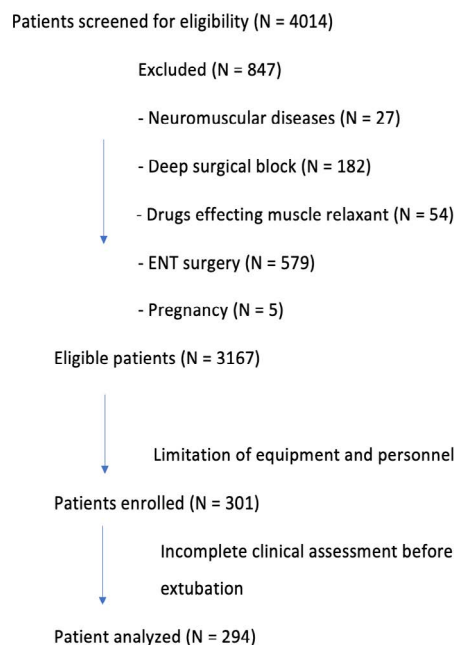


Figure 1 Consort flowchart

Table 1 Patient demographic data

Characteristics	N (%)
Age (years), median (IQR)	44.5 (38, 51)
Gender	
Male	18 (6.1)
Female	276 (93.9)
Weight (kg), median (IQR)	60.5 (52.5, 70)
Height (cm), median (IQR)	157 (154, 161)
BMI (kg/m ²), median (IQR)	24.1 (21.5, 27.7)
ASA Classification	
I	31 (10.5)
II	225 (76.5)
III	38 (12.9)
Comorbidities	
No	143 (48.6)
Yes	151 (51.4)
Baseline TOF before induction, median (IQR)	1 (1, 1)

ASA=American Society of Anesthesiologists, BMI=body mass index, TOF=train-of-four

Association between preoperative and intraoperative factors and nTOF before extubation

There were significant statistical differences found in certain factors; such as the presence of comorbidities, total dose of cisatracurium (12 mg in TOF ratio <0.9 group versus 13.5 mg in TOF ratio ≥0.9 group, p-value=0.019), total morphine equivalent dose (12 mg in TOF ratio <0.9 group versus 14 mg in TOF ratio ≥0.9, p-value=0.01) and operation time (160 minutes versus 180 minutes, p-value=0.016).

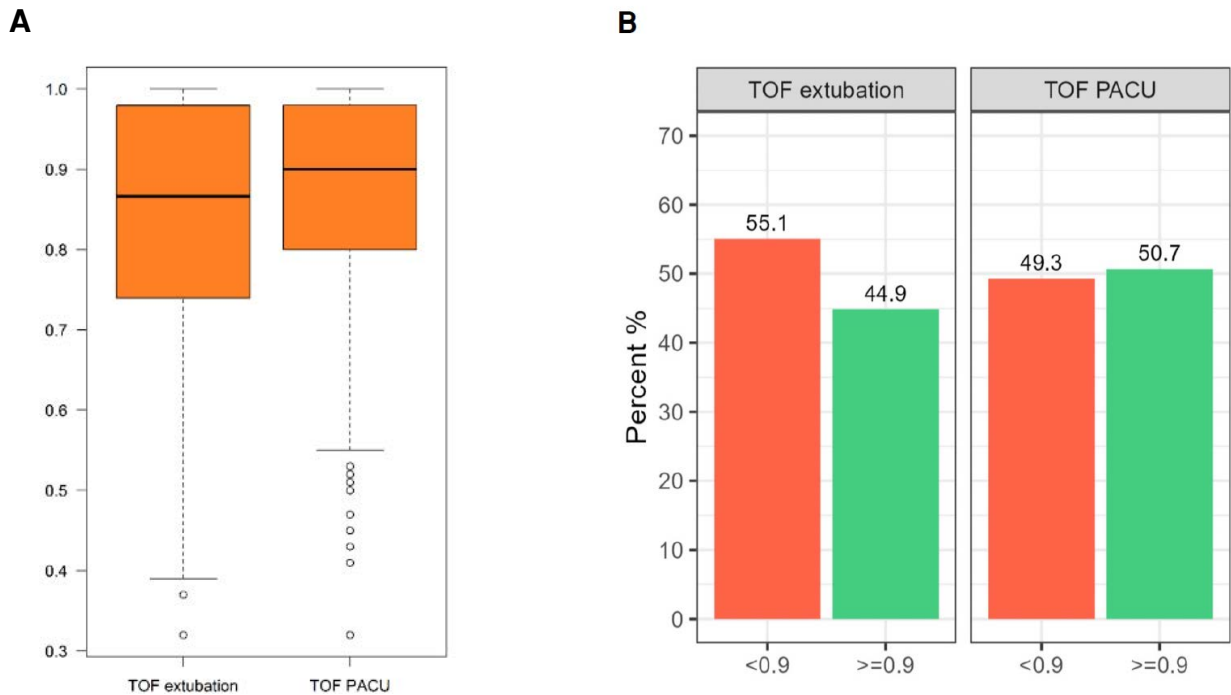
The time interval between the last dose of neuromuscular blocking agents and both neostigmine administration and extubation showed a shorter interval in the group with a TOF ratio <0.9 compared to the group with a TOF ratio ≥0.9; however, there was no significant statistical difference. Furthermore, there was no significant difference between the groups with a TOF ratio <0.9 and ≥0.9 in terms of comorbidities classified by the system, total morphine equivalent dose per hour (4.5 mg/hr vs. 4.4

mg/hr, p-value=0.38), and type of neuromuscular blocking agent: as shown in Table 2.

Association between preoperative and intraoperative factors and nTOF on PACU arrival

In comparison, the TOF ratio <0.9 group versus the TOF ratio ≥0.9 showed a significant statistical difference in the time interval between the last dose of NMBA and neostigmine administration (57 min vs 85 min, p-value=0.005), the time interval between the last dose of NMBA and extubation (68 min vs 79.5 min, p-value=0.006), the time interval between the last dose of NMBA and arrival at PACU (75 min vs 85 min, p-value=0.028), and the operation time (160 min vs 175 min, p-value=0.028).

However, there was no significant statistical difference in age, gender, ASA physical status, or comorbidity between the TOF ratio <0.9 group and the TOF ratio ≥0.9 group: as shown in Table 2.



PACU=postanesthesia care unit, nTOF=normalized train-of-four, TOF=train-of-four

Figure 2 (A) Median (interquartile range, IQR) of nTOF ratio before extubation and on PACU arrival, (B) Percentage of nTOF outcomes before extubation and on PACU arrival

As shown in Table 3, out of 294 patients, 21 experienced respiratory complications during their PACU stay; resulting in an incidence rate of 7.14%. Of these patients, 12 had an nTOF ratio <0.9, and 9 had an nTOF ratio ≥0.9 prior to extubation. Upon arrival at the PACU, 11 patients had an nTOF ratio <0.9, and 10 had an nTOF ratio ≥0.9. Notably, among the patients experiencing respiratory complications, 11 had an nTOF ratio <0.9 and 10 had an nTOF ratio ≥0.9. These patients had the same nTOF value as they did at the time of their PACU arrival.

Furthermore, there was no statistically significant difference in the nTOF ratio between patients with respiratory complications in the nTOF <0.9 group and those in the nTOF ≥0.9 group during the three periods of nTOF measurement.

There was no statistically significant difference in respiratory complications, such as desaturation <92%, postoperative oxygen requirement, or others, between the TOF <0.9 and TOF ≥0.9 groups. Additionally, no patient had stridor nor upper airway obstruction during the PACU period, and no one required reintubation: as shown in Table 4.

There were no statistically significant differences in the factors associated with respiratory complications during the patients' PACU stay, including age, BMI, comorbidities, ASA classification, type of muscle relaxants (only a few patients received rocuronium), operation time, the interval between PACU arrival and discharge as well as postoperative respiratory complications.

Table 2 Association between preoperative and intraoperative factors and nTOF before extubation and upon PACU arrival

Preoperative factors	nTOF before extubation			nTOF upon PACU arrival		
	nTOF <0.9 N (%) or median (IQR)	nTOF ≥0.9 N (%) or median (IQR)	p-value	nTOF <0.9 N (%) or median (IQR)	nTOF ≥0.9 N (%) or median (IQR)	p-value
Number of patients	162 (55.1)	132 (44.9)		145 (49.3)	149 (50.7)	
Gender			1			0.76
Male	10 (6.2)	8 (6.1)		10 (6.9)	8 (5.4)	
Female	152 (93.8)	124 (93.9)		135 (93.1)	141 (94.6)	
Age (years), median (IQR)	44 (38,51)	45 (38,51)	0.78	44 (38,50)	45 (38,52)	0.45
BMI (kg/m ²), median (IQR)	24 (21,28)	24 (22,28)	0.36	24 (22,28)	24 (21,28)	0.71
ASA Classification			0.86			0.91
I	18 (11.1)	13 (9.8)		15 (10.3)	16 (10.7)	
II	122 (75.3)	103 (78)		110 (75.9)	115 (77.2)	
III	22 (13.6)	16 (12.1)		20 (13.8)	18 (12.2)	
Comorbidities	74 (45.7)	77 (58.3)	0.04	78 (53.8)	73 (49)	0.48
Cardiovascular	30 (40.5)	27 (35.1)	0.60	30 (38.5)	27 (37)	0.98
Respiratory	16 (21.6)	20 (26)	0.66	21 (26.9)	15 (20.5)	0.47
Renal	7 (9.5)	5 (6.5)	0.71	8 (10.3)	4 (5.5)	0.43
Endocrine	24 (32.4)	27 (35.1)	0.86	27 (34.6)	24 (32.9)	0.96
Hematologic	8 (10.8)	9 (11.7)	1	11 (14.1)	6 (8.2)	0.38
Gastrointestinal	9 (12.2)	18 (23.4)	0.11	14 (17.9)	13 (17.8)	1
Rheumatologic	2 (2.7)	3 (3.9)	1	1 (1.3)	4 (5.5)	0.20
NIMBA			0.88			0.79
Cisatracurium	142 (87.7)	114 (86.4)		125 (86.2)	131 (87.9)	
Recuronium	20 (12.3)	18 (13.6)		20 (13.8)	18 (12.1)	

Table 2 (continued)

Preoperative factors	nTOF before extubation			nTOF upon PACU arrival		
	nTOF <0.9 N (%) or median (IQR)	nTOF ≥0.9 N (%) or median (IQR)	p-value	nTOF <0.9 N (%) or median (IQR)	nTOF ≥0.9 N (%) or median (IQR)	p-value
Total cisatracurium dose (mg)	12 (8, 16)	14 (10, 16)	0.02	12 (10, 15)	12 (10, 16)	0.31
Cisatracurium dose per hour (mg/hr)	4.5 (3.8, 5.7)	4.3 (3.6, 5.2)	0.13	4.6 (3.8, 5.7)	4.2 (3.6, 5.1)	0.08
Total rocuronium dose (mg)	65 (50, 72)	60 (50, 68)	0.26	60 (50, 72)	60 (50, 70)	0.89
Rocuronium dose per hour (mg/hr)	20.4 (17.1, 26.1)	18.1 (15.1, 27.9)	0.52	21.3 (17.5, 27.4)	17.6 (15.3, 21.4)	0.15
MME (mg)	12 (8, 15)	14 (10, 18)	0.01	12 (8, 15)	13 (10, 16)	0.09
MME per hour (mg/hr)	4.5 (3.3, 6.2)	4.4 (3.5, 9)	0.38	4.6 (3.2, 6.3)	4.3 (3.1, 6)	0.41
Interval between last NMBA dose and neostigmine (min)	60 (45, 84)	67 (50, 85)	0.08	57 (42, 79)	66 (52, 85)	0.01
Interval between last NMBA dose and extubation (min)	70 (52, 92)	75 (58, 94)	0.05	68 (50, 90)	80 (60, 95)	0.01
Interval between last NMBA dose and PACU arrival (min)	N/A	N/A	N/A	75 (60, 95)	85 (70, 100)	0.01
Operation time (min)	160 (110, 220)	180 (145, 230)	0.02	160 (110, 220)	175 (145, 235)	0.03

MME=morphine milligram equivalents, NMBA=neuromuscular blocking agent

Table 3 The nTOF ratio in patients who developed respiratory complications in PACU (N=21)

Variables	nTOF <0.9 N (%)	nTOF ≥0.9 N (%)	p-value
nTOF ratio before extubation	12 (57.1)	9 (42.9)	0.54
nTOF ratio on PACU arrival	11 (52.3)	10 (47.7)	1
nTOF ratio when respiratory complications occurred	11 (52.3)	10 (47.7)	1

nTOF=normalized train-of-four, PACU=postanesthesia care unit

Table 4 Association between respiratory complications and nTOF upon PACU arrival (N=21)

Variables	nTOF <0.9 N (%)	nTOF ≥0.9 N (%)	p-value
Total	11 (52.3)	10 (47.7)	
Respiratory complications			
SpO ₂ < 92%	5 (45.5)	4 (40.0)	1
Upper airway obstruction	0	0	0.827
Oxygen supplement	11 (100)	9 (90)	0.476
Reintubation	0	0	0.827
Others	1 (91.9)	0	1

nTOF=normalized train-of-four, PACU=postanesthesia care unit, SpO₂=oxygen saturation

Discussion

It was found that approximately half of the patients who fulfilled clinical criteria for extubation demonstrated residual neuromuscular blockade with nTOF <0.9 immediately before extubation and upon PACU arrival. The number of patients having nTOF ≥0.9 was slightly higher upon PACU arrival, as compared to just before extubation, because more neuromuscular junctions were free from the effect of neostigmine as time went by. This result is lower than what was reported in a previous study by Murphy et al., who stated that 88% of patients had a TOF <0.98. However, the difference in incidence can be explained by the differing clinical criteria used to decide extubation; such as the use of a 5-second head lift, hand grip, eye-opening on command, negative inspiratory force >-20cmH₂O or a vital capacity >15ml/kg.

There are studies reporting a higher percentage of patients with nTOF ratio <0.9 at extubation (63.5%²⁰ and

64.7%²¹). The difference in results among studies may be due to the type of neuromuscular blocking agent used, reversal with neostigmine, clinical decision-making for extubation, and neuromuscular monitoring²².

This study found that the nTOF <0.9 occurred more frequently in patients without comorbidities and in those who received a lower cumulative dose of cisatracurium and morphine equivalents. The healthier patients might receive less consideration upon extubation. Baillard et al.²³ found that a high total dose of muscle relaxant (rocuronium) led to inadequate recovery from neuromuscular blockade.

Previous studies have shown that a TOF ratio measured in PACU demonstrated residual neuromuscular blockade (defined as a TOF ratio <0.9) at rates of 28.6%¹¹, 15-31%²², 31%¹⁰, and 33%²³. However, this study still found a higher incidence, with 49.32% of patients having a nTOF ratio <0.9 upon PACU arrival. This outcome is quite similar

to the findings of Debaene et al., who reported that 45% of patients had a TOF ratio <0.9 ²⁴.

Several factors associated with residual neuromuscular blockade at the PACU in this study were identified; including shorter time intervals between the last dose of the neuromuscular blocking agent and neostigmine administration or extubation, shorter operation times and shorter time intervals between the last dose of the neuromuscular blocking agent and arrival in PACU. This is consistent with findings from other studies^{10,20}, despite this study having an average interval of 75 minutes between the last dose of the neuromuscular blocking agent and arrival in PACU, which is shorter compared to other studies at 81 minutes¹⁰ and 117 minutes²³. This may explain the higher incidence of residual neuromuscular blockade in this study. Another reason may be the difference in timing of measurement, as the study by Invernizzi et al. reported measuring the TOF ratio at PACU within 15 minutes after arrival¹¹, which could result in a variation in the incidence of TOF ratios <0.9 .

Another factor that should have been taken into account was the individual's decision to extubate, as staff anesthesiologists, anesthesia residents, and certified nurse anesthetists had different experiences. However, there are clinical criteria for extubation, which serve as a checklist. Patients who did not meet these extubation criteria were excluded from this study.

Additionally, several other factors, such as interactions with other drugs, residual volatile agents, temperature, and comorbidities, such as renal or hepatic impairment^{10,11}, may also contribute to the increase in residual neuromuscular blockade.

Previous studies have reported varying rates of incidence of respiratory complications: ranging from 1.3% to 43.32%^{1,25,26}. The etiology of this event is multifactorial, such as residual neuromuscular blockade and comorbidities, such as chronic obstructive pulmonary disease, asthma,

obstructive sleep apnea, use of opioids, or poor pain control. In this study, it was found that the incidence of respiratory complications was 7.14%, with 21 out of 294 patients affected. This difference in incidence may depend on the definition of respiratory complications used in each study. For example, Murphy et al. defined respiratory complications^{26,27} as upper airway obstruction requiring intervention, mild to severe hypoxia, signs of respiratory distress, and inability to breathe. Another study defined it as the presence of stridor, desaturation, or wheezing²⁵. Differences in the methods of anesthesia, use of reversal agents, or even the use of neuromuscular monitoring during surgery may also contribute to varying incidence rates^{10,28}.

Additionally, previous studies have shown that patients with a TOF ratio <0.9 tend to have a higher incidence of respiratory complications as well as more severe symptoms of muscle weakness⁸. However, in this study, no statistically significant difference in the incidence of respiratory complications between patients with an nTOF ratio <0.9 and those with an nTOF ratio greater than or equal to 0.9, as measured at three different time points was found: before extubation, on arrival at the PACU, and at the time of respiratory complication occurrence. This may be explained by the fact that the definition of respiratory complications is not solely related to residual neuromuscular blockade but can also be caused by other factors, such as subcutaneous emphysema or anemia. The use of supplemental oxygen also contributed to the incidence of respiratory complications in this study, as recorded in the postoperative oxygen requirement.

We enrolled only a fraction of the eligible patients for this study, using convenient sampling due to limitations of equipment and personnel. Additionally, some cases started simultaneously, or there was a distance between operation rooms. Secondly, we did not exclude patients with hepatic or renal comorbidities. This could have affected the incidence of residual neuromuscular blockade. Thirdly, the TOF ratio

is not the best method to detect residual paralysis in PACU; double burst stimulation is preferred; however, it is not commonly used in clinical practice²⁹. Finally, this research was an observational study that aimed to replicate routine clinical practice. Therefore, the respiratory complications observed might differ slightly from the specific signs and symptoms of residual neuromuscular effects.

Conclusion

In patients that fulfilled clinical criteria for extubation, approximately half of them demonstrated residual neuromuscular blockade, with an nTOF <0.9 immediately before tracheal extubation and upon PACU arrival. To ensure patient safety, close observation and monitoring in patients receiving muscle relaxants must be maintained.

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