Tof-guided rocuronium administration shortens spontaneous breathing recovery and reduces consumption compared to time-based dosing: A prospective comparative study.

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Abstract

Rocuronium is commonly used in general anesthesia. It is used to aid endotracheal intubation and ensure adequate relaxation during surgery. However, time-based dosing of neuromuscular blocking agents without objective neuromuscular monitoring can result in cumulative overdosing, residual neuromuscular blocking activity, and delayed postoperative respiratory recovery. Train-of-four (TOF) neuromuscular monitoring is more accurate for titrating neuromuscular blocking agents. However, it is not commonly used. This study sought to investigate the effects of TOF-guided rocuronium administration compared with conventional time-based dosing on spontaneous respiratory recovery and the total amount of rocuronium used during elective surgery.

A prospective non-randomized comparative clinical study design was used. This design enrolled 150 adult patients classified as American Society of Anesthesiologists (ASA) I-II, aged 16-66 years, undergoing elective surgery at Al-Badari Hospital in Zakho and Azadi Teaching Hospital in Duhok between November 2024 and April 2025. They were sequentially assigned to two groups: Group T, patients who received time-based dosing, and Group S, patients who received TOF-guided dosing. All patients were administered an initial dose of rocuronium based on ideal body weight (0.6-1.2 mg/kg). Maintenance doses were administered at set time intervals in Group T. However, in Group S, TOF response was used to guide dose administration. Spontaneous breathing time from the last administered dose and total amount of rocuronium used were used as outcome measures.

Patients in the TOF group had a shorter spontaneous breathing time than those in the time-based group. They used lower doses of rocuronium. Delayed spontaneous breathing time was less common in the TOF group. This indicates that the TOF neuromuscular response is useful in the practice of anesthesia.

1. Introduction

Anaesthesiologists often use skeletal muscle relaxants, which are also known as neuromuscular blocking agents (NMBAs). Their typical applications include mechanical breathing support, patient preparation for surgery, and intubation with little tissue damage [1]. The chemical structure classifies these substances as either steroidal, benzylisoquinoline compounds, asymmetrical mixed-onium chlorofumarate, or depolarising muscle relaxants; the method by which this happens determines the category into which they fall. The structure [2], metabolism, and mode of action of NMBAs relaxants vary, but the duration of impact also plays a role in determining their therapeutic applicability. There are a number of variables that could affect how long these medications take to start working [3]. Use of NMBAs may be associated with risk of side effects and problems, notwithstanding their usefulness. Neuromuscular block must be constantly monitored, and the Train-Of-Four (TOF) method is a popular tool for this [4]. Being aware of the possible side effects and ways to mitigate them is crucial in clinical practice when dealing with these

medications. The main representative of the class of reversal medicines used to improve the management of neuromuscular block is sugammadex [5]. There are two main categories of neuromuscular blocking drugs, according to conventional wisdom: depolarising and non-depolarising. The most well-known depolarising drug, succinylcholine, has stereochemical similarities with acetylcholine and acts similarly at the neuromuscular junction [6]. This results in the endplate and surrounding muscle membrane being depolarised, and there are noticeable fasciculations in the muscles as a clinical manifestation. Depolarisation of the neuromuscular junction persists until succinylcholine diffuses out of the receptor site [7].

One way of determining the degree of neuromuscular blockade with the help of a peripheral nerve stimulator is by performing a Train of Four (TOF) test. The main aim of TOF monitoring is to ensure that the patient is sufficiently paralyzed, at the same time ensuring that the minimum effective dose of neuromuscular blocking agents (NMBAs) is administered [8]. Patients undergoing peripheral nerve stimulation can be monitored better when neuromuscular blocking agents (NMBAs) are administered, reducing the risk of unwanted side effects, including movement, paralysis, and delayed recovery as a result of drug and metabolite accumulation [9]. There are several ways of evaluating neuromuscular blockade; however, TOF is the most frequently used method, as it is one of the least painful methods of peripheral nerve stimulation in intensive care units. The process of TOF involves placing electrodes along the nerve pathway, after which the muscle twitches are counted. Under normal circumstances, when no neuromuscular blocking agents (NMBAs) are administered, every time an electrical impulse is passed down the nerve, it causes a muscle to contract equally in strength and time. However, as the degree of neuromuscular blockade increases, muscle twitches become progressively weaker, with the fourth twitch disappearing first, then the third, second, and finally, the first twitch [12].

The aim of this research was to evaluate the effectiveness of Train of Four (TOF) monitored rocuronium administration compared with traditional time-based dosing in reducing drug consumption and time to spontaneous respiratory recovery in adult patients undergoing elective surgery under general anaesthesia. The study was not conducted in a random manner; however, it was conducted in a real-world setting in two hospitals in Iraq.

2. PATIENTS AND METHODS
Study Design and Setting

Al-Badari Hospital in Zakho and Azadi Teaching Hospital in Duhok were the sites of this prospective, randomised clinical experiment. The study period began in November 2024 and ended in April 2025, a total of six months. Two weeks of training were conducted in the operating rooms of both institutions prior to data collection. The course included standardised anaesthesia techniques, neuromuscular blockade evaluation, and data recording. Neither the design nor the enrolment of the research met the criteria for a randomised controlled trial.

Study Population

Individuals scheduled for elective surgeries under general anaesthesia needing rocuronium neuromuscular blockade were included in the research. Patients' ages ranged from sixteen to sixty-six, and they were all classed as having an ASA physical status of I or II. This age range avoids the very young and very old, who may have very different neuromuscular pharmacokinetics and pharmacodynamics, and represents the adult surgical population that is most often seen in the participating centres.

Inclusion and Exclusion Criteria

Exclusion criteria included severe disorders of the heart, lungs, or neuromuscular system; renal failure; hepatic dysfunction; pregnancy; or expected difficulty with the airway. Patients were also not eligible if they had a history of serious adverse reactions to rocuronium or any other neuromuscular blocking agent, were taking any drugs known to disrupt neuromuscular transmission, such as aminoglycoside antibiotics, magnesium sulphate, or calcium channel blockers, or had any injury or surgery to their upper limbs that would prevent the electrodes from being placed correctly. Also not included were patients having surgeries that were planned to last less than an hour, because it wouldn't give us enough time to test out different maintenance dosage plans.

Sample Size and Group Allocation

A total of 150 patients were sequentially recruited over the research period, contingent upon feasibility and patient availability. There was no explicit estimate of the sample size or power analysis. Using an alternating serial number technique, patients were put into two equal groups of 75 people each. This is an example of systematic allocation, not real randomization. Group T got rocuronium based on the time of day, which is how it is usually done at the institution. Group S, on the other hand, received rocuronium based on neuromuscular monitoring. All participants provided written informed consent after a comprehensive elucidation of the research aims and methodologies.

Data Collection and Study Variables

Every patient had the same preoperative examination done. The data gathered included age, sex, height, weight, body mass index, ASA physical status, history of past operations, previous anesthesia-related problems, and the existence of neuromuscular diseases. Intraoperative factors included rocuronium induction and maintenance dosages, total cumulative dose, length of surgery, duration of neuromuscular blockade, and time to recovery of spontaneous breathing.

Rocuronium Preparation and Dosing

Utilized the ideal body weight (IBW) to figure out how much rocuronium to give as an induction dose. To get IBW for males, a formula was used: [height (cm) − 152.4] × 0.91 + 50. The formula used for women was [height (cm) − 152.4] × 0.91 + 45.5. The doctor decided how much of the drug to give the patient depending on what they believed was optimal. The dose ranged from 0.6 to 1.2 mg/kg IBW. A 50 mg vial of rocuronium has 5 mL of liquid in it (10 mg/mL). Then, it was combined with normal saline to produce a total of 20 mL, which brought the final concentration to 2.5 mg/mL. The maintenance doses were roughly one-sixth of the induction dose, and they were modified based on what was observed by clinical or neuromuscular monitoring.

Group-Specific Procedures
Group T (Time-Based Administration)

In Group T, rocuronium maintenance doses were administered at set intervals according to the institution's rules. The timing of each incremental dose, the total cumulative maintenance dose, the time to spontaneous breathing, the time between the last dose and the start of spontaneous breathing, and the overall duration of neuromuscular blockade were all noted. Rocuronium was no longer given when the skin suturing began.

Group S (Neuromuscular Monitoring–Guided Administration)

A medical-grade peripheral nerve stimulator that could give train-of-four (TOF) stimulation was used to check for neuromuscular blocking in Group S. Electrodes were positioned over the ulnar nerve at the wrist, and the contraction of the adductor pollicis muscle was recorded.

After induction, the baseline TOF response was measured, and then stimulations were done at clinically relevant times throughout the operation. Incremental dosages of rocuronium were given only when the TOF response showed that the neuromuscular blockade was not strong enough. After skin closure began, no more rocuronium was given. The recorded variables included the timing of TOF evaluations, the need for incremental dosing, the duration required for the restoration of spontaneous respiration, and the delay between the last TOF response and the onset of spontaneous breathing.

Statistical Analysis

The data were examined using IBM SPSS Statistics version 23. Shapiro–Wilk was used to test to see whether the continuous variables were normal. Data that followed a normal distribution were represented as mean ± standard deviation and analyzed using the independent samples t-test. Conversely, data that did not follow a normal distribution were represented as median (interquartile range) and analyzed using the Mann–Whitney U test. Fisher's exact test was used to compare categorical variables where they were acceptable. It was thought that a p-value of less than 0.05 was statistically significant.

3. Results
Patient Flow and Group Allocation

A total of 150 patients were included in the final analysis, with no exclusions or missing data. Seventy-five patients were allocated to the TOF-guided group and 75 to the conventional time-based group.

Baseline Characteristics of the study groups

Baseline characteristics were analyzed to examine the association between TOF nerve stimulator use and continuous variables in 150 patients. The mean (SD) age was 39.99 (11.98) years in the TOF group and 34.35 (12.38) years in the non-TOF group, with a significant mean difference of 4.640 years (95% CI: 0.711–8.569; p = 0.021). The mean (SD) height was 166.6 (8.9) cm in the TOF group and 170.9 (8.8) cm in the non-TOF group, with a significant mean difference of 4.250 cm (95% CI: 1.403–7.104; p = 0.004). Other baseline continuous variables, including weight and BMI, did not differ significantly between the groups (Table 1).

Table 1. Baseline continuous characteristics of the study groups

Characteristics	(TOF) Nerve Stimulator Groups			MD	(95% CI)		Sig.*
	With TOF (n=75)	Without TOF (n=75)	Total (n=150)		Lower	Upper	
Age, Mean (SD), years	34.35 (12.38)	39.99 (11.98)	36.7 (12.4)	4.640	0.711	8.569	0.021*
Height, Mean (SD), cm	166.6 (8.9)	170.9 (8.8)	168.8 (8.9)	4.250	1.403	7.104	0.004*
Weight, Mean (SD), kg	74.9 (13.2)	72.5 (13.6)	73.7 (13.4)	-2.373	-6.708	1.961	0.281
BMI, Mean (SD), kg/m²	29.8 (4.7)	30.7 (5.0)	30.3 (4.9)	-0.967	-2.532	0.597	0.224

* The t-test statistic are significant at the 0.05 level., Abbreviations: TOF; A train-of-four (TOF) Nerve Stimulator, BMI;
Body Mass Index, SD; Standard Deviation, MD; mean difference, (95%)

Crosstabulation analysis using chi-square tests and risk estimates showed no statistically significant association between the use of a TOF nerve stimulator and baseline categorical characteristics, including age ≥35 years, BMI ≥30, gender, ASA physical status I, and previous surgery (Table 2)

Table 2. Baseline categorical variable Characteristics for the Patients and their association with A Train-of-four (TOF) Nerve Stimulator

Characteristics		(TOF) Nerve Stimulator Group			OR	(95% CI)		Sig.*
		With TOF (n=75)	Without TOF (n=75)	Total (n=150)		Lower	Upper	
Age >=35 Years, No. (%)	Yes	42 (56.0)	33 (44.0)	75 (50.0)	1.055	0.766	1.453	0.142
	No	33 (44.0)	42 (56.0)	75 (50.0)				
BMI >=30, No. (%)	Yes	33 (44.0)	42 (56.0)	75 (50.0)	1.273	0.920	1.761	0.142
	No	42 (56.0)	33 (44.0)	75 (50)				
Gender, No. (%)	Male	35 (46.7)	33 (44.0)	68 (45.3)	1.055	0.766	1.453	0.743
	Female	40 (53.3)	42 (56.0)	82 (54.7)				
ASA I, No. (%)	Yes	55 (73.3)	46 (61.3)	101 (67.3)	1.334	0.911	1.954	0.117
	No	20 (26.7)	29 (38.7)	29 (32.7)				
Previous surgery, No. (%)	Yes	44 (58.7)	36 (48.0)	80 (53.3)	0.805	0.579	1.119	0.190
	No	31 (41.3)	39 (52.0)	70 (46.7)				

Abbreviations: TOF; A train-of-four (TOF) Nerve Stimulator, OR; Odds Ratio (TOF) Nerve Stimulator With VS Without
BMI; Body Mass Index, ASA; Refers to the American Society of Anesthesiologists (ASA) Physical Status Classification System, (95% CI); 95% Confidence Interval

Primary Outcome
Time from the Last Dose to Spontaneous Breathing Onset by TOF Group

All 150 patients were included in the analysis. Seventy-five patients were allocated to the group managed without TOF monitoring, and 75 patients to the group managed with TOF monitoring. The primary endpoint was

the time from the last administered dose of rocuronium to the onset of spontaneous breathing, measured in minutes. Descriptive statistics showed that in the without TOF group, the mean time to spontaneous breathing onset was 27.29 minutes (SD 10.46), with a median (IQR) of 25 (12) minutes and a range of 54 minutes (minimum 11, maximum 65). In the TOF group, the mean time was 23.15 minutes (SD 9.76), with a median (IQR) of 20 (10) minutes and a range of 54 minutes (minimum 10, maximum 64). For the total study population, the mean time was 25.22 minutes (SD 10.30), with a median (IQR) of 22 (11) minutes and a range of 55 minutes (minimum 10, maximum 65) (Table 3).

Table 3. Descriptive statistics of Time from Last Dose to Spontaneous breathing begins (minutes) by TOF

Descriptives statistics	(TOF) Nerve Stimulator Groups		
	Without TOF (n=75)	With TOF (n=75)	Total TOF (n=150)
Mean	27.29	23.15	25.22
Median	25	20	22.00
Std. Deviation	10.461	9.762	10.296
Range	54	54	55
Minimum	11	10	10
Maximum	65	64	65
Interquartile Range	12	10	11

Abbreviations: TOF; A train-of-four (TOF) Nerve Stimulator,

A Mann–Whitney U test was performed because the primary outcome variable was not normally distributed. The test was used to compare the time from the last administered dose of rocuronium to the onset of spontaneous breathing between patients managed with Train-of-Four (TOF) neuromuscular monitoring and those managed without TOF monitoring. Patients in the TOF-monitored group demonstrated a significantly shorter time to spontaneous breathing onset compared with the non-TOF group. The median time was 20 minutes (IQR: 10) in the TOF group versus 25 minutes (IQR: 12) in the non-TOF group. This difference was statistically significant (Mann–Whitney U = 2051.5, Z = −2.883, p = 0.004), indicating a significant association between the use of TOF monitoring and faster recovery of spontaneous breathing (Table 4).

Table 4. Primary outcome: Time from Last Dose to Spontaneous breathing begins (minutes) association with TOF Nerve Stimulator Groups

Primary outcome	(TOF) Nerve Stimulator Groups	n	Median (95% CI)	IQR	Mean Rank	Mann-Whitney U	Z	Sig.*
Time from Last Dose to Spontaneous breathing begins (minute)	Without TOF	75	25 (23 – 28)	12	85.7	2051.5	-2.883	0.004
	With TOF	75	20 (20 – 20)	10	65.4			
	Total	150	22 (20 – 25)	11				

* The Mann-Whitney Test is significant at the 0.05 level.
Abbreviations: TOF; A train-of-four (TOF) Nerve Stimulator, n; sample size, IQR; Interquartile Range

A chi-square test was performed to assess the association between the use of Train-of-Four (TOF) nerve stimulator monitoring and delayed recovery of spontaneous breathing, defined as a time ≥ 22 minutes from the last dose of neuromuscular blocking agent. There was a statistically significant association between TOF monitoring and delayed recovery of spontaneous breathing ($p < 0.001$). Patients managed without TOF monitoring had higher odds of delayed spontaneous breathing recovery compared with those managed with TOF monitoring (OR = 1.875; 95% CI: 1.327–2.651). Specifically, 64.9% of patients in the non-TOF group experienced spontaneous breathing recovery ≥ 22 minutes, compared with 35.1% in the TOF group, indicating that the use of TOF monitoring was associated with faster recovery of spontaneous breathing (Table 5).

Table 5. Primary outcome: Time from Last Dose to Spontaneous breathing begins (>= 22 minutes) association with TOF Nerve Stimulator Group

Primary Outcome		(TOF) Nerve Stimulator Groups			OR	(95% CI)		Sig.*
		Without TOF (n=75)	With TOF (n=75)	Total (n=150)		Lower	Upper	
Time from Last dose to SB >= 22 minutes, No. (%)	Yes	50 (64.9)	27 (35.1)	77 (51.3)	1.875	1.327	2.651	< 0.001
	No	25 (34.2)	48 (65.8)	73 (48.7)				

* Chi-square statistic is significant at the 0.05 level, and highly significant at < 0.001.

Abbreviations: TOF; A train-of-four (TOF) Nerve Stimulator, (95% CI); 95% Confidence Interval, OR; Odds Ratio (TOF) Nerve Stimulator Without VS With.

Secondary Outcome
Total Rocuronium Maintenance Dose (mg) of Muscle Relaxant

A Mann–Whitney U test was used to compare the total rocuronium maintenance dose between patients managed with Train-of-Four (TOF) neuromuscular monitoring and those managed without TOF monitoring, as the data were not normally distributed. Patients in the TOF-monitored group required a significantly lower total rocuronium maintenance dose compared with the non-TOF group. The median dose was 6 mg (IQR 7; 95% CI: 6–10) in the TOF group versus 15 mg (IQR 10; 95% CI: 13.9–20) in the non-TOF group. The difference between groups was statistically significant (Mann–Whitney U = 1321.5, Z = −5.665, p < 0.001), indicating that TOF-guided neuromuscular monitoring was associated with reduced rocuronium consumption (Table 6).

Table 6. Secondary outcome: Total Rocuronium Maintenance Dose (mg) association with TOF Nerve Stimulator Groups

Secondary outcome	(TOF) Nerve Stimulator Group	n	Median (95% CI)	IQR	Mean Rank	Mann–Whitney U	Z	Sig.*
Total Rocuronium Maintenance Dose (mg)	Without TOF	75	15 (13.9 to 20)	10	95.38	1321.5	-5.665	< 0.001
	With TOF	75	6 (6 to 10)	7	55.62			
	Total	150	10 (10 to 13.9)	10				

The Mann-Whitney Test is significant at the 0.05 level.

Discussion

This study evaluated the impact of quantitative train-of-four (TOF) neuromuscular monitoring on intraoperative rocuronium consumption and recovery-related outcomes during general anesthesia. The principal finding was that TOF-guided dosing was associated with more controlled neuromuscular blocker administration and improved recovery timing compared with conventional time-based dosing without objective monitoring. These findings are consistent with previous studies demonstrating that quantitative neuromuscular monitoring enhances the safety and efficiency of anesthetic management [13].

Rocuronium is widely used because of its rapid onset and intermediate duration of action; however, its pharmacodynamic profile is strongly dose dependent. In the absence of objective neuromuscular monitoring, anesthesiologists may administer additional doses preemptively to maintain adequate surgical relaxation, which can result in cumulative overdosing and delayed recovery [5,7,14]. In the present study, TOF-guided management enabled individualized titration of incremental doses based on measurable neuromuscular responses, thereby reducing unnecessary redosing and excessive cumulative exposure. Similar findings have been reported in previous studies evaluating quantitative neuromuscular monitoring [15].

An important outcome of this study was recovery timing, particularly the interval between the last rocuronium dose and the return of spontaneous respiration. Prolonged recovery intervals are clinically relevant, as they are associated with an increased risk of residual neuromuscular blockade and postoperative respiratory complications [4,9,10,16]. The lower incidence of delayed recovery observed in the TOF-monitored group supports the role of objective neuromuscular monitoring in minimizing residual neuromuscular blockade [1,2,17].

It is important to distinguish TOF-guided neuromuscular management from deep neuromuscular blockade, as these concepts are not equivalent. TOF monitoring is a method for assessing neuromuscular transmission and guiding appropriate dosing, whereas deep neuromuscular blockade refers to a pharmacological state characterized by profound suppression of neuromuscular responses [18]. The present study focused on TOF-guided

dosing during routine anesthesia and did not evaluate deep neuromuscular blockade strategies.

The findings of this study are aligned with contemporary international guidelines that recommend the routine use of quantitative neuromuscular monitoring to reduce the incidence of residual paralysis and related complications [1,2,9,19]. Despite these recommendations, the adoption of objective neuromuscular monitoring remains inconsistent, particularly in low-resource clinical settings. The present results provide further evidence supporting the implementation of TOF monitoring as a standard component of anesthetic practice.

Study Limitations
There are a few things that should be kept in mind. The non-randomized, sequential assignment of patients may result in selection bias and baseline disparities across groups, thereby compromising internal validity. The investigation was performed in two locations, which may restrict the generalizability of the results. Train-of-Four (TOF) measurements may also be affected by the properties of the device, the location of the electrodes, and the method of the operator, which might lead to measurement variability [16,20]. Additionally, quantitative monitoring was not used to evaluate postoperative neuromuscular function in the recovery unit, perhaps resulting in an underestimation of the actual incidence of residual neuromuscular blockade [9,15]. When looking at the findings, these restrictions should be kept in mind.

Clinical Implications
This work shows that, despite some constraints, quantitative TOF-guided neuromuscular monitoring enhances rocuronium dose accuracy and promotes superior recovery profiles in comparison to time-based dosing alone. These results support the existing guidelines that say neuromuscular monitoring should be done regularly [1,2]. Additional multicenter trials are necessary to validate these findings and assess postoperative outcomes.

The findings of this research demonstrate that the use of train-of-four (TOF) neuromuscular monitoring correlated with reduced cumulative maintenance doses of rocuronium and a decreased recovery time for spontaneous breathing, in contrast to traditional time-based dosing methodologies. These results indicate that quantitative neuromuscular monitoring may facilitate more accurate titration of neuromuscular blocking drugs during general anesthesia.

Recommendations
This study's results suggest that quantitative train-of-four (TOF) neuromuscular monitoring might enhance the precision of intraoperative rocuronium titration and promote the prompt resumption of spontaneous breathing. Future research with bigger sample sizes and randomized designs across many locations is advised to further corroborate these results and to examine their consistency in various clinical contexts.

Acknowledgements

Conflict of Interest
The author declares that there is no conflict of interest.

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Publisher Details