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Original Article

Anaesthesia Section

Adequacy of Reversal of Neuromuscular Blockade with or without Train-of-Four Monitoring: A Randomised Controlled Study

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ABSTRACT

Introduction: Adequate reversal of Neuromuscular Blockade (NMB) is essential when using muscle relaxants to avoid residual paralysis postoperatively. Reversal can be achieved using clinical parameters or, alternatively, by Train-of-Four (TOF) monitoring.

Aim: To evaluate the adequacy of successful NMB reversal using clinical parameters-based endpoints compared to using TOF monitoring.

Materials and Methods: The hospital-based randomised controlled study conducted in the Department of Anaesthesiology, SDM Medical College, Dharwad, Karnataka, India for a peroid of two years from November 2019 to December 2021. Consisted of 120 subjects divided into two groups: Group-C (Clinical parameters) and group T (TOF monitoring), aged 18-60 years of either sex with American Soceity of Anaesthesiologists (ASA) physical status I and II, undergoing elective surgery under general anaesthesia requiring intubation. Extubation was achieved in group C using clinical parameters like return of spontaneous respiratory efforts, adequate Tidal Volume (TV) (≥5 mL/kg), obeying simple commands, absence of excessive secretions, and in group T using TOF monitoring. The t-test was used to compare the difference between the groups. The Chi-square test was done for contingency data. A p-value of less than or equal to 0.05 (p-value ≤0.05) indicates statistical significance.

Results: In the study, both group C and group T were comparable in terms of age {(41.15±10.23 years, 41.03±11.9 years) p-value=0.95}, sex (m/f) {(46.6%/53.3% and 63.3%/36.6%) p-value=0.06}, and Basal Metabolic Index (BMI) {≤25=59.1%, 25-30=33.3%, ≥30=7.5%, p-value=0.57}, respectively. Five patients in group C had residual paralysis, whereas none in group T. Reversal-extubation time in minutes (min) in group C {5.9±2.2, 5.4 (2-15.2)} and group T {6.6±1.9, 6.24 (3.3-12.2)} (p-value=0.07), TOF value at the time of extubation in group C {72.1±11.6, 72 (41-91)}, group T {72.75±2.74, 72 (70-79)} (p-value=0.69). TOF value after 10 minutes of extubation in group C {92.5±7.1, 94 (66-100)} and group T {95.6±2.7, 96 (90-100)} (p-value=0.006).

Conclusion: The TOF monitoring is better compared to a clinical parameters-based reversal strategy in reducing the incidence of residual paralysis and resulting complications whenever Neuromuscular Blocking Agents (NMBAs) are used. Hence, it is desirable to use Neuromuscular Monitoring with the use of NMBAs.

Keywords: Extubation, Muscle relaxants, Neostigmine, Paralysis, Residual

INTRODUCTION

Residual Neuromuscular Blockade (RNMB) is most commonly observed in the Post Anaesthetic Care Unit (PACU) when NMBA is used intraoperatively [1]. NMB is used more commonly to facilitate endotracheal intubation, to produce surgical relaxation in an anesthetised patient during surgery, and to assist mechanical ventilation in an anesthetised patient or critically ill patient who has poor lung compliance. Adequate reversal of NMB at the end of surgery is an essential requirement of balanced anaesthesia technique when using non depolarising NMBAs for muscle relaxation [2].

The NMB monitoring has been shown to decrease the incidence of RNMB and reduce the occurrence of postoperative airway and respiratory complications. The current standard for adequate recovery from NMB is the return of TOFR ≥0.9 measured at the adductor pollicis muscle [3].

Although pharmacological reversal based on clinical signs was superior to spontaneous recovery, it did not prevent postoperative RNMB, regardless of the reversal agent used [4]. The only reliable method available to detect the presence or absence of incomplete NMB is quantitative neuromuscular monitoring. However, these monitors are not frequently used by anesthetists in the perioperative period due to insufficient dosages of reversal agents, underestimation of NMB depth by anaesthetists, infrastructure and facility constraints, and lack of clinical guidelines [5]. Since there is no widespread adoption of neuromuscular monitoring in routine clinical practice due to cost and infrastructure constraints, the present study aimed to evaluate the effectiveness of adoption of clinical endpoints for reversing NMB and assess the safety of such practice. Although there are few studies on the adequacy of NMB reversal without TOF monitoring, the present study aimed to further enhance knowledge in this area and evaluate the safety of this practice [6,7].

The TOFR <0.9 [8] results in postoperative residual paralysis, characterised by upper airway obstruction requiring intervention (jaw thrust, oral or nasal airway), a decrease in oxygen saturation (hypoxemia) despite the application of high-flow oxygen via a facemask. Signs of respiratory distress include a Respiratory Rate (RR) >20 cycles per minute, use of accessory muscles of respiration, tracheal tug, pharyngeal muscle weakness leading to difficulty in swallowing, breathing, and speaking, which may necessitate reintubation in the PACU. Clinical evidence or suspicion of pulmonary aspiration after tracheal extubation is also reported, as observed by gastric contents in the oropharynx and hypoxemia [1,9-11].

Since the device for quantitative neuromuscular monitoring is not widely available or feasible at all times and places, the adequacy of NMB reversal can be achieved by using clinical parameters as an alternative to TOF monitoring [11]. The present study aimed to evaluate whether the usage of clinical parameters for NMB reversal is equal or inferior to TOF monitoring.

MATERIALS AND METHODS

The randomised controlled study was conducted in the Department of Anaesthesiology at SDM Medical College and Hospital, Dharwad,

Karnataka, India for a period of two years from November 2019 to December 2021.

Sample size calculation: A sample size of 120 patients was obtained based on the reversal extubation time (17.4±4.8 min and 12.3±8.4 min without and with TOF monitoring) from a previous study [11], with a significance level of 5% and power of 90% for each group.

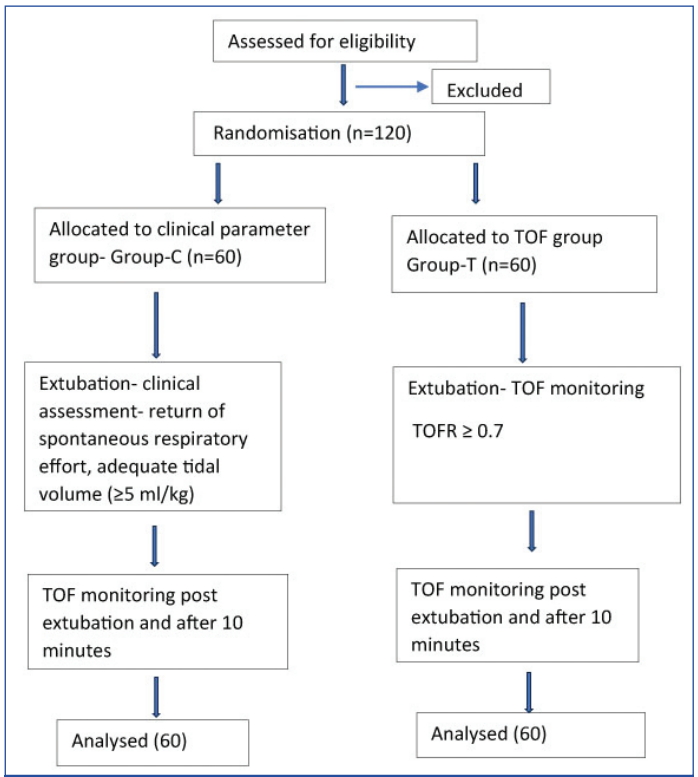
After obtaining permission from the Institutional Ethical Committee (SDMIEC: 188: 2019), informed consent was obtained from 120 patients.

Inclusion criteria: Adult anesthetised and intubated patients of either sex undergoing elective surgeries with ASA physical Status-I and II, between 18 and 60 years of age were included in the study.

Exclusion criteria: Patient refusal, post-surgery intensive care admission, elective surgery lasting less than one hour, BMI ≥35 kg/m^2, hepatic disease, renal insufficiency, neuromuscular disease, difficulty accessing the TOF measurement in the ulnar nerve, and consumption of drugs known to affect NMT. A total of 120 patients were included, and none were excluded during the study.

Study Procedure

The study was conducted on adult patients undergoing elective non head and neck surgeries. All patients meeting the inclusion criteria were allocated into two groups: Group C (Clinical parameters) and group T (TOF monitoring) based on computerised randomisation [Table/Fig-1]. A preformed and pretested proforma was used to collect information.



[Table/Fig-1]: Consolidated Standards of Reporting Trails (CONSORT) flow chart.

All patients underwent a thorough preoperative evaluation, and relevant laboratory investigations were conducted the day before surgery. Patients were kept nil per oral as per the guidelines before being transferred to the preoperative room. They were given oral medications, including tab pantoprazole 40 mg and tab alprazolam 0.5 mg, on the night before surgery and on the morning of surgery as pre-anaesthetic medication.

In the operation theatre, an 18 Gauge Intravenous (i.v) line was secured in the non dominant upper limb, and i.v. fluid administration was initiated. Routine monitors such as electrocardiography, pulse oximeter, and non invasive blood pressure were attached to the patient, and baseline values were recorded. Two electrodes were placed along the medial aspect of the distal forearm to study ulnar nerve transmission for NMT monitoring. The distal electrode was positioned at the wrist crest, while the proximal electrode was placed 3-6 cm proximal to it. The NMT sensor was placed between the thumb and the forefinger. Both the electrodes and NMT sensor were connected to the monitor via an NMT sensory cable. The patient was preoxygenated with 100% oxygen for three minutes.

Anaesthesia induction was performed using inj. fentanyl 2 µg/kg i.v., followed by inj. propofol 2 mg/kg i.v. NMT monitoring was initiated once the patient was induced, and baseline strength of current was noted. Muscle relaxation was achieved by administering inj. vecuronium 0.1 mg/kg i.v. The patient was mask ventilated with 100% oxygen for three minutes, and endotracheal intubation was performed using direct laryngoscopy with an appropriately sized endotracheal tube. After inflating the cuff, bilateral equal air entry was confirmed. Balanced anaesthesia was maintained using isoflurane, with the Minimal Alveolar Concentration (MAC) kept in the range of 1-1.2, and a delivery gas mixture of N_2O/O_2 in a 50:50 ratio. End-tidal Carbon Dioxide ($EtCO_2$) was maintained between 35-45 mmHg. For analgesia, inj. morphine 0.1 mg/kg i.v. was administered. Muscle relaxation was maintained by administering 0.02 mg/kg of vecuronium every 30 minutes.

Towards the end of surgery, if the administration of the last dose of vecuronium was ≥30 minutes ago, reversal was initiated. In group C, if respiratory efforts with TV of ≥0.5 mL/kg of body weight were achieved, reversal with 0.04 mg/kg of neostigmine and 0.001 mg/kg of glycopyrrolate was given over a period of 1-2 minutes [11]. Once the patient had a TV of ≥5 mL/kg, the patient was extubated. NMT monitoring was started, and the TOF Ratio (TOFR) [8] was noted immediately after extubation and again at 10 minutes post-extubation in the Operating Theatre (OT).

In Group T, reversal was performed when the TOF Count (TOFC) reached ≥2. Reversal with 0.04 mg/kg of neostigmine and 0.001 mg/kg of glycopyrrolate was given over a period of 1-2 minutes. Once the TOFR reached ≥0.7, patients were extubated. TOFR was again noted 10 minutes post-extubation. Patients were considered to have residual paralysis if the TOFR was <0.9 after 10 minutes of post-extubation [8].

The TOF monitoring involves delivering four supramaximal stimuli of equal intensity at intervals of 0.5 seconds (2 Hz), and each stimulus in the train causes the muscle to contract [12]. TOFR is the ratio of the amplitude of the fourth response or twitch to that of the first (T4:T1), i.e., the fade in the train of responses, expressed as a percentage or fraction [13]. TOFC is the number of discernible responses after TOF stimulation. In a non depolarising block, there is progressive depression of height with each twitch, i.e., fade, which is inversely proportional to the degree of NMB. As the block deepens, the 4th twitch will be eliminated first, then the 3rd, and so on. Following the recovery or reversal of non depolarising NMB, the TOFC increases until there are four responses, then decreases [13]. Determining TOFR requires all four twitches to be present, and it cannot be used to monitor a deep block. When used continuously, an interval of at least 10-12 seconds should be allowed between each set (train) of four stimuli to avoid fade during the measurement [14].

STATISTICAL ANALYSIS

The duration of anaesthesia, total dose of vecuronium, reversal-extubation time, TOF value at extubation and after 10 minutes, and the incidence of residual paralysis were studied. The data were analysed using Graph Pad Prism 9 and Excel. Categorical variables are presented in frequency tables, while continuous variables are reported as either Mean±Standard Deviation (SD) or Median (Min, Max). A t-test was used to compare differences between groups, and a chi-square test was conducted for contingency data. A

p-value less than or equal to 0.05 indicates statistical significance. Observations were analysed using Graph Pad Prism 9 and Excel.

RESULTS

In the study, both Group C and Group T were comparable in terms of age (41.15±10.23 years, 41.03±11.9 years; p-value=0.95), sex (male/female; 46.6%/53.3% and 63.3%/36.6%; p-value=0.06), and BMI (≤25=59.3%, 25-30=33.1%, ≥30=7.5%; p-value=0.57), respectively [Table/Fig-2]. There were no differences in parameters such as duration of anaesthesia, reversal to extubation time, and TOF value at the time of extubation between the two groups [Table/Fig-3].

Variables			Group T (n=60)	Group C (n=60)	Total (n=120)	t-test value	Chi-square value	p-value
Age (in years)		Mean±SD	41.15±10.23	41.03±11.9	41.09±11.06	0.057		0.95
		Median (Min, Max)	41.5 (18-60)	40 (18-60)	41 (18-60)			
Gender	Male	Count	28	38	66		3.3	0.06
		% within group	46.6	63.3	54.95			
	Female	Count	32	22	54			
		% within group	53.3	36.6	44.95			
BMI (kg/m²)	≤25	Count	35	36	71			0.57
		% within group	58.3%	60%	59.1%			
	25-30	Count	19	21	40			
		% within group	31.6%	35%	33.3%			
	≥30	Count	6	3	9			
		% within group	10%	5%	7.5%			

[Table/Fig-2]: Comparison of demographic variables between the two groups.

Variables		Group T (n=60)	Group C (n=60)	Total (n=120)	t-test value	p-value
Current (mA) 40	Mean±SD	40.96±12.59	39.75±13.74	40.35±13.14	0.32	0.61
	Median (Min, Max)	40 (23-72)	35.5 (17-75)	38 (17-75)		
Anaesthesia duration (Mins)	Mean±SD	127.8±57.28	133.2±67.8	130.5±62.5	0.47	0.6
	Median (Min, Max)	115.35 (63.25-330.1)	109.2 (62.3-420.4)	112.9 (62.3-420.4)		
Total vecuronium dose (mg)	Mean±SD	8.2±1.8	8.5±2.6	8.3±2.2	0.89	0.38
	Median (Min, Max)	8 (5-15)	8 (4.5-20)	8 (4.5-20)		
Time of last vecuronium (mins)	Mean±SD	43.9±14.0	43.03±11.38	43.5±12.7	0.4	0.68
	Median (Min, Max)	40.38 (7.24-90.15)	40.4 (14.4-75.4)	40.4 (7.24-90.15)		
Reversal- extubation time (mins)	Mean±SD	6.6±1.9	5.9±2.2	6.3± 2.0	1.178	0.07
	Median (Min, Max)	6.24 (3.3-12.2)	5.4 (2-15.2)	5.7 (2-15.2)		
TOF value at the time of extubation	Mean±SD	72.75±2.74	72.1±11.6	72.4±8.4	0.39	0.69
	Median (Min, Max)	72 (70-79)	72 (41-91)	72 (41-91)		

[Table/Fig-3]: Comparison of various anaesthetic parameters between the two groups.

The TOF value after 10 minutes of extubation (%) in Group C was found to be 92.5±7.1, 94 (66-100), while in Group T it was 95.6±2.7, 96 (90-100) (p-value=0.006), which was statistically significant [Table/Fig-4].

Parameter	Group	Mean±Std. Deviation	Median (Min, Max)	t-test value	p-value
TOF value after 10 minutes of extubation in %	Group T (n=60)	95.6±2.7	96 (90-100)	2.79	0.006
	Group C (n=60)	92.5±7.1	94 (66-100)		
	Total (N=120)	94.0±6.2	96 (66-100)		

[Table/Fig-4]: Comparison of TOF value after 10 minutes of extubation in % between two groups.
p-value <0.05 statistically significant

In Group C, 54 (90%) subjects had a TOFR of ≥0.9 after 10 minutes of extubation, while 6 (10%) subjects had a TOFR of ≤0.89. Out of these six subjects, 5 (8.33%) had a TOFR ≤0.79 with residual paralysis (p-value=0.02), while 1 (1.67%) had a TOFR of ≤0.86 without any evidence of residual paralysis. In Group T, 60 (100%) subjects had a TOFR of ≥0.9 after 10 minutes of extubation without any residual paralysis [Table/Fig-5].

In Group C, five patients developed residual paralysis in the form of upper airway obstruction after extubation, resulting in a fall in oxygen saturation below 90%. These patients were managed on the operating table using non invasive methods such as jaw thrust and the use of oral airways to prevent tongue fall, along with 100% oxygen supplementation. None of the patients required an additional dose of neostigmine or invasive methods like re-intubation. Patients were observed in the operating room for 10 minutes before shifting to the PAC.

Residual paralysis		Group T (n=60)	Group C (n=60)	Total (N=120)	Chi-square value	p-value
Yes	Count	0	5	5	5.2	0.02
	% within group	0	8	4		
No	Count	60	55	115		
	% within group	100	92	94		

[Table/Fig-5]: Comparison between two groups based on residual paralysis.
p-value <0.05 statistically significant

Residual paralysis in Group C could be attributed to the short time interval between reversal to extubation, which was 5.9±2.2 (3.7-8.1) minutes, resulting in a TOFR ≤0.79 in five patients. Out of these five subjects, three had a TOFR ≤0.69, and the remaining two had a TOFR between 0.70-0.79. In present study, a fixed dose of neostigmine (50 µg/kg) for the reversal of neuromuscular blockade was used, and no adverse respiratory events were found in both Group C and Group T.

DISCUSSION

The study showed comparability between the groups in demographic data such as age, sex, and BMI. There were no differences in parameters like anaesthesia duration, time for extubation, and TOF value at extubation between the two groups. However, a significant statistical difference was observed between the groups in terms of TOF value after 10 minutes of extubation and residual paralysis. In group C, five patients developed residual paralysis in the form of upper airway obstruction after extubation, resulting in a fall in oxygen saturation below 90%.

Wardhan A et al., in their study, concluded that an optimised reversal strategy without TOF monitoring is not equivalent to a reversal strategy based on quantitative TOF monitoring [11]. They suggested that TOF monitoring should be used whenever possible, even if the dose of neostigmine is optimised. Their study reported an incidence of 16.7% residual paralysis in the group without TOF monitoring. In the present study, no clinically significant difference was found between the two groups regarding recovery from neuromuscular blockade. However, a statistically significant difference was observed in the incidence of residual paralysis in group C (8%). In present study, a fixed dose of neostigmine (50 µg/kg) was used when TOFC was ≥2, while they used a variable dose of neostigmine based on the depth of blockade.

Domenech G et al., in their study, found that the group with intraoperative quantitative NMB monitoring had a lower incidence of RNMB at 1.6%, compared to 32% in the group without TOF monitoring [15]. They concluded that quantitative NMB monitoring helps in preventing RNMB and allows for the judicious use of reversal agents, if needed, prior to emergence from anaesthesia. In the present study, none of the patients in the group with TOF monitoring had RNMB. Their study used sugammadex as the reversal agent, whereas our study used neostigmine. Nevertheless, the results of both studies are comparable.

Murphy GS et al., evaluated the effect of neostigmine administration on neuromuscular recovery and found no clinical evidence of anticholinesterase-induced muscle weakness [16]. Neostigmine 40 µg/kg was administered to patients after spontaneous recovery of TOFR ≥0.9, and it did not adversely affect TOF values, respiratory function, or signs and symptoms of muscle strength. Their study reported a high incidence of incomplete neuromuscular recovery (21%) without the use of a reversal agent.

Nemes R et al., concluded that RNMB cannot be prevented without TOF monitoring, regardless of the reversal strategy [4]. They stated that a reversal strategy with neuromuscular monitoring is the most reliable way to prevent RNMB, and when combined with quantitative monitoring, a zero incidence of RNMB can be achieved. In the present study, the group with TOF monitoring showed a zero incidence of RNMB, which is similar to their findings.

Tajaate N et al., concluded that neostigmine administration can only reverse shallow neuromuscular blockade (T1 ≥25%, 1st twitch height) within 10 minutes [17]. Administering neostigmine for reversal of deep to moderate blockade resulted in a longer time to achieve TOF >0.9 from the time of reversal, and it was not possible to achieve TOF >0.9 in all patients, leading to premature extubation. This was explained by the narrow therapeutic range of neostigmine, emphasising the importance of appropriate timing and dosing to obtain the desired effects. In this study, the time for reversal to a TOF value of >0.9 was 6.6±1.9 minutes in group T, while it was 5.9±2.2 minutes in group C. Their results differ from the present study because they used a variable dose of neostigmine based on T1 (1st twitch height) 0-25% or more, whereas this study used a fixed dose of 50 µg/kg of neostigmine.

Fortier LP et al., in their study, concluded that RNMB was present in 63.5% of patients at tracheal extubation and in 56.5% upon arrival at the PACU [9]. They found that patients experienced RNMB due to early tracheal extubation soon after neostigmine administration. They suggested not relying solely on neostigmine to prevent RNMB and defined RNMB as a TOF (normalised TOF) ratio <0.9 using Acceleromyography (AMG). However, this study did not utilise the nTOF ratio and AMG to define RNMB.

Sasaki N et al., studied the neostigmine reversal of non depolarising NMBAs and its impact on postoperative respiratory outcomes. They found that neostigmine administration without appropriate guidance from Neuromuscular Transmission (NMT) monitoring was associated with an increased risk of adverse respiratory events [18]. They concluded that neostigmine is effective in reversing shallow and moderate NMB and should not be used to reverse deep NMB, as it may result in incomplete reversal. In this study, a fixed dose of neostigmine (50 µg/kg) was used for NMB reversal, and no adverse respiratory events were observed in both group C and group T. However, residual paralysis was present in group C due to a shorter period of time from neostigmine administration to extubation. In group T, neostigmine was administered when TOFC (train-of-four count) was ≥2, and there were no signs of incomplete NMB.

Kotake Y et al., in their study, found that the incidence of TOFR (train-of-four ratio) <0.9 after neostigmine and sugammadex administration was 23.9% (16.2%-33%) and 4.3% (1.7%-9.4%), respectively [5]. Although sugammadex reduced the incidence of postoperative RNMB compared to neostigmine, the risk of TOFR <0.9 in the PACU remained at least 1.7%-9.4% in a clinical setting without neuromuscular monitoring.

Yip PC et al., assessed the incidence of RNMB in the PACU, the need for airway support, and desaturation in patients with and without RNMB. They found that the majority of patients in the PACU had RNMB [19]. A greater proportion of patients with RNMB required airway support and 100% oxygen supplementation compared to those with TOFR >0.9 monitored using electromyography. The incidence of RNMB was more commonly seen in those who did not receive neostigmine for reversal. In this study, only 5% of patients had residual paralysis requiring airway support, and they were managed on the operating table before being shifted to the PACU. None of the patients in group T had residual paralysis. In this study, TOF monitoring was performed at the end of extubation and 10 minutes after extubation, unlike their study where NMB monitoring was conducted upon the patient's arrival in the PACU.

Butterly A et al., in their study, concluded that postoperative residual curarisation (TOFR <0.9) using AMG prolongs the length of stay or delays PACU discharge when intermediate non depolarising NMBAs like vecuronium are used [20]. They recommend the use of NMT monitoring whenever intermediate NMBAs are used.

Murphy GS et al., found that RNMB with a Train-of-four Ratio (TOFR) <0.9 was reduced in subjects monitored with AMG compared to those monitored with traditional TOF monitoring [1]. The incidence of RNMB was 50% in the group using traditional TOF monitoring, whereas it was 14.5% in subjects who received AMG monitoring. The present study used kinemyography instead of AMG.

Debaene B et al., observed that residual paralysis (TOF <0.9) using AMG was seen 2 hours after the administration of intermediate-acting muscle relaxants when no reversal was given at the end of surgery, after the patient was shifted to the PACU [21].

Hayes AH et al., in their study to assess the incidence of postoperative RNMB (TOF <0.9) in patients arriving in the PACU after using intermediate-acting non depolarising NMBAs, found that the majority of patients exhibited RNMB in groups where NMB monitoring was not performed and reversal agents were not used [22]. This study also had a similar finding in group C where NMT monitoring was not done, except a reversal agent was used in all study subjects.

Limitation(s)

This study employed quantitative monitoring, such as TOF monitoring and clinical parameters, to evaluate the optimised reversal strategy for NMB. However, the use of normalised TOF (nTOF) and AMG could have provided a more accurate estimation of muscle recovery quality. Additionally, while the duration of surgeries (>1 hr) was comparable, including longer duration surgeries would have provided additional insights.

CONCLUSION(S)

The study concludes that TOF monitoring is better and safer compared to a reversal strategy based solely on clinical parameters for achieving adequate reversal of NMB. In settings where quantitative neuromuscular monitoring is not available, patients can be extubated based on clinical endpoints. However, it is important for healthcare providers to remain vigilant and able to recognise signs and symptoms of residual paralysis that may lead to respiratory complications after the patient has been transferred to the PACU. The treating anaesthesiologist should possess the necessary skills to manage residual paralysis. In settings where quantitative NMT monitoring devices are available, there should be no hesitation in using these devices whenever NMBAs are employed.

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