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Original Article

Optimised reversal without train-of-four monitoring versus reversal using quantitative train-of-four monitoring: An equivalence study

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ABSTRACT

Background and Aims: Less residual paralysis in recovery room was demonstrated when train-of-four (TOF) monitoring was applied. The aim of this study was to know whether optimisation of neostigmine reversal without TOF monitoring was equivalent to reversal using TOF monitoring. **Methods:** Seventy two patients, aged 18–60 years, undergoing elective surgery under general anaesthesia (sevoflurane and rocuronium) with intubation were randomised into two interventions: an optimised neostigmine reversal strategy without TOF monitoring (group A, *n* = 36) and a neostigmine reversal strategy using quantitative TOF monitoring (group B, *n* = 36). Per-protocol analysis was performed to compare incidence of residual paralysis in the recovery room between the two groups. **Results:** Six residual paralyses occurred in group A in the recovery room, whereas one case occurred in group B. The equivalence test showed that the 95% confidence interval of this study was outside the range of equivalence margin (15%). The absolute difference was 13.9%: standard error (SE) =0.068 (*P* = 0.107; 95% confidence interval (CI): 1%, 27.2%). No subjects had TOF ratio <0.70 in the recovery room. The TOF ratio in the recovery room did not differ between the two groups (mean difference: –2.58; *P* = 0.05; 95% CI: –5.20, 0.29). One respiratory adverse event occurred in this study. **Conclusion:** An optimised reversal strategy without TOF monitoring is not equivalent to a reversal strategy based on quantitative TOF monitoring. TOF monitoring should be used whenever applicable, although neostigmine is optimised.

Key words: Neostigmine, residual paralysis, train-of-four, reversal, rocuronium

INTRODUCTION

Rocuronium, one of the most common neuromuscular blockade agents which is used for facilitating intubation for general anaesthesia, poses risks of residual paralysis. Residual paralysis after rocuronium blockade in the recovery room occurs in around 56.5% of patients, and it can increase the incidence of airway obstruction, hypoxaemia and postoperative pulmonary complications,[1,2] as well as delayed recovery room discharge.[3] However, despite these risks, it has not been widely considered as an important patient safety concern.[4]

Less residual paralysis was demonstrated when quantitative neuromuscular monitoring was applied.[5,6] However, the device is not widely available with only 9.4–22.7% of clinicians who had quantitative train-of-four (TOF) monitoring in their practice.[7,8] When it is not available, the chance of successful reversal may be increased by optimal administration of neostigmine, a reversal agent for neuromuscular blockade that has been used for decades.[9] Recent studies showed that the depth of blockade-based neostigmine dosing and reversal-extubation time have an important role in decreasing incidence of

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residual paralysis.[10-12] The depth of blockade might be determined through tidal volume parameters.[8]

The outcome of optimising neostigmine reversal strategy without TOF monitoring has never been studied. This study tested whether optimisation of neostigmine reversal strategy without TOF monitoring was equivalent to neostigmine reversal strategy using TOF monitoring to be able to inform clinical decision making where neuromuscular monitoring is not available.

METHODS

The study was conducted at a tertiary care hospital during May–July 2018. The study was approved by the Medical and Health Research Ethics Committee of FKKMK UGM and Dr. Sardjito Hospital. This trial was registered in UMIN clinical trials registry (https://www.umin.ac.jp/ctr). Informed consents were acquired from all subjects before participating in this study. The patients included for the study aged 18–60 years, with American Society of Anesthesiologists' (ASA) I–II physical status and who were going to undergo elective non-head/neck surgery using general anaesthesia with intubation. Exclusion criteria were elective surgery <1 h duration; awake extubation or postsurgery intensive care admission; body mass index >35 kg/m^2; hepatic disease (liver enzyme value >50% normal value); renal insufficiency (serum creatinine >1.8 mg/dL); neuromuscular disease; consumption of drugs known to affect neuromuscular transmission; contraindications to neostigmine and/or atropine sulphate; a history of hypersensitivity or allergic to anaesthetic agent given and difficulty accessing the TOF measuring device in the ulnar nerve.

The study subjects were allocated into two groups using stratified randomisation based on the type of surgery. Group A received optimal neostigmine reversal strategy without TOF monitoring, whereas group B had reversal strategy based on TOF quantitative monitoring. The allocated group information was given in a sealed envelope when the patient arrived at the surgery room.

In preoperative room, subjects were given midazolam 2 mg intravenous (IV). Anaesthesia was induced with propofol 1–2 mg/kg IV, fentanyl 100 μg IV and rocuronium 0.6–0.8 mg/kg IV for tracheal intubation. Anaesthesia was maintained with sevoflurane 1–3% with delivery gas N_2O/O_2 in the ratio 50:50. Sevoflurane concentration was set to maintain the bispectral index values 40–60 and mean arterial pressure (MAP) in the range of 20% base value. Ventilation was adjusted to maintain $ETCO_2$ in the range of 35–45 mmHg.

All subjects had two electrodes on the forearm. Distal electrode was placed at the wrist crest, whereas the proximal electrode was placed 3–6 cm proximal from the distal one. The thumb should be able to move freely and the other finger was fixed to the arm of bed. For group B, all TOF-Watch SX device cables (Organon, Inc., Dublin, Ireland) were then connected to the electrodes and the transducer was taped to the distal phalanx of the thumb.

Additional rocuronium was given if there was an indication and given as much as 10 mg after a spontaneous breathing was detected or the time of last rocuronium administration was more than 30 min. Towards the end of the surgery, the first researcher opened the envelope. Then, the reversal management using neostigmine was done, as shown in Figure 1. Atropine sulphate 10 μg/kg IV was given to every subject receiving neostigmine.

In group A, the first researcher counted the time since last rocuronium administration and assessed the subject's spontaneous breathing effort. The reversal strategy was based on the facts that the duration of action of rocuronium is equal to TOF count of 4; tidal volume returns to normal when TOF ratio is >0.40 and diaphragm muscles fully recover if TOF ratio is >0.70.[12-14] In addition, reversal attempt should be delayed by at least 30 min after rocuronium administration if there is no sign of recovery.[12] When the time of last rocuronium was >30 min without evidence of spontaneous breathing, neostigmine 50 μg/kg IV was given. When minimal spontaneous breathing was detected, neostigmine was given 30–40 μg/kg IV and 20–30 μg/kg if last rocuronium was given ≤30 min and ≥30 min before reversal, respectively. Subjects received neostigmine 10 μg/kg IV if they had adequate spontaneous breathing pattern.

In group B, neostigmine was given at a dose according to the measured TOF value.[13] TOF stimulation of 50 mA was given without calibration. Neostigmine administration was delayed if TOF count value was 0–1. Subjects who had TOF count of 2–4 received 50 μg/kg IV of neostigmine. If TOF ratio was ≤0.40 and in the range 0.40–0.70, then neostigmine dosing of 40 and 20–30 μg/kg IV, respectively, was given.

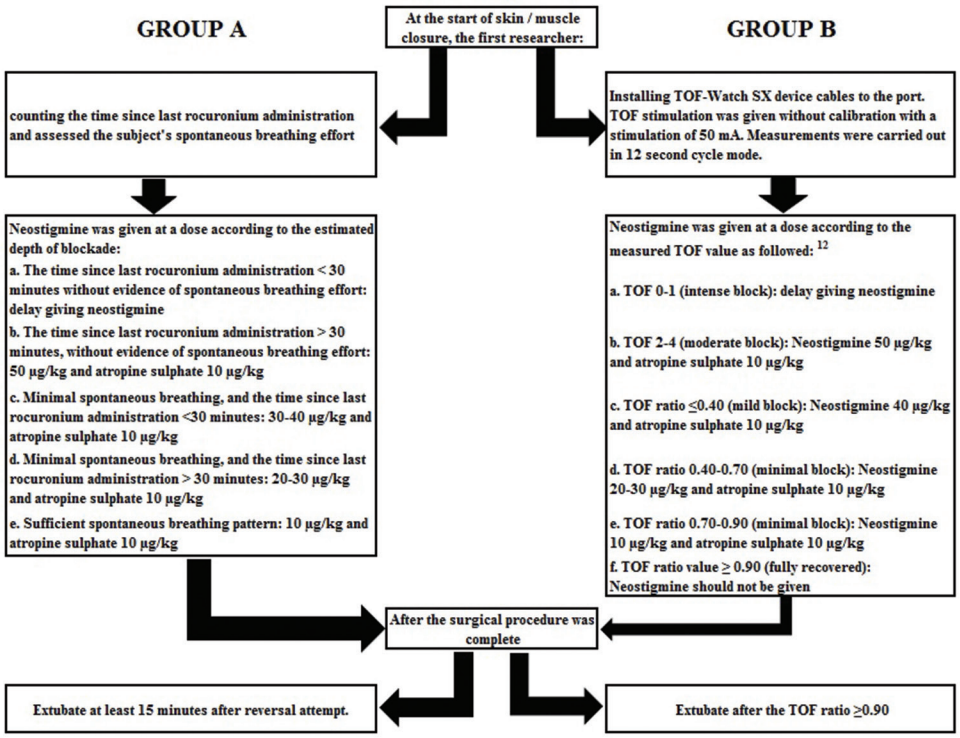

Figure 1: Reversal management after group allocation revealed at the start of skin closure

Neostigmine was administered 10 µg/kg IV if subject had minimal block.

The primary outcome was the proportion of subjects who have residual paralysis in the recovery room based on the threshold TOF value <0.90 in both groups. Oxygen supplementation via nasal cannula 3–4 L/min, SpO2, ECG and non-invasive blood pressure monitoring devices and TOF-Watch SX devices were installed on all subjects on arrival at the recovery room, and the TOF value was measured by the second researcher who did not know the type of intervention given. Measurements were done twice consecutively over 12 s. The value used was the average of both values. However, if the difference was more than 10%, the measurement was done twice more in the same way. The value collected was the average of the two closest values. All subjects were monitored for airway problems, respiration patterns, oxygen saturation, nausea and vomiting during 30 min in the recovery room.

Equivalence tests were used based on the assumption that new interventions using optimal reversal strategies without TOF monitoring offer ease of application during surgery and can be used for most practices with limited availability of TOF monitoring devices. The margin of equivalency was 15%, which was a derived value determined as half of the margin of superiority from a study by Murphy.[6] Considering the proportion of the expected incidence of residual paralysis was 5% with two-sided test size of 5% and statistical power of 80% and the dropout rate of 10%, the total number of samples needed was 80 subjects.

Analyses were done on all subjects who had received treatment according to the protocol. Data were expressed in terms of numbers and percentages, medians and ranges, mean and standard deviations. The data between the two groups were analysed for differences using independent *t*-tests for numerical data and Fisher's exact tests for categorical data. Data were analysed using SPSS 24 software computer program.

RESULTS

A total of 106 subjects were assessed for eligibility for this study. As shown in Figure 2, 26 subjects were excluded. Randomisation was done on 80 subjects. Two patients were not extubated, so measurements of TOF values in the recovery room were performed on 39 subjects in each group. Six subjects were excluded from analysis because their inhalation anaesthesia agent was switched to isoflurane. Seventy-two subjects remained for per-protocol analysis. The study

was discontinued after achieving the target number of samples.

Characteristics of the subjects are presented in Table 1. Classification of open urology surgery was merged with gynaecology because there was only one patient in the urology subgroup. There were no differences between the two groups for sex, body mass index, ASA physical status and type of surgery. However, subjects in group A were younger than those in group B.

Both groups did not differ in the parameters of the duration of the anaesthesia procedure, the total rocuronium dose, the frequency of rocuronium administration, the time of last rocuronium administration and the total neostigmine dose, as presented in Table 2. The TOF ratio in the recovery room also did not differ between the two groups (mean difference = −2.58; P = 0.053). However, the reversal-extubation time in group A was longer than in group B (mean difference = 5.08 min; P = 0.002).

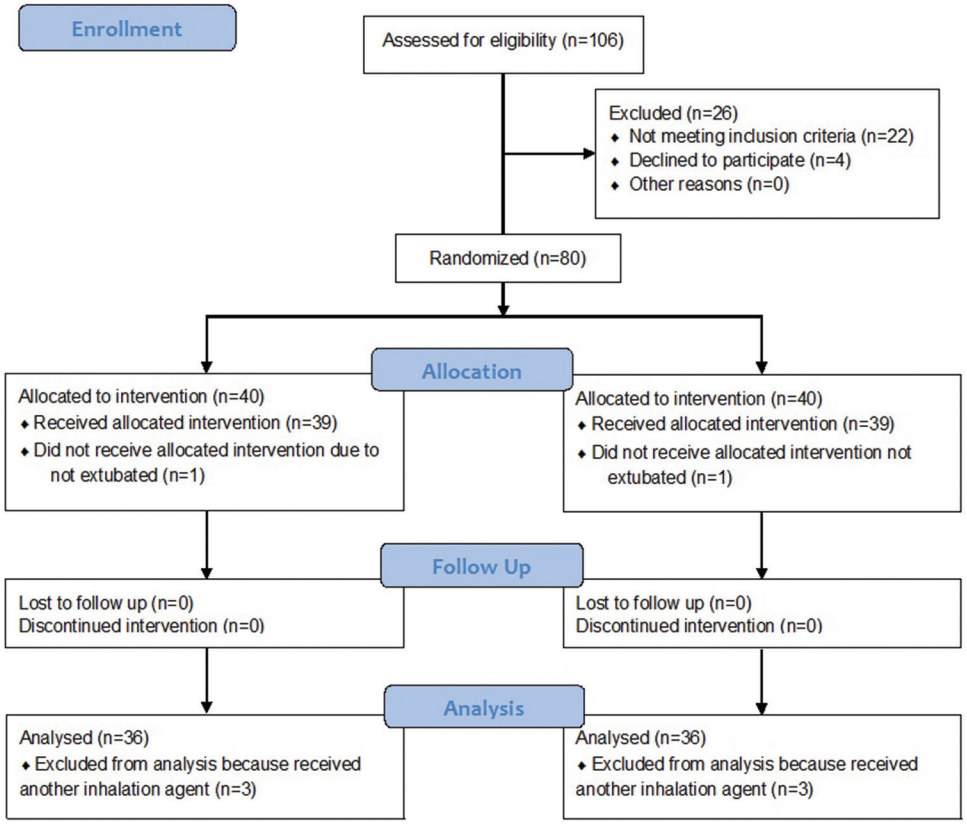

Figure 2: Flow diagram of the progress of this study

Table 1: Patient characteristics

Variable	Groups		*P* (95%CI)
	A (*n*=36)	B (*n*=36)	
Age (years)	39.14 (12.81)	45.53 (11.04)	0.026* (−12.01 to−0.77)
Male (*n*)	9 (25.0)	7 (19.4)	0.778 (−0.14 to 0.25)
Female (*n*)	27 (75.0)	29 (80.6)	
Body mass index (kg/m^2)	22.65 (3.89)	22.53 (3.58)	0.896 (−1.64 to 1.87)
The type of surgery (*n*)			
Abdominal laparoscopic (*n*)	9 (25.0)	8 (22.2)	0.991
Open digestive (*n*)	12 (33.3)	12 (33.3)	
Gynaecology and urology (*n*)	5 (13.9)	5 (13.9)	
Others (*n*)	10 (27.8)	11 (30.6)	
ASA physical status			
ASA I (*n*)	8 (22.2)	9 (25.0)	0.781 (−0.22 to 0.17)
ASA II (*n*)	28 (77.8)	27 (75.0)	

Data in number (%) or mean (SD).*P<0.05 is significant

Table 2: Perioperative data

Parameters	Groups		P (95% CI)
	A	B	
Anaesthetic duration (min)	182 (87)	163 (68)	0.294 (−17 to 56)
Total rocuronium dose (mg)	45.8 (19.9)	42.9 (17.5)	0.511 (−5.9 to 11.7)
Frequency of rocuronium administration (*n*)	2.03 (1.94)	1.59 (1.21)	0.804 (−0.58 to 0.75)
Time of last rocuronium (min)	118.5 (72)	108.5 (56)	0.509 (−20.2 to 40.3)
Reversal-extubation time (min)	17.4 (4.8)	12.3 (8.4)	0.002* (1.87 to 8.3)
Total neostigmine dose (mg)	1.28 (0.72)	1.29 (0.77)	0.956 (−0.36 to 0.34)
TOF value in recovery room (%)	92.89 (7.23)	95.47 (2.90)	0.053 (−5.20 to 0.29)
Residual paralysis (*n*/%)	6 (16.7)	1 (2.8)	0.107 (0.006 to 0.272)

Data in number (%) or mean (SD).*P<0.05 is significant

Six cases of residual paralysis in the recovery room were found in group A, whereas one case occurred in group B (16.7 versus 2.8%). There were no significant differences in the proportion of residual paralysis in the recovery room in both groups ($P = 0.107$). The absolute difference in the proportion of residual paralysis in the recovery room was 13.9% (95% confidence interval (CI): 1–27.2%). The equivalence test showed that the 95% CI value of this study was outside the range of equivalence margins [Figure 3], so that an optimal reversal strategy without TOF monitoring was not equivalent to a reversal strategy based on TOF quantitative monitoring.

Overall, no serious adverse event was found, as shown in Table 3. However, one subject experienced post extubation respiratory distress with wheezing. The subject received a dose of 3 mg neostigmine with a dose of atropine sulphate 0.5 mg. The condition was resolved after the added 0.25 mg atropine sulphate and deepened anaesthesia, without desaturation and respiratory distress in the recovery room.

Table 3: Adverse events

Parameters	Group	
	A	B
Respiratory adverse events (*n*/%)	0 (0)	0 (0)
Upper airway obstruction (*n*/%)	0 (0)	0 (0)
Mild hypoxemia (*n*/%)	0 (0)	0 (0)
Severe hypoxemia (*n*/%)	0 (0)	0 (0)
Respiratory distress (*n*/%)	0 (0)	1 (3)
Reintubation (*n*/%)	0 (0)	0 (0)
Postoperative nausea-vomitus (*n*/%)	1 (3)	1 (3)
Severe adverse events (*n*/%)	0 (0)	0 (0)

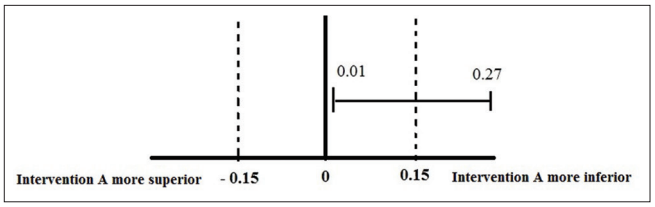

Figure 3: Hypothetical test of equivalence in this study

DISCUSSION

Reversal strategy without TOF monitoring, although optimised, was not equivalent to reversal strategy using TOF monitoring. This finding supports the latest consensus regarding the use of perioperative TOF monitoring tools.[15] A study comparing the two strategies similar to our study showed almost the same incidence of paralysis residual (TOF ratio ≤0.80) with our results (3.3 versus 16.7% in the TOF group and clinical group, respectively).[16] However, all patients with residual paralysis from the clinical group had low TOF ratios (median: 0.69). The short mean of time from reversal to extubation (5 min) may explain the clinically unacceptable TOF ratio (<0.70) in the recovery room. Another study which used neostigmine without accordance to depth of blockade (50 μg/kg IV for every patient) and shorter reversal-extubation time of 9 min had similar incidence rate (15.4%), but had three events with a TOF ratio <0.70.[17]

In our study, one case of residual paralysis (TOF value 0.87) occurred in group B even though the TOF value of 0.90 was confirmed before extubation. This result can be due to the paradox effect of muscle weakness by neostigmine or the variability of measuring devices.[18,19] However, recent evidence did not show a paradoxical effect when neostigmine was given after TOF ratio ≥0.90 was achieved.[20]

A total of 77% of subjects in group B achieved TOF ratio of 0.90 in 15 min and increased to 86% if 20 min elapsed. The longest reversal-extubation time in group A subjects who did not have residual paralysis was 30 min. This finding was supported in studies that reported neostigmine reversal required 30 min before

extubation.[21-24] Therefore, reversal strategy without TOF monitoring in inhalation anaesthesia should be optimised by extending the extubation time to 30 min after administration of neostigmine.

The use of sevoflurane and N_2O in this study contributed to the prolongation of the duration of action of rocuronium, where as much as 91.6, 77.8 and 38.9% of group B subjects still had neuromuscular blockade despite the time of last rocuronium administration were 30, 60 and 120 min, respectively. This finding confirmed that the time since last rocuronium administration cannot be the basis to not reverse in patients receiving inhalation anaesthesia.

One incident of respiratory distress due to bronchospasm occurred in this study. Patients with history of asthma may still develop bronchospasm despite anticholinergic agent administration. Without history of asthma, some subjects experienced bronchospasm due to lack of atropine sulphate dosing, so as not to offset the high concentration of acetylcholine after 3 mg of neostigmine.[25]

No significant bradycardia (resulting in hypotension and requiring additional atropine) was reported in our study. Only 7 (10%) subjects had bradycardia within 15 min of administration of neostigmine. Previous study using one dosage of neostigmine (50 μg/kg IV) reported that all subjects (n = 67) had bradycardia at 10 min after reversal and 5 of them were considered clinically significant.[21] It implied that the accuracy of the neostigmine dose in our study avoids the risk of bradycardia.

This optimisation of reversal strategy has not been studied before. This study replicates most practices at the research site, namely the determination of recovery of neuromuscular function clinically, usage of rocuronium and sevoflurane. The 50-mA electric current stimulation used in this study is considered to provide supramaximal stimulation but not perceived as painful in patients recovering from anaesthesia.[22,26]

There were several limitations in this study. First, the age of the study subjects was different in the two groups. However, this age difference was not likely to affect the duration of action of rocuronium because only the infant and geriatric age groups were known to be associated with prolonged duration of action of rocuronium.[27,28] Second, controlled ventilation was not applied to every subject, only when there was indication. Therefore, time of last rocuronium administration in this study was almost 2 h. In addition, half of the subjects received rocuronium only once which was for facilitating intubation and 66.7% of subjects in group B got a reversal when the depth of neuromuscular blockade was at most mild. The equal depth of blockade at reversal was also found in most subjects in group A (83.4%). They might contribute to the low incidence of residual paralysis in this study. Third, we did not keep core and upper extremity in a specified range during anaesthesia procedure. Both central and peripheral surface cooling can reduce the measured TOF ratio.[29] Fourth, TOF value measuring was not normalised. There is a new recommendation to increase the value of the non-normalised TOF ratio to 1.0 as the threshold for residual paralysis when using the accelerometer method.[30] Lastly, our study did not assess superiority of reversal using TOF monitoring to reversal without TOF monitoring.

This study showed that neostigmine dosing in accordance to the depth of blockade can be relied on as a reversal for rocuronium blockade. However, the assessment of the depth of blockade should be based on the quantitative TOF monitoring. When a TOF monitoring device is not available, neostigmine should be given to every patient who receives rocuronium because there is no guarantee that the patient will not have residual paralysis in the recovery room. For the next study, the reversal-extubation time should be extended to 30 min in the group without TOF monitoring. Normalisation measured-TOF value should also be performed in further studies.

CONCLUSIONS

The optimal reversal neostigmine strategy without TOF monitoring is not equivalent to reversal strategy based on quantitative TOF monitoring in order to prevent residual paralysis in the recovery room after the use of rocuronium as a neuromuscular blocking agent and sevoflurane as maintenance anaesthesia.

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Conflicts of interest
There are no conflicts of interest.

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