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Shortened time to neuromuscular recovery with lower doses of rocuronium in elderly patients

Sarah Sofie Wadland, Lars Simon Rasmussen & Matias Vested

Department of Anaesthesiology, Centre of Head and Orthopaedics, Section 6011, Copenhagen University Hospital – Rigshospitalet, Denmark

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ABSTRACT

INTRODUCTION. The effect of neuromuscular blocking agents may be reversed by administration of neostigmine, when two twitches are present using train-of-four (TOF) stimulation. However, in elderly patients, limited data are available about when to administer neostigmine. We hypothesised that time to two twitches after TOF (TOF-2) was shorter after rocuronium 0.6 mg/kg than after rocuronium 0.9 mg/kg. Also, we hypothesised that time to TOF-2 would be shorter after rocuronium 0.3 mg/kg than after rocuronium 0.6 mg/kg.

METHODS. This was a secondary analysis of 50 elderly patients > 80 years; 16 patients received rocuronium 0.6 mg/kg, another 16 patients received rocuronium 0.9 mg/kg; and, finally, 18 patients received rocuronium 0.3 mg/kg. Patients received total intravenous anaesthesia, and neuromuscular block was monitored with acceleromyography.

RESULTS. Time to TOF-2 was shorter after rocuronium 0.6 mg/kg than after rocuronium 0.9 mg/kg: 37 min. versus 59 min. (difference: 22 min. (95% confidence intervals (CI): 10 to 33 min.), p = 0.0007). Time to TOF-2 after rocuronium 0.3 mg/kg was shorter than after rocuronium 0.6 mg/kg: 19 min. versus 37 min. (difference: 18 min. (95% CI: 11 to 25 min.), p = 0.00006). However, only 33% of the patients receiving 0.3 mg/kg obtained full effect i.e. TOF-0.

CONCLUSION. Time to TOF-2 was shorter after rocuronium 0.6 mg/kg than after 0.9 mg/kg and shorter after rocuronium 0.3 mg/kg than after 0.6 mg/kg.

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TRIAL REGISTRATION. This study was a secondary analysis of two clinical trials. Clinicaltrials.gov (NCT04512313), (NCT03857750).

During anaesthesia, a neuromuscular blocking agent (NMBA), such as rocuronium, may be administered to facilitate tracheal intubation and optimise surgical conditions [1]. However, increasing age has a considerable impact on onset time and duration of NMBAs [2] due to changes in muscle mass and body fat, a decrease in cardiac output and reduced liver and renal function [3]. Furthermore, if spontaneous recovery does not occur, elderly patients have a higher incidence of complications than other patients related to residual neuromuscular blockade, such as muscle weakness and respiratory complications [4, 5].

The effect of rocuronium may be monitored by train-of-four (TOF) nerve stimulation at a peripheral nerve. If spontaneous recovery does not occur upon conclusion of anaesthesia, the reversal agent neostigmine may be administered, provided two twitches appear during TOF stimulation.

A lower dose of rocuronium is expected to lead to shorter duration of action and shorter time to recovery of a TOF count of two (TOF-2). Thus, the risk of residual curarisation would likely be reduced. However, a lower dose may not ensure a sufficient depth of neuromuscular blockade, which may potentially result in poor intubating conditions and inferior surgical conditions.

In elderly patients, data are limited on the association between rocuronium dose and time to TOF-2.

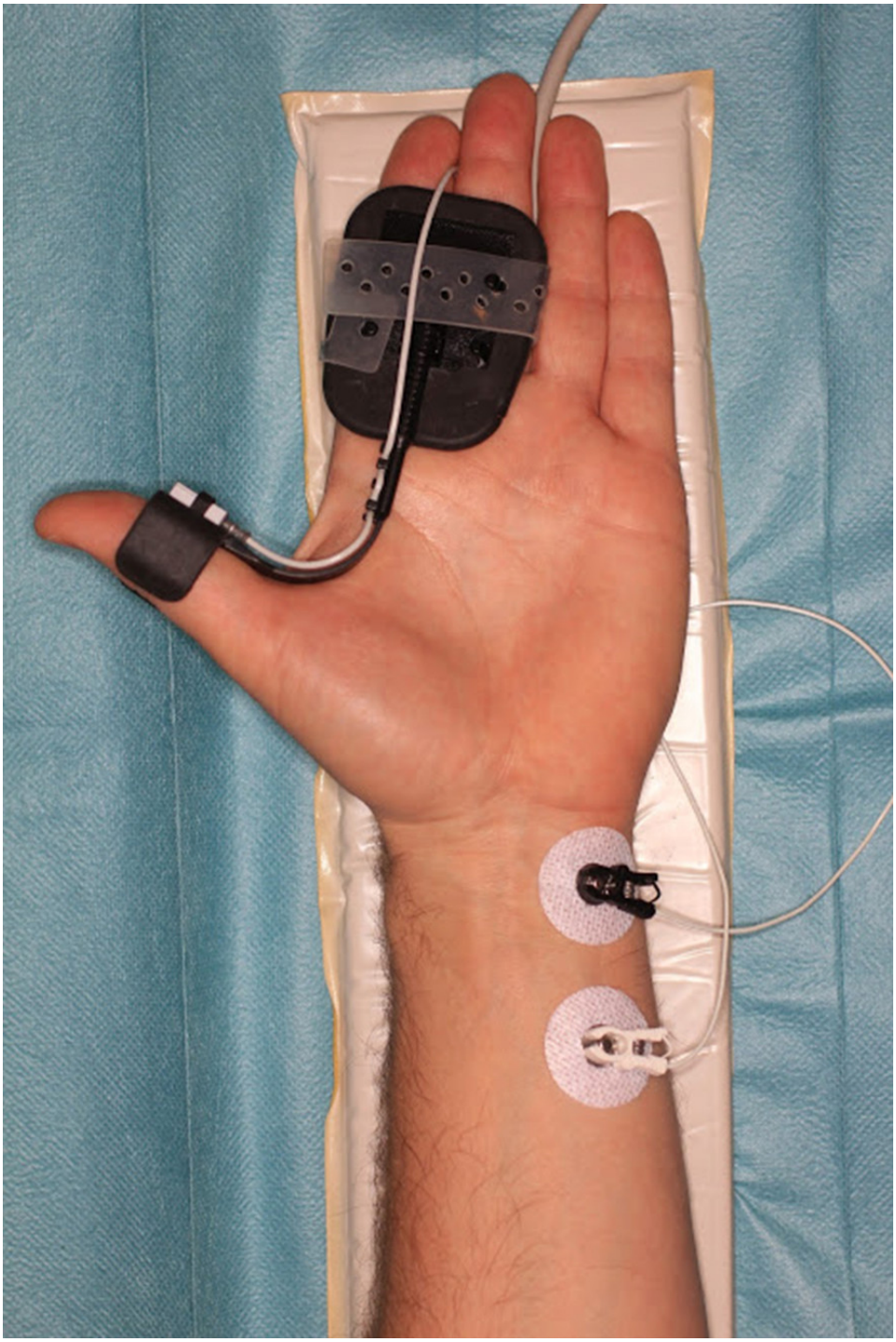
We hypothesised that time to TOF-2 would be shorter after rocuronium 0.6 mg/kg than after 0.9 mg/kg. Similarly, we hypothesised that time to TOF-2 would be shorter after rocuronium 0.3 mg/kg than after 0.6 mg/kg.

METHODS

This study was a secondary analysis of data collected from two previous studies [2, 6] on elderly patients (>80 years). The inclusion criteria comprised an American Society of Anesthesiologists (ASA) physical health class I-III, elective surgery with an anticipated duration of at least 60 min., total intravenous anaesthesia and tracheal intubation after use of rocuronium. The exclusion criteria were known allergy to rocuronium, neuromuscular disease interfering with neuromuscular monitoring and no recorded intubation conditions.

One of the studies was a randomised trial approved by the Scientific Ethics Committee, the Danish Medicines Agency and the Danish Data Protection Agency [6]. That study was registered with Clincicaltrials.gov prior to enrolment of the first patient (NCT04512313). The other study was an observational study approved by the Danish Data Protection Agency [2]. The Scientific Ethics Committee was informed about the project but decided that no formal assessment of the study was needed. This study was registered with Clinicaltrials.gov (NCT03857750). Both studies were conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients. REDCap was used for data management. Patients were included from the Departments of Anaesthesiology, Centre of Head and Orthopaedics and the Juliane Marie Centre, Rigshospitalet, University of Copenhagen, Denmark.

The methods were previously described in detail [2, 6]. In brief, anaesthesia was induced with fentanyl and propofol after preoxygenation and maintained with an infusion of propofol and remifentanil after tracheal intubation. Patients were monitored with non-invasive blood pressure, electrocardiogram, core temperature and pulse oximetry. Neuromuscular monitoring was performed according to good clinical research practice for pharmacodynamic neuromuscular studies, and neuromuscular function was monitored with acceleromyography, using TOF ulnar nerve stimulation [7]. After securing a stable signal with < 5% deviation for 2 min., rocuronium 0.3 mg/kg, 0.6 mg/kg or 0.9 mg/kg was injected over 5 sec according to allocation after calibration of the TOF Watch neuromuscular monitor.



Train-of-four (TOF) monitoring with adapter.

We recorded any administration of ephedrine from induction of anaesthesia to tracheal intubation.

After tracheal intubation, the tube was connected to the anaesthetic breathing circuit, and mechanical ventilation was initiated targeting normocapnia (end-tidal CO_2: 4.5-5.5 kPa). During surgery, supplementary doses of rocuronium were administered as needed to ensure optimal surgical conditions. Neuromuscular data on duration of action were not included in the data analysis if supplementary doses of rocuronium were given.

In both studies, ideal body weight was used to calculate the dose of rocuronium. An upper body forced-air warming system was used to secure a core temperature above 35 °C and a peripheral skin temperature above 32

°C. Patients were extubated upon full recovery from neuromuscular block (TOF ratio > 0.9). If spontaneous recovery was not observed, reversal was performed with either sugammadex or neostigmine. The primary endpoint was time to recovery of TOF-2, defined as the time from the end of rocuronium injection to two twitches were detected. The secondary endpoints were onset time, defined as the time from the end of rocuronium injection until no response to TOF stimulation (TOF-0) was measured and duration of action, defined as the time from the end of rocuronium injection to the reappearance of TOF ratio > 0.9. Findings related to onset time and duration of action have been reported previously [2, 6].

Statistical analysis

Patient characteristics were reported as median with interquartile ranges or count with frequencies. Parametric data were presented as mean with standard deviations (SD) and compared using Student's T-test. Proportions were compared using the χ^2 test. Differences were reported with 95% confidence intervals (CI). A $p < 0.05$ was considered statistically significant. The sample size calculation was based on our secondary analysis of pooled data from two studies. A difference of 10 min. in time to recovery of TOF-2 between the groups who received either 0.6 or 0.9 mg/kg rocuronium was considered clinically relevant. We calculated that 15 patients in each group would allow us to detect this difference at a power of 80% and a risk of type 1 error of 5% with a SD of 10 min.

Trial registration: This study was a secondary analysis of two clinical trials. Clinicaltrials.gov (NCT04512313), (NCT03857750).

RESULTS

A total of 53 elderly patients were included in the two studies from 27 March 2019 to 21 May 2021 (**Table 1**). Two patients, one in Group Rocuronium 0.3 mg/kg and one in Group Rocuronium 0.9 mg/kg, did not receive the study medicine due to logistic issues after randomisation. Onee patient in Group Rocuronium 0.3 mg/kg withdrew consent after randomisation. Ten patients had no data on time to TOF-2. Accordingly, data from 40 patients were analysed. Two patients in Group Rocuronium 0.9 mg/kg received sevoflurane. A total of 55% of patients in Group Rocuronium 0.3 mg/kg were given ephedrine before TOF-0 was obtained. The corresponding proportion in Group Rocuronium 0.9 mg/kg was 35%

TABLE 1 Baseline characteristics of patients above 80 years of age, receiving rocuronium 0.3 mg/kg, 0.6 mg/kg or 0.9 mg/kg.

	0.3 mg/kg ($N_{0.3}$ = 20)	0.6 mg/kg ($N_{0.6}$ = 16)	0.9 mg/kg ($N_{0.9}$ = 17)
Age, mean (IQR), yrs	83 (82-84)	84 (81-85)	85 (84-86)
Sex M/F, n	10/10	3/13	4/13
BMI, mean (± SD), kg/m²	25.4 (± 2.7)	26.7 (± 4.9)	25.1 (± 6.0)
ASA class I/II/III, n	0/9/11	1/8/7	0/10/7
Daily medicine, n (%)			
Diuretics	7 (35)	8 (50)	8 (47.1)
Magnesium	1 (5)	1 (6.3)	1 (5.9)
Comorbidity, n (%)			
Renal disease	0	2 (12.5)	1 (5.9)
Diabetes	3 (15)	3 (18.8)	1 (5.9)
Hypertension	12 (60)	13 (81.3)	11 (64.7)
Heart disease	4 (20)	7 (43.8)	6 (35.3)

ASA = American Society of Anesthesiologists Physical Status Classification System; F = female; IQR = interquartile range; M = male; SD = standard deviation.

In Group Rocuronium 0.6 mg/kg, the mean time to TOF-2 was 37 min. (SD: ± 10 min.). In Group Rocuronium 0.9 mg/kg, the mean time to TOF-2 was 59 min. (SD: ± 17 min.) with a mean difference of 22 min. (95% CI: 10 to 33 min.) (p = 0.0007) (**Table 2**).

TABLE 2 Intraoperative data including onset time, time to recovery of two responses to train-of-four (TOF) stimulation (TOF-2), and duration of action of rocuronium (time to TOF ratio > 0.9) for rocuronium 0.6 mg/kg and 0.9 mg/kg in patients above 80 years of age.

	0.6 mg/kg ($N_{0.6}$ = 16)	0.9 mg/kg ($N_{0.9}$ = 16)	Difference (95% CI)	p value
NMB reached TOF-0, n (%)	15 (100)	16 (100)	0%	-
Patients with available data, n	15	16		
Onset time of rocuronium, sec	165 (76)	109 (40)	56 (12-101)	0.01
Patients with available data, n	15	16		
Time to recovery of TOF-2, min.	37 (10)	59 (17)	22 (10-33)	0.0007
Patients with available data, n	13	14		
Duration of action of rocuronium, min.	86 (25)	115 (42)	29 (–59-2)	0.065
Patients with available data, n	13	11		
Duration of anaesthesia, min.	166 (59)	209 (84)	-	-
Duration of surgery, min.	104 (51)	126 (61)	-	-
Type of surgery, n			-	-
Orthopaedic	0	7		
Plastic/breast	9	6		
Gynaecology	1	1		
Other	6	2		

CI = confidence interval; NMB = neuromuscular blockade.

A shorter onset time was found in Group Rocuronium 0.9 mg/kg than in Group Rocuronium 0.6 mg/kg; mean 109 sec (SD: ± 40 sec) versus 165 sec (SD: ± 76 sec) (p = 0.01); with a difference of 56 sec (95% CI: 12 to 101 sec). The duration of action of rocuronium 0.9 mg/kg was not significantly longer than that of rocuronium 0.6 mg/kg; mean 115 min. (SD: ± 42 min.) versus 86 min. (SD: ± 25 min.) (p = 0.065); with a difference of 29 min. (95% CI: –59 to 2 min.) (Table 2).

In Group Rocuronium 0.3 mg/kg, the mean time to TOF-2 was 19 min. (SD: ± 6 min.). Compared with Group Rocuronium 0.6 mg/kg, this constitutes a mean 18 min. difference (95% CI: 11 to 25 min.) (p = 0.00006). However, only 33% of the patients receiving 0.3 mg/kg rocuronium obtained TOF-0 (**Table 3**).

TABLE 3 Intraoperative data including onset time, time to recovery of two responses to train-of-four (TOF) stimulation (TOF-2), and duration of action of rocuronium (time to TOF ratio > 0.9) for rocuronium 0.3 mg/kg and 0.6 mg/kg in patients above 80 years of age.

	0.3 mg/kg ($N_{0.3}$ = 18)	0.6 mg/kg ($N_{0.6}$ = 16)	Difference (95% CI)	p value
NMB reached TOF-0, n (%)	6 (33)	15 (100)	67 (45-88)%	0.00007
Patients with available data, n	18	15		
Onset time of rocuronium, sec	227 (140)	165 (76)	62 (–85-209)	0.34
Patients with available data, n	6	15		
Time to recovery of TOF-2, min.	19 (6)	37 (10)	18 (11-25)	0.00006
Patients with available data, n	13	13		
Duration of action of rocuronium, min.	46 (13)	86 (25)	40 (24-56)	0.00005
Patients with available data, n	16	13		
Duration of anaesthesia, min.	205 (75)	166 (59)	-	-
Duration of surgery, min.	121 (55)	104 (51)	-	-
Type of surgery, n			-	-
Orthopaedic	9	0		
Plastic/breast	7	9		
Gynaecology	1	1		
Other	1	6		

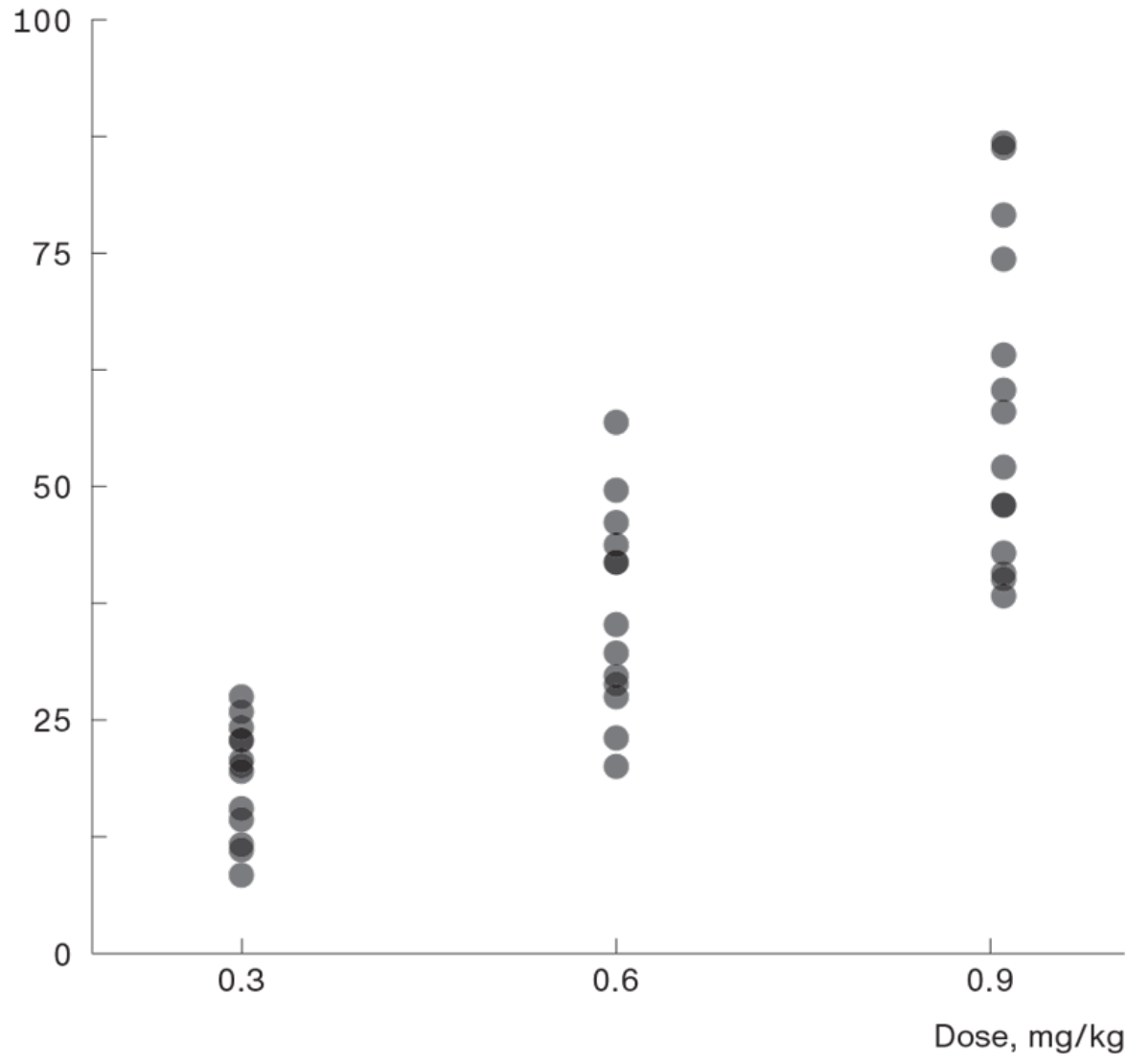
CI = confidence interval; NMB = neuromuscular blockade.

The onset time of rocuronium was 227 sec (SD: ± 140 sec) in Group Rocuronium 0.3 mg/kg and 165 sec (SD: ± 76 sec) in Group Rocuronium 0.6 mg/kg (p = 0.34), resulting in a difference of 62 sec (95% CI: –85 to 209 sec). The duration of action of rocuronium 0.3 mg/kg was 46 min. (SD: ± 13 min.); that of rocuronium 0.6 mg/kg, 86 min. (SD: ± 25 min.) (p = 0.00005); difference of 40 min. (95% CI: 24 to 56 min.) (Table 3).

DISCUSSION

We found that the time to TOF-2 was significantly shorter in elderly patients receiving rocuronium 0.6 mg/kg than in those receiving rocuronium 0.9 mg/kg. Furthermore, time to TOF-2 was significantly shorter in elderly patients receiving 0.3 mg/kg than in patients receiving rocuronium 0.6 mg/kg (**Figure 1**). However, only 33% of patients administered 0.3 mg/kg obtained full neuromuscular blockade, defined as TOF-0.

FIGURE 1 Time to train-of-four (TOF)-2 after three different doses of rocuronium.



One strength of this study was that we performed neuromuscular monitoring according to research guidelines thereby minimising the risk of variability and imprecise neuromuscular data. Furthermore, the two studies had similar inclusion and exclusion criteria and used the same type of anaesthesia. Moreover, neuromuscular monitoring was performed by trained personnel.

There were some limitations to our study. Duration of action in Group Rocuronium 0.9 mg/kg may have been prolonged by the administration of sevoflurane in two patients [8]. Additionally, onset time may have been shortened in patients receiving ephedrine before TOF-0 was obtained as ephedrine increases cardiac output. Finally, in Group Rocuronium 0.6 mg/kg, three patients undergoing laparoscopic surgery needed supplementary

doses of rocuronium. Thus, no data were available on their duration of action.

No significant difference was found in duration of action between Group rocuronium 0.6 mg/kg and Group rocuronium 0.9 mg/kg, but a risk exists of type 2 error as the confidence interval was very wide (–59 to 2 min.). A clinically important difference may therefore have been overlooked.

Another study of elderly patients receiving rocuronium 0.6 mg/kg found a longer onset time (190 sec compared with 165 sec) and a shorter duration of action (78 min. compared with 86 min.) [9]. These results may reflect the large interindividual variation in both onset time and duration of action of rocuronium especially in elderly patients.

Alternatively, rocuronium may be reversed regardless of the depth of NMB by administration of sugammadex, arguably making measurements of time to TOF-2 less relevant. Studies have also indicated that sugammadex may be the preferable choice of reversal agent owing to faster NMB recovery [10, 11] and a lower incidence of post-operative pulmonary complications (POPC) [12]. However, the latter has been questioned by other studies [13, 14]. Nevertheless, administration of sugammadex requires adequate objective monitoring of the depth of the NMB to guide the correct dose [15]. Furthermore, sugammadex is more expensive than neostigmine [16]. Additionally, some clinicians may be reluctant to administer sugammadex due to the challenges that may arise following a potential reoperation requiring administration of rocuronium within the first 24 hrs post-operatively [8]. Finally, sugammadex is not recommended in patients with significantly decreased kidney function (glomerular filtration rate below 30 ml/min, including dialysis) [17], and sugammadex has been correlated with a higher incidence of anaphylaxis than neostigmine [18].

Neostigmine has been associated with a dose-dependent increase in pulmonary complications [19], but these results may reflect overdosing of neostigmine due to a lack of neuromuscular monitoring. Thus, a recent study confirmed that the appropriate use of neostigmine guided by neuromuscular monitoring may reduce the incidence of POPC [20].

We found a clinically relevant difference in time to TOF-2 as it will be possible to reverse a neuromuscular block with neostigmine 22 min. earlier in elderly patients receiving rocuronium 0.6 mg/kg than in elderly patients receiving rocuronium 0.9 mg/kg.

Especially in elderly patients, it may be tempting to administer smaller doses of rocuronium due to the increased risk of residual NMB. However, only 33% of patients in Group Rocuronium 0.3 mg/kg obtained full effect, i.e. TOF-0. This observation indicates that rocuronium 0.3 mg/kg may be insufficient in obtaining complete neuromuscular relaxation and facilitating tracheal intubation. Only 22% of the patients receiving rocuronium 0.3 mg/kg exhibited excellent tracheal intubating conditions [6]. Therefore, opting for a smaller dose of rocuronium does not seem to be reasonable even though the time to TOF-2 is shorter.

CONCLUSION

In elderly patients, a shorter time to TOF-2 was found after rocuronium 0.6 mg/kg than after rocuronium 0.9 mg/kg; the mean difference was 22 min. Furthermore, a shorter time to TOF-2 was found after rocuronium 0.3 mg/kg than after rocuronium 0.6 mg/kg; the mean difference was 18 min. However, not all patients receiving 0.3 mg/kg obtained full effect.

Correspondence *Sarah Sofie Wadland*. E-mail: sarah.sofie.wadland@ regionh.dk

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