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Effectiveness of partial and adjustment neostigmine dose as a neuromuscular reversal for single dose rocuronium

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ABSTRACT

Background: Routine reversal (neostigmine) and the use of quantitative monitoring of neuromuscular blockade (Train of Four Ratio (TOFR)) are recommended to prevent the occurrence of residual paralysis. This study attempted to determine the effectiveness between neostigmine partial dose 0.02 mg/kgBW and adjusted dose based on TOFR value in recovering neuromuscular blockade of single dose rocuronium 0.6 mg/kg BW.

Methods: This randomized clinical trial was performed in the operating room of Integrated Surgical Care Unit of Cipto Mangunkusumo General Hospital and Kirana Clinic. Sixty-one patients who underwent elective surgery with general anaesthesia were randomized into 2 groups: administration of neostigmine in partial dose 0.02 mg/kgBW (group A) and adjusted dose based on TOFR value (group B). Quantitative monitoring evaluation of neuromuscular blockade was performed four times: after adequate spontaneous breathing, 5, 10, and 15 minutes after reversal.

Result: The mean of TOFR values in group A and group B respectively: after spontaneous breathing, 42% and 50% (p=0.436); 5 minutes after reversal, 80.2% and 89.2% (p=0.083); 10 minutes after reversal, 92.2% and 94% (p=0.399); 15 minutes after reversal, 94.3% and 94.9% (p=0.526). After the 5 minutes of reversal, group B (80.6%) reaches a TOFR value ≥ 90% which is more than group A (63.3%) (p=0.132).

Conclusion: Neostigmine partial dose 0.02 mg/kgBW was as effective as administering neostigmine in adjustment dose based on TOFR values to achieve complete recovery from the neuromuscular block effect of single-dose rocuronium 0.6 mg/kg BW. This study also shows the complete recovery of the neuromuscular block when TOFR value ≥ 90%.

Keywords: reversal, neostigmine, rocuronium, neuromuscular block, neuromuscular block residual, residual paralysis, partial dose, Train-of-Four, TOF value ratio

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INTRODUCTION

The incidence of the residual neuromuscular blockade in the recovery room is high (30-50%)[1-5] with a Train of Four Ratio (TOFR) < 90%.[2,6] This condition can increase morbidity of dyspnea, airway obstruction, hypoxia, and the mortality.[1,2,7,8]

Many trials that prevented residual neuromuscular blockade suggest to use a monitoring device for neuromuscular blockades and give reversal agents for every neuromuscular blocking agent administration.[5,9,10-12] Practice Guidelines for Postanaesthetic Care recommends that neuromuscular blockade device is effective to detect neuromuscular dysfunction and the administration of neostigmine is as effective as residual neuromuscular blockade antagonist.[13] However, the recommendation has not been done routinely, not all of the anaesthesiologists use a neuromuscular blockade device[14] and many anaesthesiologists still depend on clinical evaluation for assessing neuromuscular block.[15,16]

Reversal agents are always suggested to be given for every neuromuscular blocking agent administered by considering the administration time and the dose.[1,5,9,10-13] The most common reversal agent is neostigmine (0.04-0.07 mg/kgBW).[1,17] A new study suggests giving an adjusted neostigmine dose based on the TOFR value postoperative leads to complete recovery from neuromuscular blocking agent effect with minimal muscarinic effect.[1,11,12]

Routine administration of reversal has been done in Cipto Mangunkusumo General Hospital by neostigmine 0.02 mg/kgBW and 0.4 mg of atropine sulfate for each 1 mg of neostigmine. However, the residual event is still high (43%). This study aims to determine the effectiveness of reversal routine dose (neostigmine partial dose 0.02 mg/kgBW) in Cipto Mangunkusumo General Hospital and adjusted dose based on the TOFR value against single dose administration of rocuronium 0.6 mg/kgBW.

DESIGN AND METHODS

This was a double-blind randomized clinical trial in the Integrated Surgical Care Unit of Cipto Mangunkusumo General Hospital and Kirana Clinic. Ethical approval from Ethics Committee

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of Faculty Medicine of Universitas Indonesia was obtained for this study.

This study utilized a consecutive sampling with randomization for all patients who undergo elective surgery from November to December 2016. The inclusion criteria were patients aged 18-60 years old, physical status ASA I-II, planned to undergo general anaesthesia for 60-120 minutes, and accepted to participate this study. The exclusion criteria were patients who had a BMI ≥ 30 kg/ m^2, severe liver or kidney disease, neuromuscular disorder, and asthma. Patients who fulfilled the inclusion criteria and did not meet exclusion criteria were divided into 2 groups by randomization: patients were given neostigmine partial dose 0.02 mg/kgBW (Group A) and adjusted dose based on the TOFR (Group B). Five patients were removed from this study because the duration of surgery was less than 60 minutes or more than 120 minutes.

After patients arrived in the operation room, routine anaesthesia monitoring devices (4 leads ECG, pulse oximeter, and noninvasive blood pressure) were attached. Oxygen 100% was given as preoxygenation. Midazolam 0.01 mg/kgBW was administrated as co-induction. After 1 minute, fentanyl 3 μg/kgBW was given. Three minutes after fentanyl administration, propofol 1-2 mg/kgBW was given for induction. Laryngeal mask airway insertion or endotracheal intubation was done with rocuronium 0.6 mg/kgBW.

The ventilator was set to pressure controlled ventilation or volume controlled ventilation mode, targeted tidal volume 6-8 mL/kgBW, respiratory rate 12 breaths per minute, I:E ratio 1:2, fresh gas flow 1-2 L/min with O_2 fraction 30-50% by mix O_2 and compressed air. Sevoflurane 1.2% and fentanyl 1.2 μg/kgBW/min were given for maintenance anaesthesia. Maintenance fluid using crystalloid was adjusted to the "4:2:1 Rule". The temperature was monitored during surgery and patient wore a blanket to reach normothermia (36-37°C).

When the surgery was done, fentanyl was stopped and the patients were observed until adequate spontaneous breathing (tidal volume ≥ 5 mL/kgBW) commenced before being evaluated for the TOFR value by TOF-watch. Before the reversal agent was administered, the anaesthetic gas was stopped, the duration of surgery was noted and the TOFR postoperative values were done.

Neostigmine administration in both groups was given with atropine sulfate (0.4 mg per 1mg of neostigmine combination). After the reversal agent administration, the TOFR was assessed every 5 minutes until TOFR ≥ 90% before definitive airway equipment was removed.

If the reversal agent administration TOFR did not reach ≥ 90% after 10 minutes, the second reversal would be given. Second reversal dose for Group A was same like before, but group B will be given adjusted dose based on last TOFR value (Table 1). TOFR value evaluation was continued every 5 minutes until TOFR ≥ 90% and then the definitive airway equipment was removed.

Data analysis was done using SPSS 21.0 software. If the data distribution was not normal, the numerical data is presented as a mean ± standard deviation. If the data distribution was normal, the data is presented as a mean (minimum value – maximum value). The unpaired T-Test or Mann-Whitney Test was used to compare two numeric variables. Categorical data was presented in n (%) and tested by the Chi-square or Fisher test. Results are considered as statistically significant if $p < 0.05$.

Table 1 **Adjusted dose of neostigmine based on the TOFR value**[11]

Evaluation	TOF	Action
Quantitative (AMG)	TOF *count* 1 or no response	Postpone reversal agent administration until TOF *count* ≥ 2
	TOF *count* 2 atau 3	Give neostigmine 0.05 mg/kgBW. Extubate after TOFR achieves 0.9
	TOFR < 40%	Give neostigmine 0.04 mg/kgBW. Extubate after TOFR achieves 0.9
	TOFR 40-90%	Give neostigmine 0.02 mg/kgBW
	TOFR > 90%	No reversal agent administration

Table 2 **Basic characteristics of subjects**

Data	Group A (Partial dose)	Group B (Adjusted dose)
Age (year)	40 (18-60)	36 (19-59)
Sex (n%)		
Male	20 (66,7)	17 (54,8)
Female	10 (33,3)	14 (45,2)
ASA (n%)		
I	14 (46,7)	11 (35,5)
II	16 (53,3)	20 (64,5)
Body weight (kg)	59 ± 8	61 ± 8
Height (m)	161 ± 7	162 ± 8
BMI (kg/m^2)	23,02 ± 2,44	23,14 ± 2,11
Duration of surgery (minute)	80 (60-120)	70 (60-120)

RESULTS

There were 945 patients undergoing general anaesthesia in the Integrated Surgical Care Unit and Kirana Clinic of Cipto Mangunkusumo General Hospital. Sixty-six patients fulfilled the inclusion criteria and did not have exclusion criteria. Five patients were removed because the duration of surgery was less than 60 minutes or more than 120 minutes. The total subjects were divided by

Table 3 Comparison of the TOFR value between partial dose neostigmine and adjusted dose neostigmine

Time	TOFR Value		*p* value
	Group A (Partial dose)	Group B (Adjusted dose)	
After adequate breathing	42 (2-97)	50 (3-100)	0.436*
5 minutes after reversal	80.2 ± 22.7	89.2 ± 14.8	0.083†
10 minutes after reversal	92.2 ± 9.2	94.0 ± 6.76	0.399†
15 minutes after reversal	94.3 ± 3.9	94.9 ± 3.62	0.526†

* = Mann Whitney Test; † = T Test. Statistical test was done by using transformed data to get normal distribution. Data was significant if p<0.05

Table 4 Comparison of time required to reach TOFR ≥ 90% between Group A and Group B

Monitoring Time	TOFR Value	Group A*	Group B*	*p* Value
		N (%)	N (%)	
After adequate breathing	< 90%	26 (86.7%)	26 (83.9%)	0.758†
	≥ 90%	4 (13.3%)	5 (16.1%)	
5 minutes after reversal	< 90%	11 (36.7%)	6 (19.4%)	0.132†
	≥ 90%	19 (63.3%)	25 (80.6%)	
10 minutes after reversal	< 90%	2 (6.7%)	1 (3.2%)	0.534†
	≥ 90%	28 (93.3%)	30 (96.8%)	
15 minutes after reversal	< 90%	0 (0%)	0 (0%)	
	≥ 90%	30 (100%)	31 (100%)	

*= Categorical data presented as n (%);†= Fisher test. Fisher test was done because the requirement of Chi square test and T test was not fulfill. Data will be considered as statistically significant if *p*<0.05

Table 5 Comparison of total neostigmine dose required for reach TOFR ≥ 90% between Group A and Group B

Neostigmine Dose	Group A (Partial dose)	Group B (Adjusted dose)	*p* value
Total neostigmine dose for reach TOFR ≥ 90% (mg)	1,19 (0,96-2,44)*	1,3 (0-3,85)*	0,175†

* =Numerical data with non normal distribution presented as median (minimum-maksimum value) † = Mann Whitney Test. Mann Whitney test was done because the requirement of Chi square test and T test was not fulfill. Data will be considered as statistically significant if *p*<0.05

Table 6 Characteristics of first and second reversal agent administration

Neostigmine dose	Group A (Partial dose)		Group B (Adjusted dose)	
	1st Reversal*	2nd Reversal†	1st Reversal*	2nd Reversal†
Not given	-	-	5 (16.12%)	-
0.02 mg/kgBW	30	2	15 (48.38%)	1
0.04 mg/kgBW	-	-	10 (32.25%)	-
0.05 mg/kgBW	-	-	1 (3.22%)	-

* =after adequate breathing, † = at 10 minutes after first reversal agent administration

randomization into 2 groups: Group A (30 subjects) and Group B (31 subjects).

This study evaluated neuromuscular blockade at 5 time intervals: after adequate spontaneous breathing in the ending of surgery, at 5 minutes, 10 minutes, 15 minutes, and 20 minutes after the reversal agent administration. All subjects reached TOFR ≥ 90% in 15 minutes after reversal agent administration thus assessment of the TOFR value in 20 minutes after reversal agent administration was not done.

Comparison of the TOFR value between Group A and Group B can be seen in Table 3. The monitoring of TOFR value did not reach 90% at the end of surgery after the patient had adequate breathing. The mean of TOFR value in Group A was 42% (2-97%) while Group B was 50% (3-100%) (*p*=0.494). The mean TOFR value at 5 minutes after a reversal in both groups was almost 90% (Group A (80.2 ± 22.7%); Group B (89.2 ± 14.8%); *p*=0.083 based on T-test). The mean TOFR value at 10 minutes after a reversal in both groups had reached 90% (Group A 92.2 ± 9.2%; Group B 94.0 ± 6.76%; *p*=0.399). The mean TOFR value at 15 minutes after a reversal in both groups had reached ≥ 90% (Group A 94.3 ± 3.9%; Group B 94.9 ± 3.62%). Both groups were analyzed by GLM repeated measurement using normalization TOFR value to compare the mean of postoperative TOFR and the result was not statistically different (*p*=0.253).

Comparison of the time required to reach TOFR ≥ 90% between Group A and Group B was done by comparing the total patients who had reached TOFR ≥ 90% at every monitored time interval of neuromuscular block (Table 4). At 5 minutes after reversal, the total subjects in Group B (80.6%; 25 subjects) was higher than Group A (63.3%; 19 subjects) with *p*=0.132. At 10 minutes after reversal, subjects of both groups that had reached a TOFR value ≥ 90% was more than 90% (Group A 93.3%; Group B 98,8%; *p*=0.534). All subjects reached TOFR ≥ 90% at 15 minutes after the reversal.

Group A and Group B had nearly the same mean of total neostigmine dose required to reach TOFR ≥ 90% (Group A 1.19 (0.96-2.44) mg; Group B 1.3 (0.3-8.5) mg). However, this difference was not statistically significant (*p*=0.175) (Table 5).

This study had additional data regarding the characteristics of reversal agent administration in both groups (Table 6). Group B contained 15 subjects (48.38%) that were given neostigmine 0.02 mg/kgBW, 5 patients (16.12%) that were not given neostigmine because their TOFR was ≥ 90%,

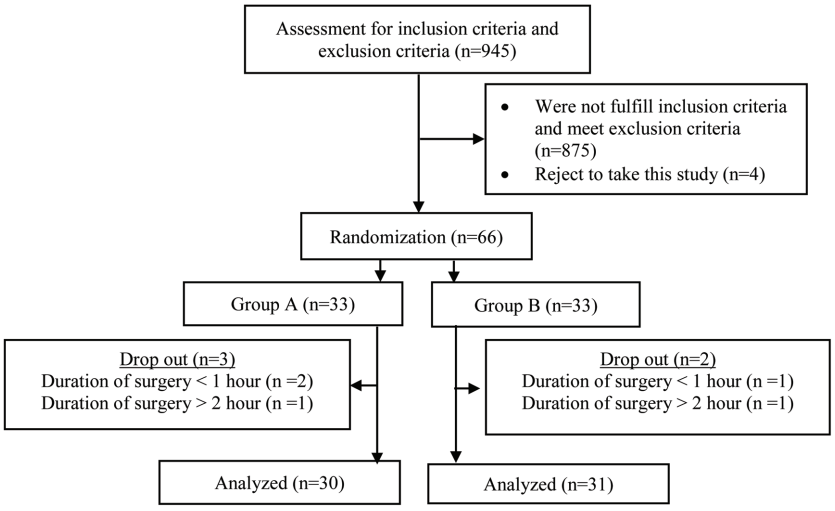

Figure 1 Schematic of subject selection

10 patients (32.25%) that were given neostigmine 0.04 mg/kgBW, and only 1 patient (3.22%) that was given neostigmine 0.05 mg/kgBW. A second reversal agent administration at the 10th minute after first administration was given to 3 subjects.

DISCUSSION

Complete recovery from neuromuscular block postoperative is important because residual neuromuscular block may increase morbidity (dyspnea, airway obstruction, hypoxia).[1,2,7,8] Routine reversal agent administration and the usage of quantitative monitoring of neuromuscular blockage intraoperative are recommended to prevent residual neuromuscular blockage. However, both things were not routinely done until now thus the residual case still often happens.

A neostigmine therapeutic dose is 0.04 – 0.07 mg/kgBW while a toxic dose is 0.08 mg/kgBW. Neostigmine administration has limitations such as muscarinic effect,[1,18] recurarization,[18] ceiling effect,[19] no effect for high dose second reversal administration (0.07 mg/kgBW)[20] and weakness of respiratory muscle.[18,21] Some adverse effects of neostigmine are dose-dependent. New studies aim to know the lowest neostigmine dose for recovery of neuromuscular block (TOFR 90%) without adverse effects.[20,22]

The distribution of basic characteristics in this study is proportionate by age, sex, body weight, body mass index, and duration of surgery in both groups. Thus, the impact of both groups may be considered as the same and there is no need to process the controlling of confounding variables.

The duration of surgery in this study was limited to 60 – 120 minutes due to the consideration of rocuronium pharmacokinetics. Rocuronium has a moderate duration of action between 35-75 minutes.[17] However, Debane et. al found that the effect of rocuronium is still available until 120 minutes after single dose administration.[9] Limitation of the duration of surgery intends to select only single dose neostigmine without an intraoperative intermittent dose. If the patients needed to get neuromuscular blocking agents intraoperative, neuromuscular blocking agents were given but the patients were dropped out of this study.

Prolonged duration of action of rocuronium can occur because of an interaction with sevoflurane. Sevoflurane increases potency and prolongs the duration of action of neuromuscular blocking agents, thus the recovery time will be longer.[23,25,26] Interactions between intravenous anaesthetic and neuromuscular blocking agents slightly increase the potency of neuromuscular blocking agents but there is no effect on humans.[24] Other factors that can prolong the duration of action have been eliminated by the inclusion and exclusion criteria.[27-36]

This study compares TOFR values, duration time and total neostigmine dose required to reach TOFR ≥ 90% between neostigmine partial dose 0.02 mg/kgBW (Group A) and adjusted dose based on the TOFR (Group B). Neostigmine partial dose was considered effective if mean of the TOFR and mean of the total neostigmine dose reached TOFR ≥ 90% while being equal to the adjusted dose.

This study showed that partial dose of neostigmine (0.02 mg/kgBW) was as effective as adjusted dose based on the TOFR value for reversal of single dose rocuronium 0.6 mg/kgBW. This can be seen because there is no statistically significance at 5 minutes and 10 minutes after reversal agent in both groups.

Theoretically, neostigmine adjusted dose based on the TOFR as reversal ensures that there is no occurrence of residual neuromuscular block postoperative. A muscarinic side effect of neostigmine may be avoided due to the adjustment of the deep neuromuscular blockade.[11,12,37] The main objective of reversal administration is to maximise nicotinic transmission by minimising the muscarinic effect.[38]

The TOFR value can represent how many nicotinic receptors in motor end plate bind the neuromuscular blocking agents. The TOFR represents how deep the neuromuscular blockade is. The lower the TOFR value, the deeper the neuromuscular blockade. Burton et. al found that 70% of receptors must be blocked to avoid muscle contraction.[39] Padmaja et. al showed that TOF count 4 represents <70% blocked receptors by neuromuscular blocking agents.[40] Waud et. al showed that total bound receptors in TOF count 4 are 70-75%.[41] TOF count 4 is the best time for reversal administration by qualitative evaluation. However, after quantitative

monitoring of neuromuscular blockade was discovered, the reversal is suggested to be given when the neuromuscular block is shallow (TOFR 40-60%) by neostigmine partial dose (0.02 mg/kgBW) thus the muscarinic effect could be avoided.

In this study, neostigmine adjusted dose based on the TOFR was not more effective than partial dose. Based on the previous study, complete recovery of neuromuscular blockade was not only influenced by reversal dose but also by the administration time of the last drug and the degree of neuromuscular blockade.[22,38] This study found that the mean of TOFR at the end of the surgery after adequate breathing in both groups was higher than 40%. The depth of neuromuscular blockade was influenced by the rocuronium pharmacokinetics itself. Before reversal is given, there is retribution and elimination of the neuromuscular block. Neuromuscular blocking agents migrate from the motor end plate to the central circulation before being eliminated from the circulated blood via the synaptic cleft.

Group B participants with a TOFR of 40-90% after adequate breathing were given neostigmine 0.02 mg/kgBW, which was the same dose in Group A. This is similar to several previous studies that showed neostigmine 0.02 mg/kgBW can successfully reach a TOFR ≥ 90%.[10,11,20,38]

This study compared the duration of time required to reach TOFR ≥ 90% between Group A and B by assessing the total patients reaching TOFR ≥ 90% at every neuromuscular blockade. This was possible because the TOFR monitoring times in this study had been set.

This study showed that total subjects who reached TOFR ≥ 90% at 5 minutes after reversal administration in Group B was a lot more than in Group A (80.6%, 63.3%, respectively). Ten minutes after reversal administration, both groups had already reached TOFR ≥ 90% (Group A 93.3%, Group B 98.8%). However, the differences were not statistically significant (p=0.132; p=0.534). All subjects in both groups had already reached TOFR ≥ 90% in 15 minutes after reversal administration. This occurred because when reversal was given when the degree of neuromuscular block was shallow (TOFR 40-60%).

The other data in this study showed that mean of the time required to reach TOFR ≥ 90% after reversal was 10-15 minutes. This time was not much different than the study by Fuchs-Buder et. al which showed that the time required was 10 minutes.[20] Likewise, another study by Kajal et. al showed that the recovery time of the patient was 10 minutes after neostigmine 0.01-0.03 mg/kgBW with a shallow degree of neuromuscular block at the end surgery.[22]

The total dose of neostigmine to reach TOFR ≥ 90% in Group B was higher than Group A (Group A 1.19 mg, Group B 1.3 mg). However, statistic tests showed that the difference was not significant (p=0.175). This result was expected because the TOFR value after adequate breathing in the end of surgery in Group B had already reached 40-90%. If this value adjusted to the table of adjusted neostigmine dose based on TOFR, Group B would be given neostigmine 0.02 mg/kgBW which was same as Group A.

CONCLUSION

The administration of neostigmine partial dose (0.02 mg/kgBW) as a reversal is as effective as the administration of neostigmine adjusted dose based on the TOFR value for recovery after a neuromuscular block by single dose rocuronium 0.6 mg/kgBW. There is no statistically significance in the time to required to reach TOFR ≥ 90% and postoperative TOFR values between a partial dose and an adjusted dose of neostigmine.

The total dose of neostigmine to reach TOFR ≥ 90% by neostigmine partial dose was 1.19 mg. The total dose of neostigmine to reach TOFR ≥ 90% by neostigmine adjusted dose was 1.3 mg.

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