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Optimal Doses of Succinylcholine and Rocuronium during Electroconvulsive Therapy: A prospective, randomized, crossover trial

Hooman Mirzakhani, Henk-Jan Guchelaar, Charles A. Welch, Cristina Cusin, Mary E. Doran Teresa O. MacDonald, Edward A. Bittner, Matthias Eikerman, and Ala Nozari

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ABSTRACT

Background

Neuromuscular blockade is required to control excessive muscle contractions during electroconvulsive therapy (ECT). In a crossover, assessor-blinded, prospective randomized study, we studied the optimal effective dose of succinylcholine and rocuronium for ECT, defined as the lowest dose to provide acceptable control of muscle strength during induced convulsions.

Methods

Succinylcholine (0.8 $mg.kg^{-1}$) or rocuronium (0.4 $mg.kg^{-1}$) were randomly administered in 227 ECT sessions to 45 patients. The dose was incrementally increased or decreased by 10% based on two psychiatrists' (blinded to treatment) assessment of 'acceptable' or 'not acceptable' control of evoked muscle contractions (sufficient vs. insufficient or excessive paralysis). The neuromuscular transmission was monitored quantitatively until full recovery.

Results

The optimal effective doses of succinylcholine and rocuronium in 50% of patients (OED_{50}) were 0.85 $mg.kg^{-1}$ (95% CI: 0.77-0.94) and 0.41 $mg.kg^{-1}$ (95% CI: 0.36-0.46), and the 90^{th} percentile of the applied optimal doses (OED_{90}) 1.06 $mg.kg^{-1}$ (95% CI: 1.0-1.27) and 0.57 $mg.kg^{-1}$ (95% CI: 0.51-0.62), respectively. Nadir twitch height for acceptable muscle activity was 0% [0-4] and 4% [0-30] ($p<0.001$), and the time to recovery of the neuromuscular transmission after optimized induced seizure 9.7 ± 3.5 and 19.5 ± 5.7 min, respectively. The inter-individual variability of the OED_{50} (coefficient variation) was 1.24-fold greater for succinylcholine than rocuronium.

Conclusion

A twitch suppression of more than 90% is needed for control of motor contractions during ECT. Succinylcholine doses of 0.85-1.06 $mg.kg^{-1}$ produce acceptable muscle blockade. Rocuronium is a safe alternative if appropriately dosed (0.41-0.57 $mg.kg^{-1}$) and monitored.

INTRODUCTION

Electroconvulsive therapy (ECT) is a treatment in which generalized seizures are induced by transcutaneous electrical stimuli to the brain to treat specific psychiatric conditions such as therapy-resistant depression, catatonia and therapy-resistant schizophrenia. [1, 2] The quality and duration of the induced seizure by ECT have been associated with the efficacy of the procedure. Anesthetic drugs and neuromuscular blocking agents (NMBAs) are administered to ensure patient comfort and safety, but need also be titrated to provide optimal conditions for the induced seizure activity during the treatment, while allowing a rapid recovery upon its completion.[3] Due to its rapid onset and short duration of action, succinylcholine is considered the NMBA of choice for ECT. However, a non-depolarizing NMBA needs to be considered in some patients with metabolic, neuromuscular or neurological comorbidities, or other contraindications to succinylcholine (e.g. immobilization or pseudocholinesterase deficiency).[4] Despite the importance of NMBAs to provide favorable conditions for ECT, the optimal NMBA dose to achieve acceptable level of muscle contracture using neuromuscular blockade without excessive or untoward effects has not previously been identified in a prospective randomized fashion and using objective monitoring techniques.[5] The aim of this study is, therefore, to identify the optimal NMBA doses of two commonly used neuromuscular blocking agents (succinylcholine and rocuronium), defined as the lowest dose to provide optimized muscle strength modulation during ECT.

MATERIALS AND METHODS

This cross-over randomized controlled, assessor blinded clinical trial was conducted in the post-anesthesia care unit at Massachusetts General Hospital in Boston, MA, USA. Institutional Review Board approved the study protocol, and written informed consent was obtained from all participating patients.

Patients

Two hundred and twenty-seven ECT sessions were conducted in 45 hospitalized patients aged 24-80 years with American Society of Anesthesiologist Class I -III, admitted for a series of ECT treatments at a frequency of 3 times per week. The indication for ECT in all enrolled patients was major depressive disorder or bipolar disorder, and all patients were taking psychotropic medications including antidepressants and antipsychotics, as indicated by their psychiatric condition. Only patients within 20% of the ideal body weight were included. Exclusion criteria included an age of <18 years, patients with illness or medications known to influence neuromuscular transmission, significant renal or liver dysfunction, electrolyte abnormalities and pregnant women.

Protocol

The flow of patients through the study is depicted in figure 2. Following screening by the psychiatrist and anesthesiologist responsible for the clinical treatment of each patient, informed consent was obtained and patients were enrolled. After preoxygenation with 100% oxygen for 3 minutes through a facemask, anesthesia was induced with propofol (1.2 $mg.kg^{-1}$ intravenously over 5 sec). Continuous neuromuscular transmission monitoring was applied after stabilization and baseline calibration to establish a control twitch response prior to NMBA injection (see below). Succinylcholine (Quelicin®, Hospira Inc., Lake Forest, IL) 0.8 ($2.67 \times ED_{95}$) $mg.kg^{-1}$ or rocuronium-bromide (Zemuron®, Oganon USA Inc) 0.4 $mg.kg^{-1}$ ($1.33 \times ED_{95}$) was then administered intravenously over 5 sec via an intravenous catheter in the arm contralateral to the side of neuromuscular transmission monitoring, which was then flushed with a 10 ml bolus of normal saline. These initial doses were selected as the median of applied succinylcholine and rocuronium doses to achieve acceptable ECT induced motor activity in pilot study of 10 patients. Ventilation was assisted until recovery of normal spontaneous ventilation via a facemask and an Ambu-bag with supplemental 100% oxygen. After the peak effect of neuromuscular transmission blockade was established, an electrical stimulus at approximately 6x seizure threshold was delivered with right unilateral application of electrodes with a MECTA Model SR II apparatus (MECTA Corp., Portland, OR, USA). The treating psychiatrists, blinded to the type and dose of the NMBA (see discussion), determined the stimulus parameters for the applied ECT (level, dynamic, energy, intensity and duration of stimulus) and the subsequent duration of seizure (Table 2). The duration of seizure was monitored by EEG and recorded from EEG activity.

Systolic and diastolic blood pressures (SBP and DBP) were recorded every 3 min and the heart rate (HR), and oxygen saturation (SpO_2) were monitored and recorded continuously throughout the procedure and until full recovery. Temperature was monitored and maintained ≥ 35°C. Labetalol (10-50 mg IV) or esmolol (40-80 mg IV) was administered to treat hypertension and tachycardia, when necessary.

After termination of seizure and when appropriate, as determined by the practicing anesthesiologist, the rocuronium-induced neuromuscular blockade was reversed with neostigmine 50 $microgram.kg^{-1}$, administered with glycopyrrolate 10 $microgram.kg^{-1}$. [6] After return of normal spontaneous breathing, patients were placed in a lateral decubitus position. Neuromuscular monitoring was continued until full recovery of the neuromuscular blockade was recorded (T1 =100% or TOF ratio of > 0.9 for succinylcholine and rocuronium, respectively). [7]

Neuromuscular transmission monitoring

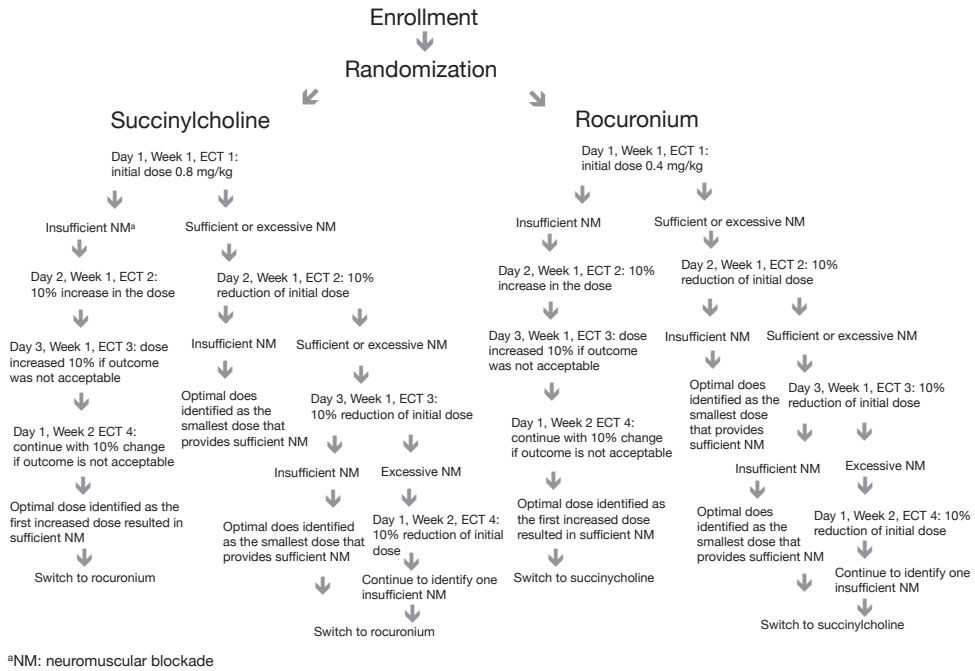
Neuromuscular transmission was monitored using acceleromyography and a TOF-Watch SX® monitor (Organon, Roseland, NJ, USA) connected to a laptop computer. Before induction of anesthesia, the subject's arm was taped in a stable and comfortable position, skin was cleansed and surface electrodes were placed (3-5 cm apart) over the ulnar nerve at the wrist. A hand adaptor (Organon International Inc., Roseland, NJ, USA) was used to fix the thumb position to minimize the potential variability in evoked muscle contraction. The TOF-watch was calibrated by using the standard calibration with default supramaximal stimulation (CAL1: 10 sec stimulation current of 50 mA), and ulnar nerve stimulation was resumed with single twitch stimulation at 0.1 Hz and continued till observation of less than 5% variation of twitch heights for 2-3 min, after which a bolus dose of the NMBA was injected.[8] The same mode of stimulation was continued until the peak effect of neuromuscular transmission blockade was established (first of three consecutive twitches with the same/increasing value or ≥ 95% depression of twitch). [8] After completion of the ECT- induced seizure, twitch stimulation was continued in patients who had received succinylcholine until a twitch height of 100% of control (baseline) with response variation less than 5% for 2 min was recorded.[8] For rocuronium-treated patients the mode of stimulation was changed to TOF-stimulation with square wave pulses of 0.2 msec duration delivered at 2 Hz every 15 sec, and continued until three consecutive responses with a TOF ratio ≥ 0.9 were recorded. All twitch height values during the recovery phase were normalized to final twitch value, and were expressed as percentages of control values. [8]

NMBA randomization and crossover

Patients were randomized to receive either succinylcholine or rocuronium at a standard initial dose, as listed above, during their first ECT. During each subsequent ECT treatment (two days apart), patients received a 10% higher (if insufficient paralysis) or lower (if sufficient or excessive paralysis) dose of the same NMBA until the *minimum effective dose* that resulted in acceptable muscle relaxation (defined as the *optimal dose*) was identified. When the optimal dose of the first NMBA was identified, each patient received the second NMBA (i.e. succinylcholine if rocuronium had been administered, and vice versa) for his or her subsequent ECT treatments, and the dose was increased or decreased in 10% increments according to the same protocol until the minimum acceptable dose for the second NMBA was established (Figure 1, study design).

Quality assessment of muscle relaxation

The quality of muscle relaxation during seizure was independently assessed using a dichotomous scale of 'acceptable' or 'not acceptable' by two psychiatrists, who were blinded to the dose and type of NMBA. A grading system was used to score the two



[a]NM: neuromuscular blockade

Figure 1. Study design

psychiatrists' evaluation. Each psychiatrist provided a single score based on defined criteria for 'acceptable' or 'not acceptable' ECT conditions (Table 1). A summed score of more than or equal to two was considered as 'acceptable' level of induced muscle relaxation. Any summed score of less than two was considered as 'not acceptable' level of induced muscle relaxation. Consequently, NMBA trials were continued until the lowest dose that provided acceptable relaxation during induced seizure was identified.

Outcome Variables

The primary clinical outcome of the study was to define the optimal effective dose (OED) of succinylcholine and rocuronium for each subject to achieve acceptable level of muscle relaxation, defined as the smallest dose of succinylcholine or rocuronium that resulted in adequate muscle relaxation and safe application of ECT in 50% of the cases (OED_{50}). We also provide the NMBA dose that resulted in adequate relaxation in 90 and 95% of the population (OED_{90} and OED_{95}) and the nonparametric bootstrap confidence intervals for the upper tail distribution of the optimal doses. The measured OED_{50}s of succinylcholine and rocuronium and the corresponding T1 suppression for acceptable motor activity during ECT are comparable to their ED_{95}s (median dose corresponding to more than 95% twitch

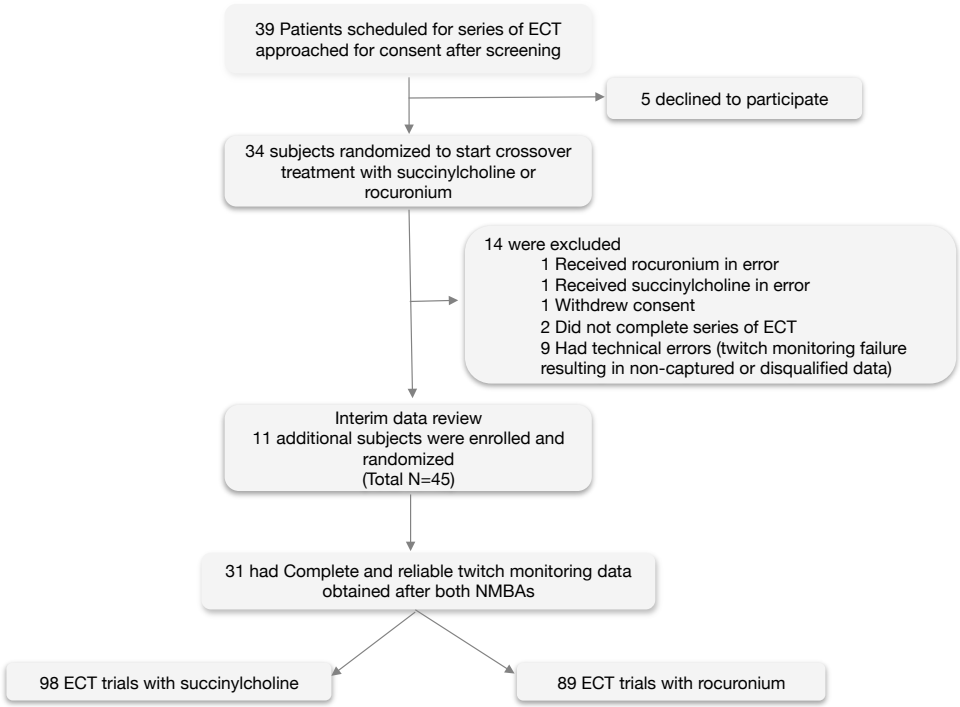


Figure 2: Schema of the study methods. After screening for eligibility criteria, we enrolled consecutive patients who scheduled for series of electroconvulsive therapy after consenting to participate in the study. Only captured data from patients who completed the series of treatments with reliable neuromuscular monitoring were used for analysis.

depression[9]), i.e. m×ED_{95} under the conditions studied (ECT).

The secondary outcome was the duration of the neuromuscular transmission blockade; defined as the time to complete recovery from neuromuscular blockade after a single bolus dose of the OED_{50}, i.e. return of the twitch height to its baseline if succinylcholine had been administered, or TOF ratio ≥ 0.9 if rocuronium was used. All patients were monitored until full recovery from neuromuscular blockade (twitch height of 100% or TOF ratio ≥ 0.9 for succinylcholine and rocuronium, respectively).

Additionally, the coefficient of variation (CV), a measure to show the relative variability of OEDs in each treatment group (succinylcholine and rocuronium), was calculated and compared, as well as the quartile coefficient of dispersion of the OEDs to make comparison of dispersion of OEDs within and between the treatment groups.

Table 1. Definitions of conditions and terms for assessing the quality of "acceptable" or "not-acceptable" muscle relaxation during ECT induced seizure. Each assessor (psychiatrist) provided a separate score. A minimum summed scores of 2 or more was considered as "acceptable" muscle relaxation.

Condition	Term	Score
Excessive relaxation during seizures	Evidence of electric seizure present from EEG monitoring or increase in heart rate, but complete absence of clonic movements or generalized tonic–clonic seizure less than 15 sec	0 (Poor)
Insufficient relaxation during seizures	Sudden/brisk muscle jerks at the stimulus delivery in limbs, trunk or neck, or subsequently during the seizure presence of tonic-clonic movements in one or more limbs (entire limb), or trunk	0 (Poor)
Adequate relaxation during seizures	Freely movable joints from loss of muscle tone, absence of a plantar withdrawal response, disappearance of deep tendon reflexes, disappearance of fasciculation**,** generalized tonic–clonic of more than 15 sec	1 (Good) or 2 (Excellent)

Statistical Analysis

Data are presented as mean ± SD or [range] unless otherwise specified. Based on the results from previous NMBA dose-repose studies, we considered a minimum samples size of 24 to be adequate for the estimation of ED50 with 80% power and with a reasonable degree of assurance. [10, 11] In addition, we conducted a power analysis to determine the sample size needed for our secondary outcome parameters; the duration of block and time to recovery. In our pilot data from10 patients, a 3-min difference in recovery endpoints (100% twitch height recovery or TOF ≥0.9 for succinylcholine and rocuronium, respectively) with a standard deviation of 5 min was observed. Assuming a normal distribution of the data, we calculated a sample size of 31 to achieve 90% power to detect a mean of paired differences of 3.0, with a known standard deviation of differences of 5.0 and with a significance level (alpha) of 0.05 using a two-sided Wilcoxon test. Accordingly, we concluded that a sample size of 31 would provide adequate power for both of our clinical outcome parameters.

All the calculations were performed using "SPSS Statistics for Windows, Version 19.0 (Armonk, NY: IBM Corp., USA, IBM Corp. 2010)", "PASS 11 (NCSS, LLC. Kaysville, Utah, USA, 2011)" and SigmaPlot 11 (Systat Software, San Jose, CA). R Package 'MBESS' was used to construct the confidence interval for the CVs of succinylcholine and rocuronium OEDs and other applied doses. [12] Normality assumption of the measured variables was

Table 2. ECT parameters as well as hemodynamic, acceleromyographic and clinical characteristics of subjects after muscle relaxation with succinylcholine or rocuronium under optimized induced seizure activity (* significant at p-value cutoff of 0.01)

Variables	Optimized Induced Neuromuscular Transmission		Mean differences (SD)	P value	Correlation	P value
	Succinylcholine N=31	Rocuronium N=31				
ECT parameters (range)						
Pulse width (miliampere)	0-2	0-2				
Energy (joule)	38-110	32-116	+2.1	0.631	-0.1	0.54
Duration (sec)	3-8	2-8	-0.14 (1.9)	0.642	-0.02	0.32
Mode (up/down)	Up	Up				
Frequency (hertz)	40-90	40-90				
Duration of seizure (sec)						
Mean (SD)	27 (14)	31 (11)	-4 (18)	0.003*	-0.03	0.85
Range	10-90	10-51				
Nadir preprocedural SpO_2						
Mean (SD)	92 (4) %	94 (3) %	-2 (4)	0.011	0.16	0.33
Range	79-99 %	85-100 %				
Propofol dose (mg)						
Mean (SD)	100 (28)	107 (29)	-7 (33)	0.463	0.16	0.334
Pre-ECT heart rate (per min)						
Mean (SD)	80 (18)	81 (16)	-1 (17)	0.818	0.46	0.81
Range	42-119	53-125				
Pre-ECT systotlic blood pressure (mmHg)						
Mean (SD)	130 (17)	128 (15)	+2 (25)	0.655	-1.35	0.412
Range	101-175	94-159				
Pre-ECT diastolic blood pressure (mmHg)						
Mean (SD)	72.3 (12)	71.8 (10)	0.5 (15)	0.845	0.063	0.7
Range	54-102	53-94				
Post-ECT heart rate (per min)						
Mean (SD)	76.1 (18)	77.6 (17)	-1.5 (20)	0.647	0.37	0.65
Range	37-118	46-115				
Post-ECT systolic blood pressure (mmHg)						
Mean (SD)	147.6 (33)	152.6 (42)	-5 (53)	0.564	-0.027	0.87
Range	85-208	65-215				
Post-ECT diastolic blood pressure (mmHg)						
Mean (SD)	81 (19)	86 (23)	-5 (29)	0.337	0.081	0.62
Range	51-132	33-131				
Nadir T1						
Median, Mode	0, 0	4, 0	-4 (7)	<0.001*	-0.15	0.36
Range	0-10	0-30				
Time to 100% T1 recovery (min)						
Mean (SD)	9.7 (3.5)	13.2 (3.3)	-3.5 (5)	<0.001*	-0.19	0.25
Range	3-20	7-24				
Time to TOF > 0.9 (min)						
Mean (SD)	n/a	19.5 (5.7)	-	-	-	-
Range		8-30				
Time to first spontaneous breathing (min)						
Mean	4.4 (1.2)	6.6 (1.6)	-2 (1.5)	<0.001*	0.18	0.27
Range	2-9	4-10				
Time to Eye Opening (min)						
Mean (SD)	10 (3.3)	13 (3.4)	-3 (3.3)	<0.001*	0.134	0.4
Range	2-18	6-22				

assessed using the Lilliefors test (all $p > 0.12$ and N=31). Welch's t-test was conducted to compare the measured variables (e.g. recovery time, duration of seizure, and hemodynamic

variables etc.) obtained under succinylcholine and recouronium conditions ($p > 0.01$). [13, 14] Cohen's Kappa for inter-rater reliability was used to assess inter-rater reliability between the two assessors of motor seizure activity during ECT. The optimal effective dose of NMBA (OED) was defined as the lowest dose that provided completion of ECT under acceptable conditions. The "optimal" doses obtained from the study patients (31 optimal doses for either of treatment groups, succinylcholine or rocuronium) were resampled 10000 times using the nonparametric bootstrap method.[15] The 25th, 50th (median), 75th, 90th and 95th percentiles of these samples and the corresponding 95% and 99% confidence intervals were then calculated.

Covariates included were age, ASA Physical Status, anesthetic dose, and the ECT parameters. A p-value < 0.05 (unless otherwise specified) was considered statistically significant and reported for a two tailed test.

RESULTS

Two hundred and twenty-seven ECT treatments in 45 enrolled subjects were recorded. Thirty-one subjects completed their series of treatment, generating a total of 187 qualified ECTs for data analysis (Figure 1). Four to 8 observations were recorded for each patient with both NMBAs. The mean age and body weight of the subjects were 50 ± 8 years [24-80, F/M: 15/16] and 80 ± 20 kg [49-109], respectively. Median of ASA physical status was II. There were no significant differences between the two groups (treated patients with optimal doses of succinylcholine or rocuronium) in baseline values of SpO_2, HR, SBP and DBP. The dose of propofol used to induce anesthesia was not different in the succinylcholine and rocuronium treatment groups (100 ± 28 mg vs. 105 ± 29 mg, $p > 0.05$) No significant difference was observed between the groups in the dose of any medications administered during ECT (e.g. esmolol and labetalol).

Primary Clinical Outcome: Optimal Effective Dose of NMBA dose and onset time

OED_{50} of succinylcholine and rocuronium were 0.85 mg.kg^{-1} (95% CI: 0.77-0.94) and 0.41 mg.kg^{-1} (95% CI: 0.36-0.46), respectively. The 90th and 95th percentile of optimal doses were amounted to 1.06 mg.kg^{-1} (95% CI: 1.0- 1.27), 1.16 mg.kg^{-1} (95% CI: 0.8-1.5) for succinylcholine and 0.57 mg.kg^{-1} (95% CI: 0.51-0.62), 0.59 mg.kg^{-1} (95% CI: 0.56-0.63) for rocuronium, respectively. The range of applied optimal doses for succinylcholine and rocuronium were [0.46-1.22] mg.kg^{-1} and [0.26-0.59] mg.kg^{-1}, respectively. Table 3 demonstrates 99% CI of the OED percentiles.

Table 3. 95% and 99% nonparametric bootstrap confidence intervals (CI) of the percentiles of optimal effective doses (OED) for succinylcholine and rocuronium. The intervals calculated using the adjusted bootstrap percentile (BCa) method.

Succinylcholine	Dose (mg/kg)	95% CI	99% CI
OED25	0.704225	(0.6077-0.7392)	(0.5979-0.7834)
OED50	0.846446	(0.7664-0.9381)	(0.7163- 0.9467)
OED75	1.019541	(0.870-1.087)	(0.859-1.103)
OED90	1.062941	(1.021-1.266)	(1.020-1.555)
OED95	1.163164	(1.085-1.555)	(1.064-1.555)
OED99	1.425879	(1.158-1.555)	(1.135-1.555)
Rocuronium			
OED25	0.365957	(0.3169-0.3932)	(0.3060-0.3952)
OED50	0.412794	(0.3577-0.4568)	(0.3471-0.4669)
OED75	0.506449	(0.4356-0.5463)	(0.4264-0.5512)
OED90	0.567167	(0.5071-0.6117)	(0.5060-0.6117)
OED95	0.587320	(0.5563-0.6294)	(0.5187, 0.6294)
OED99	0.5996132	(0.5669-0.6294)	(0.5571-0.6294)

The CV for the optimal dose of succinylcholine was 1.24-fold greater than that of rocuronium (25.7% [CI: 21-29] vs. 20.86% [CI: 20-27]). These values were not different compared to the CV of other applied doses for each NMBA (25% [CI: 22-30] and 21% [CI: 18-25] for succinylcholine and rocuronium, respectively). The quartile coefficient of dispersion succinylcholine OEDs was 1.11 that of rocuronium OEDs (0.185 vs. 0.167).

Acceptable ECT induced seizure contracture was achieved after 1.4 ± 0.5 min and 3.7 ± 1 min in the succinylcholine and rocuronium groups, respectively (p<0.001). Nadir twitch suppression to achieve an acceptable controlled seizure quality (muscle activity) was 0 ± 2% [0-10, frequency of 0: 92.5%] for succinylcholine and 4 ± 6% [0-30, frequency of 0: 40%] for rocuronium. A twitch suppression of 0-10% resulted in 100% acceptable muscle relaxation after succinylcholine (97.5%: 0-4%, 2.5%: 5-10%). When rocuronium was used, a T1 twitch value of 0-10% of baseline resulted in acceptable level of muscle relaxation in 95% of cases (60% of these patients had a T1 value of 0-4% baseline, and 35% had T1 of 5-10% baseline).

Secondary Clinical Outcome: Time to recovery from neuromuscular blockade

The time to 90% twitch recovery after succinylcholine was 9.37 ± 3.2 min, while 100 % twitch recovery was obtained after 9.7 ± 3.5 (3-20) min (Figure 3). The time to TOF recovery >0.9 was 19.5 ± 5.7 min after rocuronium (Table 2).

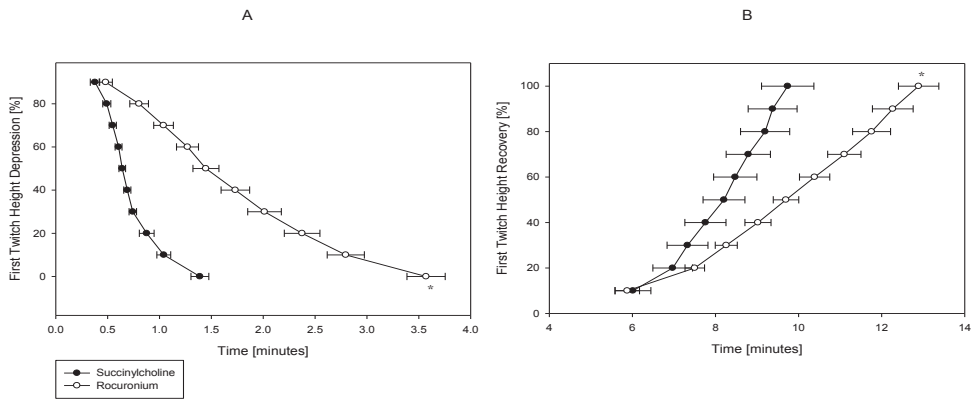


Figure 3. Time course of single twitch height (percent baseline) after injection of succinylcholine or rocuronium (Means ± SE) in optimized ECT-induced seizure quality. * P value<0.05 A. Onset of action and suppression of twitch height B. Recovery of twitch height

ECT Parameters, Hemodynamic Variables and Ancillary Data

No clinically significant differences were identified in the recorded EEG parameters or seizure quality when adequate neuromuscular blockade was obtained with rocuronium instead of succinylcholine. ECT parameters including pulse width, energy, frequency and duration were similar in both treatment groups (Table 2). No differences in HR, SBP and DBP data were observed between or within the succinylcholine and rocuronium groups. Nadir SpO_2, defined as the lowest recorded periprocedural oxygen saturation, were 94 ± 3% [85-100] and 92 ± 4% [79-99] for rocuronium and succinylcholine, respectively (p> 0.05).

The inter-rater reliability for the raters was found to be Kappa = 0.862 (p <0.001), 95% CI (0.801- 0.923). Duration of motor seizure activity following succinylcholine and rocuronium amounted to 27 ± 14 and 31 ± 11 sec, respectively (p<0.001, Table 2).

DISCUSSION

The findings reported herein indicate that near-complete twitch suppression is required for optimal neuromuscular blockade during ECT. The time to achieve acceptable neuromuscular blockade was increased by approximately 2.3 min when rocuronium was used, resulting in a total of approximately 12 min increased procedure time.

Optimal Dose of Succinylcholine and Time to Onset of Maximal Effect

Although a single best dose of succinylcholine for ECT has yet not been identified in the literature, doses between 0.5–1 mg.kg^{-1} are often used based on anecdotal reports and previous experience of anesthesia providers. [5, 16-18] Consistent with the report from Murali and his colleagues,[19] our data suggest that succinylcholine doses close to 1 mg.kg^{-1} may provide acceptable ECT conditions and also highlight the importance to avoid early application of ECT after the administration of succinylcholine (<1.4 min, time to onset of acceptable relaxation), even in the absence of a twitch response to nerve stimulation. This observation is also consistent with previous finding by Beale and colleagues[20] that the muscle response to ulnar nerve stimulation can be extinguished long before cessation of muscle fasciculation, and suggests that the time to onset of adequate relaxation for ECT is longer than the traditional 60 sec that is used for rapid sequence intubation (1 mg.kg^{-1}of succinylcholine, 3.5 × ED_{95}). [21-23] This difference in time to obtain acceptable ECT conditions as compared to that for endotracheal intubation may be attributed to a difference in sensitivity to succinylcholine in different muscle groups (e.g. oropharynx versus extremities), but can also indicate that a deeper neuromuscular blockade is needed for acceptable ECT conditions as compared to endotracheal intubation. Kopman et al.[24] showed that the speed of onset of succinylcholine might be dependent on rapid plasma clearance such that in patients with normal plasma cholinesterase activity, following an ED_{95} dose of succinylcholine time to peak effect (95% twitch depression) occurs in less than 2 min (109 sec ± 15).

The 90th percentile of the optimal effective dose of 1.06 mg.kg^{-1} (≈3.5 × ED_{95}) succinylcholine in our study and an induced twitch height suppression of 0-4% for acceptable motor seizure modification are in line with findings by Murali and his colleagues, who recommended a dose of 1.0 mg.kg^{-1} and twitch suppression to 0-5% of baseline.[19] The 95th percentile of optimal dose of succinylcholine (1.17 mg.kg^{-1}) has also been used in other clincal trials (1.2 mg.kg^{-1}). [25-28]

Duration of Paralysis and Time to Recovery after Succinylcholine

The time required for 90% twitch recovery (9.4 min) after optimal dose of succinylcholine is comparable with the reported recovery time by others after a single dose of 1 mg.kg^{-1} (9.3 min). [29, 30] Similarly, the time required for 100% twitch recovery (9.7 min) in our study is similar to that in previously published pharmacokinetic studies of this NMBA (10 minutes after applying the dose of 1.0 mg.kg^{-1}). [31, 32] Accordingly, our data suggest that the seizure-induced release of acetylcholine into the neuromuscular junction does not significantly alter the duration of succinylcholine-induced neuromuscular blockade.

Rocuronium as an Alternative to Succinylcholine during ECT

Rocuronium is increasingly employed as an alternative to succinylcholine for neuromuscular blockade during ECT, primarily in the elderly and patients with cardiovascular and neurological comorbidities. Immobilized patients and elderly or those who have suffered a stroke are particularly susceptible to succinylcholine-induced hyperkalemia due to depolarization of upregulated nicotinic (neuronal) alpha-7 acetylcholine receptors. [5] On the other hand, ECT is highly effective and is increasingly applied in the elderly and those with increased incidence of prolonged immobilization and higher risk of hyperkalemia. [5] Nondepolarizing NMBAs do not cause hyperkalemia and can be given to these patients and those with susceptibility to malignant hyperthermia or contraindications to succinylcholine, but are often avoided because of their relatively long duration of action, typically exceeding the ECT time. Moreover, there is a significant variability in the sensitivity and the time needed to obtain appropriate neuromuscular blockade after non-depolarizing NMBAs. This might explain why higher doses are often chosen to reliably obtain neuromuscular blockade for ECT, with the consequence of potentially inducing a prolonged paralysis and recovery.

Currently, rocuronium is given as a single bolus of 0.3 to 0.6 $mg.kg^{-1}$ prior to ECT treatment.[5] Doses beyond 0.4 $mg.kg^{-1}$, for ECT, have been used in combination with the reversal agent sugammadex, a selective relaxant-binding agent (currently not available in the USA), which has also been used to reverse profound rocuronium-induced neuromuscular blockade in adult surgical patients. [5] Its rapid effect on rocuronium-induced neuromuscular blockade yields recovery times that are comparable to that of succinylcholine during ECT. [5] Our study confirms that even in absence of this selective reversal agent, in patients with contraindications to the use of succinylcholine [3], the rocuronium-neostigmine combination can provide a safe and relatively time-effective alternative to succinylcholine.

Optimal Dose of Rocuronium and Time to Onset of Maximal Effect

The OED_{90} in our study (0.57 $mg.kg^{-1} \approx 2 \times ED_{95}$) is comparable to the dose that has previously been reported to induce > 95% block in 98% of subjects. [33, 34] The time needed to achieve acceptable conditions for ECT is also consistent with previous studies, with a twitch suppression to 10% baseline after 2.9 ± 1.0 min and 0% after 3.7 ± 1.0 min. The time from NMBA injection to acceptable ECT conditions is hence approximately 2.3 minutes longer with rocuronium as compared to succinylcholine. As the anesthetic agents affect the duration of the ECT-induced convulsions, clinicians should consider this difference in time from anesthesia induction to ECT application with rocuronium versus succinylcholine, and adjust the dose and timing of their hypnotic agents accordingly.

Duration of Paralysis and Time to Recovery after Rocuronium

Bevan and colleagues[35] reported the time to 90% recovery of the first twitch (T1 90) to be more than 10 min. Consistent with their data, our study showed that a twitch value of 90% was obtained after 12 min. However, in the former study, the TOF ratio of 0.9 was achieved 28 min after rocuronium-induced paralysis (0.45 $mg.kg^{-1}$). In our study, a TOF ratio of 0.9 was recorded after 19.5 min, which is comparable with a recovery time of 21 ± 4 min reported by Fuchs-Buder and colleagues [36] (after rocuronium 0.4 $mg.kg^{-1}$) and 19.4 ± 5.1 min by Lederer et al.[37] (rocuronium 0.4 $mg.kg^{-1}$).

ECT Quality and Seizure Duration after Rocuronium versus Succinylcholine

Using subjective tools to assess the recovery from neuromuscular blockade, Turkal et al.[38] reported that motor seizure duration was greater after 0.3 $mg.kg^{-1}$ rocuronium as compared to 1 $mg.kg^{-1}$ succinylcholine (33 and 24 sec, respectively). Similarly, Hoshi and colleagues [39] reported longer duration of seizure with rocuronium as compared to succinylcholine. Our data is consistent with these previously published studies confirming a small difference in seizure duration, which may be attributed to a decline in propofol-induced EEG suppression [40] after rocuronium associated with the 2 min delay in achieving appropriate muscle relaxation. As there is an association between clinical effectiveness of ECT and the duration of induced seizure[41], the American Psychiatric Association task force advocates seizure lengths > 20 sec for effective ECT treatment. [42] This recommendation underscores the importance of titrating the dose of the NMBA to achieve an adequate neuromuscular blockade. EEG monitoring is also recommended for induced seizure monitoring [43], particularly in patients who might need higher doses of an NMBA to achieve acceptable modified seizure. Further studies are needed to assess the therapeutic effects of the cumulative seizure time in a series of ECTs using optimal doses of these NMBAs.

Dose Variability with Succinylcholine versus Rocuronium

The observed inter-individual variability for the OEDs of rocuronium and succinylcholine is consistent with previously reported studies (coefficient variation of 25%, range: 15-27% for N>24[12]). As compared to rocuronium, succinylcholine showed relatively higher inter-individual variability (coefficient variation ratio of 1.24) and dispersion (the quartile coefficient dispersion ratio of 1.1) for the applied effective doses that resulted in acceptable neuromuscular blockade and controlled ECT induced seizure.

Inter-individual differences in the expression and activity of butyrylcholinesterase enzyme (BChE) is known to be of importance for the metabolism of succinylcholine [31, 44, 45], and may explain the observed difference in its dose variability when compared to rocuronium. [30] A relatively smaller OED variability for rocuronium might clinically have a greater significance

if achieving the optimized induced seizure activity is important to rapidly maximize the therapeutic effect of sequential ECTs, particularly if the use of succinylcholine is contraindicated. However, if the initial dose of rocuronium (0.4 mg.kg^{-1}) is insufficient and increasing doses are required, the duration of the induced neuromuscular blockade is less predictable. Longer recovery times that may even extend beyond the duration of the ECT should be considered. [29, 46]

Clinical implications

Due to the documented inter-individual variability in the $OED_{50\text{-}ECT}$ of succinylcholine, an initial dose of 0.85 mg.kg^{-1} is reasonable for the first ECT session, with dose adjustments in 0.1 mg.kg^{-1} increments or decrements, based on the quality of the observed motor seizure activity for each individual during subsequent treatments.

As an alternative and if clinically indicated, we suggest a 0.4 mg.kg^{-1} bolus of rocuronium as the initial dose of the applied NMBA. ECT should be applied after a twitch suppression of >90% is documented or, if twitch monitoring is not available, after sufficient time has been provided to ensure > 90% peak effect from the administered rocuronium (i.e. 3 min). If excessive or insufficient neuromuscular block is noticed during the induced seizure, dose adjustment with 0.05 mg.kg^{-1} decrements or increments is advisable. After the treatment, the rocuronium-induced neuromuscular blockade should be reversed in the regular fashion with neostigmine (50 microgram.kg^{-1}). Due to inter-individual variability in the time to recovery, particularly if doses in excess of 0.6 mg.kg^{-1} are administered, quantitative NMT monitoring is recommended to evaluate adequate level of relaxation and to ensure sufficient recovery of the induced neuromuscular blockade, in order to minimize the risk for adverse respiratory events. [5, 47] Clinicians should ensure that all patients stay under close observations by appropriately trained personnel, and continue to monitor the neuromuscular function until complete recovery of the neuromuscular transmission has been verified (e.g. sustained head lift or tongue depressor test). [48]

In summary, the presented data shows that a twitch suppression of > 90% is required for acceptable neuromuscular blockade during ECT. The time to achieve acceptable neuromuscular blockade is increased by approximately 2.3 min when rocuronium is used instead of succinylcholine, resulting in an average of 12 min increased procedure time. When appropriately dosed and monitored, rocuronium can be a safe alternative NMBA for electroconvulsive therapy in patients with contraindications to succinylcholine.

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SUPPLEMENTARY APPENDIX

Bootstrap method for estimation of OED_5 confidence intervals (CI) and resampling for evaluating the effect of sample size on estimated confidence limit

The data from of 31 subjects who were evaluated in our randomized crossover trial for application of rocuronium and succinylcholine in ECT were used for analysis. This approach resulted in 31 minimum effective doses of rocuronium and 31 minimum effective doses of succinylcholine resulted in acceptable induced seizures among subjects. Using "boot" package in R statistical software, 10000 bootstrap replications, bias corrected 95% and 99% confidence intervals (CIs) for the median of the optimal effective doses (OED_{50}) of rocuronium and succinylcholine were estimated. Similarly, CIs of 90 and 95 percentiles of the optimal effective doses of rocuronium and succinylcholine were calculated (OED_{90} and OED_{95}).

To confirm that 31 subjects were sufficient to obtain reasonable 95% and 99% confidence limits of optimal effective doses of succinylcholine and rocuronium, 10, 15, 20, 25 and 30 subjects were separately resampled from the optimal effective doses. The above bootstrap technique with 10000 replications was performed in each one of the new datasets and 95% and 99%confidence limits for the estimates of the OED_{50} of each dataset were obtained. The results for the effects of sample sizes are shown below:

Variable estimate	Percentile	Number of subjects				
Succinylcholine		10	15	20	25	30
OED50	5	0.6305	0.7042	0.7135	0.7163	0.7392
	95	1.0195	1.0213	0.9504	0.9467	0.9071
	0.1	0.6117	0.7146	0.6991	0.6991	0.7246
	0.99	1.0823	1.0195	1.0305	1.0414	0.9553
Rocuronium						
OED50	5	0.3329	0.3731	0.3725	0.3674	0.3877
	95	0.5463	0.5174	0.4864	0.4746	0.4568
	0.1	0.3169	0.3660	0.3572	0.3489	0.3660
	0.99	0.5488	0.5507	0.5117	0.5064	0.4669