Minimum Effective Doses of Succinylcholine and Rocuronium During Electroconvulsive Therapy: A Prospective, Randomized, Crossover Trial

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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 minimum effective dose (MED) of succinylcholine and rocuronium for ECT. The MED was the lowest dose to provide a predefined qualitative measure of acceptable control of muscle strength during induced convulsions.

METHODS: Succinylcholine (0.8 mg kg^{-1}) or rocuronium (0.4 mg kg^{-1}) was randomly administered in 227 ECT sessions to 45 patients. The dose was incrementally increased or decreased by 10% based on 2 psychiatrists' (blinded to treatment) assessment of "acceptable" or "not acceptable" control of evoked muscle contractions (sufficient versus insufficient or excessive paralysis). The neuromuscular transmission was monitored quantitatively until full recovery.

RESULTS: In our study, the MEDs of succinylcholine and rocuronium to produce acceptable ECT conditions in 50% of patients ($MED50_{ECT}$) were 0.85 mg kg^{-1} (95% confidence interval [CI], 0.77–0.94) and 0.41 mg kg^{-1} (95% CI, 0.36–0.46) and in 90% of patients ($MED90_{ECT}$) were 1.06 mg kg^{-1} (95% CI, 1.0–1.27) and 0.57 mg kg^{-1} (95% CI, 0.5–0.6), respectively. Nadir twitch height for acceptable muscle activity was 0% (0–4) and 4% (0–30; $P < 0.001$), respectively, and the time to recovery of the neuromuscular transmission was 9.7 ± 3.5 and 19.5 ± 5.7 minutes, respectively.

CONCLUSIONS: A twitch suppression of >90% is needed for control of motor contractions during ECT. The initial ECT dose of succinylcholine should be selected based on each patient's preprocedural condition, ranging between 0.77 and 1.27 mg kg^{-1} to produce acceptable muscle blockade in 50% to 90% of patients. Rocuronium–neostigmine combination is a safe alternative if appropriately dosed (0.36–0.6 mg kg^{-1}) and monitored. (Anesth Analg 2016;XXX:00–00)

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 major depressive or cyclothymic disorders.[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 on its completion.[3] Because of its rapid onset and short duration of action, succinylcholine is considered the NMBA of choice for ECT; however, a nondepolarizing NMBA needs to be considered in some patients with metabolic, neuromuscular, or neurologic 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 NMBA dose to achieve acceptable level of muscle contracture via the use of neuromuscular blockade without excessive or untoward effects has not been identified in a prospective randomized fashion and via the use of objective monitoring techniques.[5] The aim of this study is, therefore, to identify the minimum effective starting NMBA doses of 2 commonly used neuromuscular blocking drugs (succinylcholine and rocuronium), defined as the lowest dose to provide optimized muscle strength modulation during ECT.

METHODS

This crossover, randomized controlled, assessor-blinded clinical trial was conducted in the postanesthesia care unit at Massachusetts General Hospital in Boston, Massachusetts. The IRB approved the study protocol, and written informed consent was obtained from all participating patients. The study was registered before patient enrollment. Registry Url:

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Patients

Two hundred twenty-seven ECT sessions were conducted in 45 hospitalized patients aged 24 to 80 years with ASA physical status I to 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 age <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 1. After 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} IV over 5 seconds). Continuous neuromuscular transmission monitoring was applied after stabilization and baseline calibration to establish a control twitch response before NMBA injection (see the Neuromuscular Transmission Monitoring section). Succinylcholine (Quelicin®, Hospira Inc., Lake Forest, IL) 0.8 (2.67 × ED_{95}) mg kg^{-1} or rocuronium-bromide (Zemuron®, Organon USA Inc., a subsidiary of Merck & Co. Inc., Roseland, NJ) 0.4 mg kg^{-1} (1.33 × ED_{95}) was then administered IV over 5 seconds through an IV 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 a pilot study of 10 patients. Ventilation was assisted until recovery of normal spontaneous ventilation through 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 6× seizure threshold was delivered with right unilateral application of electrodes with a MECTA Model SR II apparatus (MECTA Corp., Portland, OR). 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 1). The duration of seizure was monitored by electroencephalogram (EEG) and recorded from EEG activity.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded every 3 minutes, and the heart rate (HR) and oxygen saturation (Spo_2) were monitored and recorded continuously throughout the procedure and until the patient's full recovery. Temperature was monitored and maintained at ≥35°C. Labetalol (10–50 mg IV) or esmolol (40–80 mg IV) was administered to treat hypertension and tachycardia, when necessary.

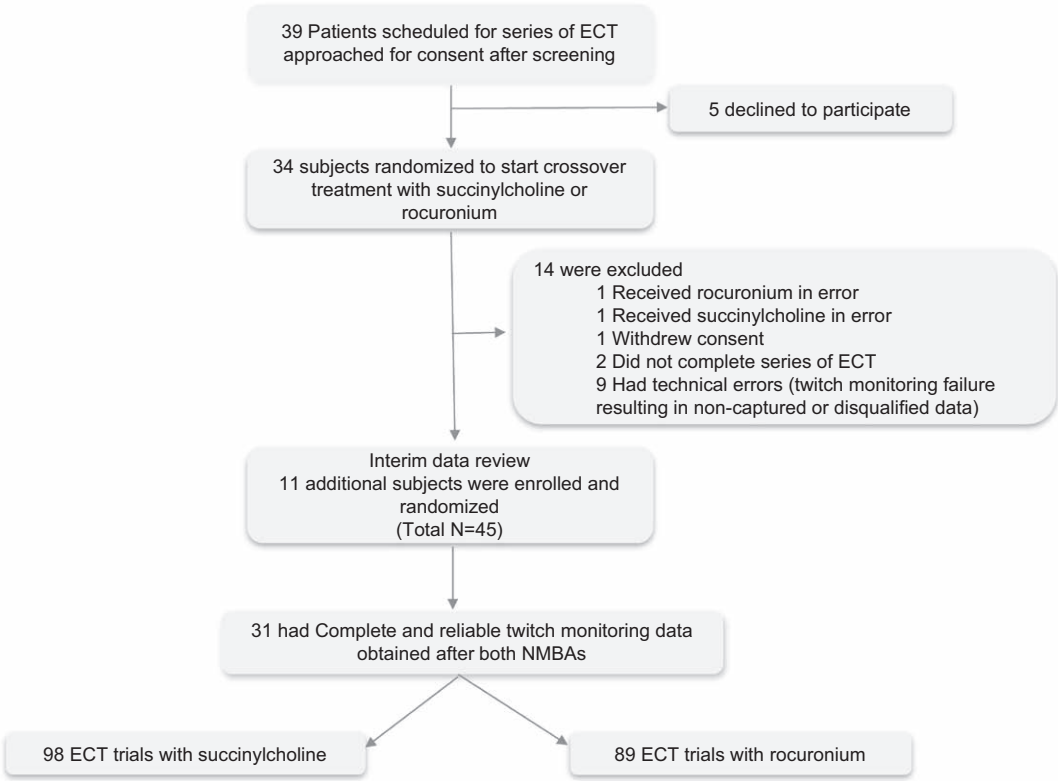

Figure 1. Schematic representation of the study methods. After screening for eligibility criteria, we enrolled consecutive patients who scheduled for series of ECT after consenting to participate in the study. Only captured data from patients who completed the series of treatments with reliable neuromuscular monitoring were used for analysis. ECT = electroconvulsive therapy.

Table 1. ECT Parameters and Hemodynamic, Acceleromyographic, and Clinical Characteristics of Subjects After Muscle Relaxation with Succinylcholine or Rocuronium Under Optimized ECT-Induced Seizure Activity

Variables	Optimized ECT-induced neuromuscular transmission: Succinylcholine (*n* = 31)	Optimized ECT-induced neuromuscular transmission: Rocuronium (*n* = 31)	Mean differences (SD)	*P* value	Correlation	*P* value
ECT parameters (range)						
Pulse width (mA)	0–2	0–2				
Energy (J)	38–110	32–116	2.1	0.631	−0.1	0.54
Duration (s)	3–8	2–8	−0.14 (1.9)	0.642	−0.02	0.32
Mode (up/down)	Up	Up				
Frequency (Hz)	40–90	40–90				
Duration of seizure (s)						
Mean (SD)	27 (14)	31 (11)	−4 (18)	0.003[a]	−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 systolic blood pressure (mm Hg)						
Mean (SD)	130 (17)	128 (15)	2 (25)	0.655	−1.35	0.412
Range	101–175	94–159				
Pre-ECT diastolic blood pressure (mm Hg)						
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 (mm Hg)						
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 (mm Hg)						
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[a]	−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[a]	−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[a]	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[a]	0.134	0.4
Range	2–18	6–22				

ECT = electroconvulsive therapy; TOF = train of four.
[a]Significant at *P* value cutoff of 0.01.

After termination of seizure and when appropriate, as determined by the practicing anesthesiologist, the rocuronium-induced neuromuscular blockade was reversed with 50 μg kg^{-1} neostigmine in conjunction with 10 μg kg^{-1} glycopyrrolate.[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 train-of-four [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) was 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) was used to fix the thumb position to minimize the potential variability in evoked muscle contraction. The TOF-Watch was calibrated by use of the standard calibration with default supramaximal

stimulation (CAL1: 10-second stimulation current of 50 mA), and ulnar nerve stimulation was resumed with single twitch stimulation at 0.1 Hz and continued till observation of <5% variation of twitch heights for 2 to 3 minutes, 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 3 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 <5% for 2 minutes was recorded.[8] For rocuronium-treated patients, the mode of stimulation was changed to TOF stimulation with square wave pulses of 0.2-milliseconds duration delivered at 2 Hz every 15 seconds and continued until 3 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 assigned randomly to receive either succinylcholine or rocuronium at a standard initial dose, as listed previously, during their first ECT. During each subsequent ECT treatment (2 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 (MED) that resulted in acceptable neuromuscular blockade (MED_{ECT}) was identified. When the MED_{ECT} 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 MED_{ECT} dose for the second NMBA was established (Supplemental Digital Content 1, Supplemental Fig. 1, study design, http://links.lww.com/AA/B372).

Quality Assessment of Neuromuscular Blockade

The quality of neuromuscular blockade during seizure was independently assessed by the use of a dichotomous scale of "acceptable" or "not acceptable" by 2 psychiatrists blinded to the dose and type of NMBA. A grading system was used to score the 2 psychiatrists' evaluation. Each psychiatrist provided a single score based on the defined criteria for "acceptable" or "not acceptable" ECT conditions (Table 2). A summed score of ≥2 was considered as acceptable level of induced muscle relaxation. Any summed score of <2 was considered as a not acceptable level of induced neuromuscular blockade. Consequently, NMBA trials were continued until the lowest dose that provided acceptable neuromuscular blockade during induced seizure was identified.

Outcome Variables

The primary clinical outcome of the study was to define the MED_{ECT} of succinylcholine and rocuronium for each subject to achieve our definition of an acceptable level of neuromuscular blockade. $MED50_{ECT}$ was, hence, 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. We also provide the NMBA dose that resulted in adequate relaxation in 90% and 95% of the population ($MED90_{ECT}$ and $MED95_{ECT}$, respectively) and the nonparametric bootstrap confidence intervals (CIs) for the upper tail distribution of the optimal doses. The measured $MED50_{ECT}$ of succinylcholine and rocuronium and the corresponding T1 suppression for acceptable motor activity during ECT were compared with their ED_{95}s (median dose corresponding to >95% adductor pollicis twitch depression[9]), i.e., $m \times ED_{95}$ under the conditions studied (ECT). As a coprimary outcome, the estimated CIs for each MED_{ECT} are calculated to identify the range of MEDs for each applied NMBA for 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 $MED50_{ECT}$, 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).

Statistical Analysis

Data are presented as mean ± SD or (range) unless otherwise specified. On the basis of results from previous NMBA dose–response studies, we considered a minimum sample size of 24 to be adequate for the estimation of $MED50_{ECT}$ with 80% power and with a reasonable degree of assurance.[10,11] We also used resampling and bootstrap method for estimation of $MED50_{ECT}$ CIs to investigate the adequacy of sample size on the estimated confidence limits (Supplemental Digital Content 2, http://links.lww.com/AA/B373). In addition, we conducted a power analysis to determine the sample size needed for our secondary outcome parameters, i.e., the duration of block and time to recovery. In our pilot data from10 patients, a 3-minute difference in recovery end points (100% twitch height recovery or TOF ≥0.9 for succinylcholine and rocuronium, respectively) with a SD of 5 minutes 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 SD of differences of 5.0 and with a significance level (α) of 0.05 using a 2-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 (IBM Corp., Armonk, NY, 2010), PASS 11 (NCSS, LLC., Kaysville, UT), and SigmaPlot 11 (Systat Software, San Jose, CA).

Normality assumption of the measured variables was assessed using the Lilliefors test (all $P > 0.12$ and $N = 31$). The Welch t test was conducted to compare the measured variables (e.g., recovery time, duration of seizure, and hemodynamic variables) obtained under succinylcholine and rocuronium conditions ($P > 0.01$).[12,13] Cohen κ for interrater reliability was used to assess interrater reliability between the 2 assessors of motor seizure activity during ECT. The MED of NMBA was defined as the lowest dose that provided

Table 2. Definitions of Conditions and Terms for Assessing the Quality of "Acceptable" or "Not-Acceptable" Muscle Relaxation During ECT-Induced Seizure

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 of <15 s	0 (Poor)
Insufficient relaxation during seizures	Sudden/brisk muscle jerks at the stimulus delivery in the limbs, trunk, or neck, or subsequently during the seizure presence of tonic–clonic movements in 1 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, and generalized tonic–clonic seizure of >15 s	1 (good) or 2 (excellent)

Each assessor (psychiatrist) provided a separate score. A minimum summed scores of 2 or more was considered as "acceptable" muscle relaxation.
ECT = electroconvulsive therapy; EEG = electroencephalogram.

completion of ECT under our definition of acceptable conditions (MED_{ECT}). The minimum acceptable doses obtained from the study patients (31 minimum doses for either of crossed-over groups, succinylcholine or rocuronium) were resampled 10,000 times using the nonparametric bootstrap method.[14] The 25th, 50th (median), 75th, 90th, and 95th percentiles of these samples ($MED25_{ECT}$, $MED50_{ECT}$, $MED75_{ECT}$, $MED90_{ECT}$, $MED95_{ECT}$, and $MED99_{ECT}$, respectively) and the corresponding 95% and 99% CIs 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 2-tailed test.

RESULTS

Two hundred 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 (Fig. 1). To identify the optimal dose of each NMBA, a range of 2 to 4 observations was needed, yielding a total of 187 qualified ECTs for data analysis. The mean age and body weight of the subjects were 50 ± 8 years (range, 24–80 years, female/male: 15/16) and 80 ± 20 kg (range, 49–109 kg), respectively. Median of ASA physical status was II. There were no significant differences between the 2 groups (treated patients with 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 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: Minimum Effective Dose of NMBA and Onset Time

$MED50_{ECT}$ 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 $MED90_{ECT}$ and $MED95_{ECT}$ doses (the MEDs that provided optimal ECT conditions in 90% and 95% of patients, respectively) were 1.06 mg kg^{-1} (95% CI, 1.02–1.27) and 1.16 mg kg^{-1} (95% CI, 1.08–1.5) for succinylcholine and 0.57 mg kg^{-1} (95% CI, 0.51–0.61) and 0.59 mg kg^{-1} (95% CI, 0.56–0.63) for rocuronium, respectively. The range of applied MED_{ECT} for succinylcholine and rocuronium were 0.46 to 1.22 mg kg^{-1} and 0.26–0.59 mg kg^{-1}, respectively. Table 3 demonstrates 95% and 99% CI of the MED percentiles.

Acceptable ECT-induced seizure contracture after applying MED_{ECT}s was achieved after 1.4 ± 0.5 minutes and 3.7 ± 1 minutes 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. An adductor pollicis twitch suppression of 0% to 10% resulted in 100% acceptable neuromuscular blockade after succinylcholine (97.5%: 0%–4%; 2.5%: 5%–10%). When rocuronium was used, a T1 twitch value of 0% to 10% of baseline resulted in acceptable level of neuromuscular blockade in 95% of cases (60% of these patients had a T1 value of 0%–4% baseline, and 35% had T1 of 5%–10% baseline).

Table 3. Ninety-Five Percent and 99% Nonparametric Bootstrap Confidence Intervals of the Percentiles of MEDs for Succinylcholine and Rocuronium to Achieve Acceptable Induced Neuromuscular Blockade During ECT (MED_{ECT})

	Dose (mg/kg)	95% CI	99% CI
Succinylcholine			
$MED25_{ECT}$	0.70	0.60–0.74	0.56–0.78
$MED50_{ECT}$	0.85	0.77–0.94	0.72–0.95
$MED75_{ECT}$	1.02	0.87–1.09	0.86–1.10
$MED90_{ECT}$	1.06	1.02–1.27	1.02–1.50
$MED95_{ECT}$	1.16	1.08–1.50	1.06–1.50
$MED99_{ECT}$	1.40	1.16–1.50	1.13–1.50
Rocuronium			
$MED25_{ECT}$	0.36	0.32–0.39	0.30–0.39
$MED50_{ECT}$	0.41	0.36–0.46	0.35–0.47
$MED75_{ECT}$	0.51	0.43–0.55	0.43–0.55
$MED90_{ECT}$	0.57	0.51–0.61	0.51–0.61
$MED95_{ECT}$	0.59	0.56–0.63	0.52–0.63
$MED99_{ECT}$	0.60	0.57–0.63	0.56–0.63

The intervals calculated using the adjusted bootstrap percentile method.
CI = confidence interval; ECT = electroconvulsive therapy; MEDs = minimal effective doses.

Secondary Clinical Outcome: Time to Recovery from Neuromuscular Blockade

The time to 90% twitch recovery after succinylcholine was 9.37 ± 3.2 minutes, whereas 100% twitch recovery was obtained after 9.7 ± 3.5 (3–20) minutes (Fig. 2). The time to TOF recovery >0.9 was 19.5 ± 5.7 minutes after rocuronium (Table 1).

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

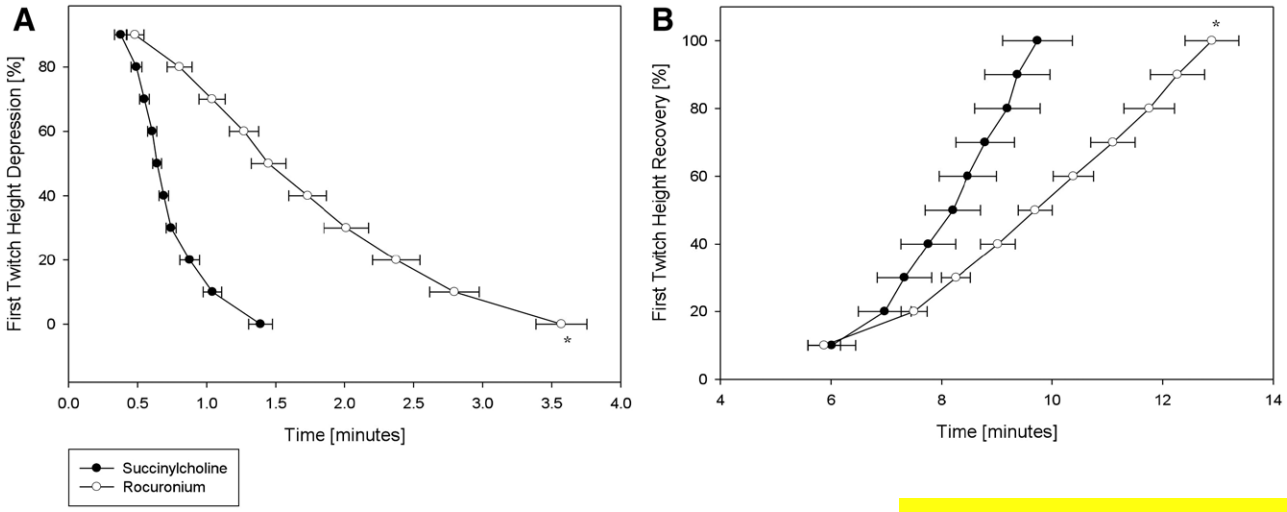

Figure 2. Time course of single twitch height (percentage baseline) after injection of succinylcholine or rocuronium (means ± SE) in optimized electroconvulsive therapy-induced seizure quality. *$P < 0.05$. A, Onset of action and suppression of twitch height; B, recovery of twitch height.

instead of succinylcholine. ECT parameters including pulse width, energy, frequency, and duration were similar in both groups (Table 1). 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, was 94% ± 3% (85–100) and 92% ± 4% (79–99) for rocuronium and succinylcholine, respectively ($P > 0.05$).

The interrater 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 after succinylcholine and rocuronium amounted to 27 ± 14 and 31 ± 11 seconds, respectively ($P < 0.001$, Table 1).

DISCUSSION

The findings reported herein indicate that near-complete twitch suppression is required for optimal neuromuscular blockade during ECT. The $MED50_{ECT}$ for succinylcholine and rocuronium was 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 time to achieve acceptable neuromuscular blockade was increased by approximately 2.3 minutes with rocuronium compared with succinylcholine, resulting in a total of approximately 12 minutes increased procedure time.

Minimum Effective Dose of Succinylcholine and Time to Onset of Maximal Effect

Although a single best dose of succinylcholine for ECT has not been identified in the literature, doses between 0.5 and 6 mg kg^{-1}, 0.8 and 1 mg kg^{-1}, and even up to 1.4 mg kg^{-1} have been recommended on the basis of the anecdotal reports, previous experience of anesthesia providers, or limited clinical studies.[5,15–19] The methodologic differences of these observations, interindividual and intraindividual variability, and particularly the lack of objective assessment in most occasions could explain the wide range of the recommended effective doses of succinylcholine for ECT.

The optimal dose of an NMBA is determined not only by its pharmacodynamics but also by its clinical use and the individual patient's preexisting medical conditions. As an example, the recommended intubating dose for rocuronium is 2 × its adductor pollicis ED_{95}, whereas for rapid sequence intubation, a significantly greater dose of 4 × ED_{95} is used. Similarly, for an elderly patient with severe osteoporosis, a clinician may choose to start the ECT treatments using a greater dose of NMBA (e.g., $MED90_{ECT}$) to minimize the risk of insufficient neuromuscular blockade, excessive muscle contractions, and potentially bone fractures, whereas in a younger and healthier patient, $MED50_{ECT}$ may be more desirable because of the lower risk for complications from a "suboptimal" muscle relaxation and the benefits of a more rapid recovery from anesthesia and the procedure. The applied initial dose in both examples can then be adjusted in subsequent ECT treatments based on the initial response.

Consistent with the reports from the study by Murali et al.[20] and Bryson et al.,[21] our data suggest that succinylcholine doses close to 1 mg kg^{-1} ($MED90_{ECT}$ in this study) may provide acceptable ECT conditions in most patients and also highlight the importance of avoiding early application of ECT after the administration of succinylcholine (<1.4 minutes, time to onset of acceptable neuromuscular blockade), even in the absence of a twitch response to nerve stimulation. This observation also is consistent with the previous finding by Beale et al.[22] 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 seconds used for rapid sequence intubation (1 mg $kg^{-1}$of succinylcholine, 3.5 × its adductor pollicis ED_{95}).[23–25] This difference in time to obtain acceptable ECT conditions compared with that for endotracheal intubation may be attributed to a difference in sensitivity to succinylcholine in different muscle groups (e.g., oropharynx versus extremities) but also can indicate that a deeper neuromuscular blockade is needed for acceptable ECT conditions compared with endotracheal intubation. Kopman et al.[26] showed that the onset speed of succinylcholine might be dependent on the rapid plasma clearance such that, in patients with normal plasma cholinesterase activity, after an

ED_{95} dose of succinylcholine, time to peak effect (95% twitch depression) occurs in <2 minutes (109 ± 15 seconds).

The $MED90_{ECT}$ of 1.06 mg kg^{-1} succinylcholine (≈3.5 × its adductor pollicis ED_{95}) in our study and an induced twitch height suppression of 0% to 4% for acceptable motor seizure modification are in line with the findings by Murali et al.[20], who recommended a dose of 1.0 mg kg^{-1} and twitch suppression to 0% to 5% of baseline. The $MED95_{ECT}$ (1.16 mg kg^{-1}) has also been used in other clinical trials (1.2 mg kg^{-1}).[27–30]

Duration of Paralysis and Time to Recovery After Succinylcholine

The time required for 90% twitch recovery (9.4 minutes) after succinylcholine in each subject is comparable with the reported recovery time by others after a single dose of 1 mg kg^{-1} (9.3 minutes).[31,32] Similarly, the time required for 100% twitch recovery (9.7 minutes) 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}).[33,34] 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 used increasingly as an alternative to succinylcholine for neuromuscular blockade during ECT, primarily in the elderly and in patients with cardiovascular and neurologic comorbidities. Immobilized patients and elderly or those who have suffered a stroke are particularly susceptible to succinylcholine-induced hyperkalemia because of depolarization of upregulated nicotinic (neuronal) α-7 acetylcholine receptors.[5] Conversely, 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 with contraindications to succinylcholine.

Currently, rocuronium is given as a single bolus of 0.3 to 0.6 mg kg^{-1} before ECT treatment.[5] Our result is consistent with the previous applied doses and provides the estimation of recommended initial doses in the range of 0.36 to 0.6 mg kg^{-1} ($MED50_{ECT}$–$MED99_{ECT}$). Our study also confirms that, 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 if appropriately dosed and monitored.

Minimum Effective Dose of Rocuronium and Time to Onset of Maximal Effect

The $MED90_{ECT}$ in our study (0.57 mg kg^{-1} ≈ 2 × ED_{95}) is comparable with the dose that has been reported to induce >95% block in 98% of subjects.[35,36] 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 minutes and 0% after 3.7 ± 1.0 minutes. The time from NMBA injection to acceptable ECT conditions is hence approximately 2.3 minutes longer with rocuronium compared with succinylcholine. As anesthetics 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 et al.[37] reported the time to 90% recovery of the first twitch (T1 90) to be >10 minutes. Consistent with their data, our study showed that a twitch value of 90% was obtained 12 minutes after rocuronium was administered; however, in the former study, the TOF ratio of 0.9 (indicating the average recovery time for induced acceptable neuromuscular blockade) was achieved 28 minutes after rocuronium-induced paralysis (0.45 mg kg^{-1}), whereas it was recorded after only 19.5 minutes in this study. This time is also shorter than the recovery time reported by Wierda et al.[38] (0.4 mg kg^{-1} rocuronium), but it is comparable with a recovery time of 19.4 ± 5.1 minutes reported by Lederer et al.,[39] who applied 0.05 mg kg^{-1} neostigmine 5 minutes after injection of 0.4 mg kg^{-1} rocuronium.

Similarly, the observed recovery times after 0.5 to 0.6 mg kg^{-1} rocuronium for some subjects to achieve acceptable induced seizure activity in our study were shorter than what has been reported after a comparable dose in procedures other than ECT.[40,41] This observed difference may imply that during induced convulsions, the release of acetylcholine into the neuromuscular junction may reduce the duration of the induced neuromuscular blockade from rocuronium.

In line with our findings, in an ECT study by Turkkal et al.,[42] the reported recovery time for the tongue depressor test was 15 ± 2 minutes after a single dose of 0.3 mg kg^{-1} rocuronium and after reversal with 20 μg kg^{-1} of neostigmine. Of note, the tongue depressor test is considered a sensitive and practical bedside test to assess the recovery from neuromuscular blockade, and it is reported to correspond with a TOF ratio recovery to 0.8.[43] These observations may indicate that the recovery time is dependent not only on the applied dose and the time at which reversal agent is given but also dependent possibly on the quality and vigor of the induced seizures. Regardless of these observations, it is prudent to use standard neuromuscular reversal criteria and monitoring before allowing the patient to emerge from anesthesia.

ECT Quality and Seizure Duration After Rocuronium Versus Succinylcholine

By using subjective tools to assess the recovery from neuromuscular blockade and as stated earlier, Turkkal et al.[42] reported that motor seizure duration was greater after 0.3 mg kg^{-1} rocuronium compared with 1 mg kg^{-1} succinylcholine (33 and 24 seconds, respectively). Similarly, Hoshi et al.[44] reported longer duration of seizure with rocuronium compared with succinylcholine. Our data are 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[45] after rocuronium associated with the 2-minute delay in achieving appropriate muscle relaxation. Because there is an

association between clinical effectiveness of ECT and the duration of induced seizure,[46] the American Psychiatric Association task force advocates seizure lengths >20 seconds for effective ECT outcome.[47] 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,[48] particularly in patients who might need greater 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.

CLINICAL IMPLICATIONS

In a single-dose approach, an initial $MED50_{ECT}$ dose of each NMBA can be considered if a 50% risk of providing suboptimal relaxation as defined in this study (Table 2) is clinically acceptable. If there are clinical concerns that our definition of adequate neuromuscular blockade is insufficient for a specific patient (e.g., in an elderly patient with severe osteoporosis), clinicians should instead consider an initial greater dose of each NMBA, such as an $MED90_{ECT}$ dose of succinylcholine at 1 mg kg^{-1}, or rocuronium at 0.57 mg kg^{-1} to provide controlled seizure activity during ECT. Subsequent adjustments may be needed to further optimize the ECT response with the minimal dose of either NMBA. Accordingly, the presented data suggest that an initial succinylcholine dose of 0.85 mg kg^{-1} is reasonable for the first ECT session in most patients, with dose adjustments in 0.1 to 0.2 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 in healthier patients without osteoporosis. 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 minutes).

If excessive or insufficient neuromuscular blockade is noticed during the induced seizure, dose adjustment with 0.05 to 0.1 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 μg kg^{-1}). Quantitative neuromuscular transmission (NMT) monitoring should be used to evaluate adequate suppression of neuromuscular blockade, and to ensure sufficient recovery of the induced neuromuscular blockade, to minimize the risk for adverse respiratory events.[5,49] Clinicians should ensure that all patients remain under close observation by appropriately trained personnel and should continue to monitor the neuromuscular function until complete recovery of the neuromuscular transmission has been verified (e.g., tongue depressor test).[43]

A limitation of this study was our inability to completely blind the seizure quality assessors to the type of NMBA, because we could not mask the fasciculations (if significant) after succinylcholine. Moreover, this study does not systematically explore a single optimal dose for each NMBA that requires several further treatment sessions of each subject and a notably larger sample size to apply the identified MED for capturing the intrasubject variability of response to neuromuscular blockers. In general, using >1 crossover could be a better approach for defining the optimal doses of NMBAs for each patient and for determining its variability for any given patient or population.

In summary, the presented data show 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 minutes when rocuronium is used instead of succinylcholine, resulting in an average of 12 minutes increased procedure time. When appropriately dosed and monitored, rocuronium can be a safe alternative NMBA for ECT in patients with contraindications to succinylcholine. ■

DISCLOSURES

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Attestation: Hooman Mirzakhani has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
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REFERENCES

1. Rasmussen K. The practice of electroconvulsive therapy: recommendations for treatment, training, and privileging (second edition). J ECT 2002;18:58–9
2. Wilkins KM, Ostroff R, Tampi RR. Efficacy of electroconvulsive therapy in the treatment of nondepressed psychiatric illness in elderly patients: a review of the literature. J Geriatr Psychiatry Neurol 2008;21:3–11
3. Ding Z, White PF. Anesthesia for electroconvulsive therapy. Anesth Analg 2002;94:1351–64
4. Booij LH. Is succinylcholine appropriate or obsolete in the intensive care unit? Crit Care 2001;5:245–6
5. Mirzakhani H, Welch CA, Eikermann M, Nozari A. Neuromuscular blocking agents for electroconvulsive therapy: a systematic review. Acta Anaesthesiol Scand 2012;56:3–16
6. Kopman AF, Eikermann M. Antagonism of non-depolarising neuromuscular block: current practice. Anaesthesia 2009;64(Suppl 1):22–30
7. Viby-Mogensen J. Clinical assessment of neuromuscular transmission. Br J Anaesth 1982;54:209–23
8. Fuchs-Buder T, Claudius C, Skovgaard LT, Eriksson LI, Mirakhur RK, Viby-Mogensen J; 8th International Neuromuscular Meeting. Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. Acta Anaesthesiol Scand 2007;51:789–808
9. Barash PG, Cullen BF, Stoelting RK, Cahalan MK, Stock MC, eds. Clinical Anesthesia. 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2009
10. Kopman AF, Lien CA, Naguib M. Neuromuscular dose-response studies: determining sample size. Br J Anaesth 2011;106:194–8
11. Pace NL, Stylianou MP. Advances in and limitations of up-and-down methodology: a précis of clinical use, study design, and dose estimation in anesthesia research. Anesthesiology 2007;107:144–52
12. Zhou XH, Gao S, Hui SL. Methods for comparing the means of two independent log-normal samples. Biometrics 1997;53:1129–35
13. Wellek S, Blettner M. On the proper use of the crossover design in clinical trials: part 18 of a series on evaluation of scientific publications. Dtsch Arztebl Int 2012;109:276–81
14. Efron B, Tibshirani R. Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. Stat Sci 1986:54–75
15. Konarzewski WH, Milosavljevic D, Robinson M, Banham W, Beales F. Suxamethonium dosage in electroconvulsive therapy. Anaesthesia 1988;43:474–6
16. Fredman B, Smith I, d'Etienne J, White PF. Use of muscle relaxants for electroconvulsive therapy: how much is enough? Anesth Analg 1994;78:195–6
17. Gaines GY III, Rees DI. Electroconvulsive therapy and anesthetic considerations. Anesth Analg 1986;65:1345–56
18. Pitts FN Jr, Woodruff RA Jr, Craig AG, Rich CL. The drug modification of ECT. II. Succinylcholine dosage. Arch Gen Psychiatry 1968;19:595–9
19. Cheam EW, Critchley LA, Chui PT, Yap JC, Ha VW. Low dose mivacurium is less effective than succinylcholine in electroconvulsive therapy. Can J Anaesth 1999;46:49–51
20. Murali N, Saravanan ES, Ramesh VJ, Gangadhar BN, Jananakiramiah N, Kumar SS, Christopher R, Subbakrishna DK. An intrasubject comparison of two doses of succinylcholine in modified electroconvulsive therapy. Anesth Analg 1999;89:1301–4
21. Bryson EO, Aloysi AS, Popeo DM, Bodian CA, Pasculli RM, Briggs MC, Kellner CH. Methohexital and succinylcholine dosing for electroconvulsive therapy (ECT): actual versus ideal. J ECT 2012;28:e29–30
22. Beale MD, Kellner CH, Lemert R, Pritchett JT, Bernstein HJ, Burns CM, Duc T, Roy R. Skeletal muscle relaxation in patients undergoing electroconvulsive therapy. Anesthesiology 1994;80:957
23. Ferguson A, Bevan DR. Mixed neuromuscular block: the effect of precurarization. Anaesthesia 1981;36:661–6
24. Mehta MP, Sokoll MD, Gergis SD. Accelerated onset of non-depolarizing neuromuscular blocking drugs: pancuronium, atracurium and vecuronium. A comparison with succinylcholine. Eur J Anaesthesiol 1988;5:15–21
25. Curran MJ, Donati F, Bevan DR. Onset and recovery of atracurium and suxamethonium-induced neuromuscular blockade with simultaneous train-of-four and single twitch stimulation. Br J Anaesth 1987;59:989–94
26. Kopman AF, Klewicka MM, Kopman DJ, Neuman GG. Molar potency is predictive of the speed of onset of neuromuscular block for agents of intermediate, short, and ultrashort duration. Anesthesiology 1999;90:425–31
27. Avramov MN, Stool LA, White PF, Husain MM. Effects of nicardipine and labetalol on the acute hemodynamic response to electroconvulsive therapy. J Clin Anesth 1998;10:394–400
28. Recart A, Rawal S, White PF, Byerly S, Thornton L. The effect of remifentanil on seizure duration and acute hemodynamic responses to electroconvulsive therapy. Anesth Analg 2003;96:1047–50
29. Yoshino Y, Ozaki Y, Kawasoe K, Ochi S, Niiya T, Sonobe N, Matsumoto T, Ueno S. Combined clozapine and electroconvulsive therapy in a Japanese schizophrenia patient: a case report. Clin Psychopharmacol Neurosci 2014;12:160–2
30. Avramov MN, Husain MM, White PF. The comparative effects of methohexital, propofol, and etomidate for electroconvulsive therapy. Anesth Analg 1995;81:596–602
31. Kopman AF, Zhaku B, Lai KS. The "intubating dose" of succinylcholine: the effect of decreasing doses on recovery time. Anesthesiology 2003;99:1050–4
32. Viby-Mogensen J. Correlation of succinylcholine duration of action with plasma cholinesterase activity in subjects with the genotypically normal enzyme. Anesthesiology 1980;53:517–20
33. Durant NN, Katz RL. Suxamethonium. Br J Anaesth 1982;54:195–208
34. Vanlinthout LE, van Egmond J, de Boo T, Lerou JG, Wevers RA, Booij LH. Factors affecting magnitude and time course of neuromuscular block produced by suxamethonium. Br J Anaesth 1992;69:29–35
35. Kopman AF, Klewicka MM, Neuman GG. Reexamined: the recommended endotracheal intubating dose for nondepolarizing neuromuscular blockers of rapid onset. Anesth Analg 2001;93:954–9
36. Meistelman C, Plaud B, Donati F. Rocuronium (ORG 9426) neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis in humans. Can J Anaesth 1992;39:665–9

37. Bevan JC, Collins L, Fowler C, Kahwaji R, Rosen HD, Smith MF, de Scheepers LD, Stephenson CA, Bevan DR. Early and late reversal of rocuronium and vecuronium with neostigmine in adults and children. Anesth Analg 1999;89:333–9
38. Wierda JM, Beaufort AM, Kleef UW, Smeulers NJ, Agoston S. Preliminary investigations of the clinical pharmacology of three short-acting non-depolarizing neuromuscular blocking agents, Org 9453, Org 9489 and Org 9487. Can J Anaesth 1994;41:213–20
39. Lederer W, Reiner T, Khuenl-Brady KS. Neostigmine injected 5 minutes after low-dose rocuronium accelerates the recovery of neuromuscular function. J Clin Anesth 2010;22:420–4
40. Cooper RA, Mirakhur RK, Maddineni VR. Neuromuscular effects of rocuronium bromide (Org 9426) during fentanyl and halothane anaesthesia. Anaesthesia 1993;48:103–5
41. Schultz P, Ibsen M, Østergaard D, Skovgaard LT. Onset and duration of action of rocuronium–from tracheal intubation, through intense block to complete recovery. Acta Anaesthesiol Scand 2001;45:612–7
42. Turkkal DC, Gokmen N, Yildiz A, Iyilikci L, Gokel E, Sagduyu K, Gunerli A. A cross-over, post-electroconvulsive therapy comparison of clinical recovery from rocuronium versus succinylcholine. J Clin Anesth 2008;20:589–93
43. Kopman AF, Yee PS, Neuman GG. Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. Anesthesiology 1997;86:765–71
44. Hoshi H, Kadoi Y, Kamiyama J, Nishida A, Saito H, Taguchi M, Saito S. Use of rocuronium-sugammadex, an alternative to succinylcholine, as a muscle relaxant during electroconvulsive therapy. J Anesth 2011;25:286–90
45. San-juan D, Chiappa KH, Cole AJ. Propofol and the electroencephalogram. Clin Neurophysiol 2010;121:998–1006
46. Lalla FR, Milroy T. The current status of seizure duration in the practice of electroconvulsive therapy. Can J Psychiatry 1996;41:299–304
47. American Psychiatric Association. The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training and Privileging: A Task Force Report. Washington (DC): American Psychiatric Association Press, 2001
48. Girish K, Gangadhar BN, Janakiramaiah N. Merits of EEG monitoring during ECT: a prospective study on 485 patients. Indian J Psychiatry 2002;44:24–8
49. Brull SJ, Naguib M. What we know: precise measurement leads to patient comfort and safety. Anesthesiology 2011;115:918–20

Muscle Relaxation With Succinylcholine in Electroconvulsive Therapy

To the Editor

We read with interest the carefully performed study by Mirzakhani et al[1] regarding dosing of muscle relaxants during electroconvulsive therapy (ECT). In our practice, we have reached similar conclusions about the optimal mean dose of succinylcholine for acceptable muscle relaxation during ECT. We previously published these data showing a mean succinylcholine dose of 0.9 mg/kg[2]; this is very similar to the reported 0.85-mg/kg dose of the Mirzakhani et al's study. We would like to point out, however, that a small but not insignificant number of patients are outliers in regard to their succinylcholine requirements. Some patients will need dose increases, whereas others will need far less succinylcholine than predicted. This may be because of various reasons, including genetic variability in enzyme level, concomitant medications, or other, harder-to-elucidate mechanisms.

We reviewed 500 patients who received ECT at Mount Sinai Hospital in New York. Assuming that these data fit a standard normal distribution, we found that the mean dose of succinylcholine required was 0.96 mg/kg with a standard deviation of 0.26 mg/kg. The minimum required dose in our sample was 0.29 mg/kg, whereas the maximum dose was 2.10 mg/kg. Six patients (1.2%) required succinylcholine doses >2 standard deviations below the mean, or <0.43 mg/kg. Twenty-three patients (4.6%) required succinylcholine doses >2 standard deviations above the mean, or >1.48 mg/kg. In this sample, patients were more likely to need and to tolerate higher doses of succinylcholine rather than lower doses for adequate muscle relaxation.

In medicine, we strive to achieve predictability, replicability, and patient safety. Among the drugs we use in ECT, succinylcholine is the least predictable. Our data suggest that standard dosing will result in inadequate muscle relaxation for approximately 5% of patients. Inadequate muscle relaxation results in cosmetically unattractive treatments and a small risk of musculoskeletal injury. Most of the drugs used in ECT are highly predictable, including succinylcholine for most patients. However, providers must be aware that significant variability in response does exist and should adjust succinylcholine dose accordingly for efficacy and safety.

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REFERENCES

1. Mirzakhani H, Guchelaar HJ, Welch CA, et al. Minimum effective doses of succinylcholine and rocuronium during electroconvulsive therapy: a prospective, randomized, crossover trial. *Anesth Analg*. 2016;123:587–596.
2. Bryson EO, Aloysi AS, Popeo DM, et al. Methohexital and succinylcholine dosing for electroconvulsive therapy (ECT): actual versus ideal. *J ECT*. 2012;28:e29–e30.

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bromide under balanced and volatile anesthesia. *Acta Anaesthesiol Belg*. 1994;45:41–47.
9. Naguib M. Neuromuscular effects of rocuronium bromide and mivacurium chloride administered alone and in combination. *Anesthesiology*. 1994;81:388–395.
10. Foldes FF, Nagashima H, Nguyen HD, Schiller WS, Mason MM, Ohta Y. The neuromuscular effects of ORG9426 in patients receiving balanced anesthesia. *Anesthesiology*. 1991;75:191–196.
11. Lederer W, Reiner T, Khuenl-Brady KS. Neostigmine injected 5 minutes after low-dose rocuronium accelerates the recovery of neuromuscular function. *J Clin Anesth*. 2010;22:420–424.
12. Wright PM, Caldwell JE, Miller RD. Onset and duration of rocuronium and succinylcholine at the adductor pollicis and laryngeal adductor muscles in anesthetized humans. *Anesthesiology*. 1994;81:1110–1115.
13. Kim KS, Cheong MA, Lee HJ, Lee JM. Tactile assessment for the reversibility of rocuronium-induced neuromuscular blockade during propofol or sevoflurane anesthesia. *Anesth Analg*. 2004;99:1080–1085.
14. McCourt KC, Mirakhur RK, Kerr CM. Dosage of neostigmine for reversal of rocuronium block from two levels of spontaneous recovery. *Anaesthesia*. 1999;54:651–655.
15. Kirkegaard H, Heier T, Caldwell JE. Efficacy of tactile-guided reversal from cisatracurium-induced neuromuscular block. *Anesthesiology*. 2002;96:45–50.

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In Response

Effective Doses of Neuromuscular Blockers During Electroconvulsive Therapy

We thank Drs Kopman and Naguib for their interest in our recently published article on neuromuscular blocking agents (NMBAs) for electroconvulsive therapy (ECT), particularly Dr Kopman who also served as 1 of our reviewers in the peer review process.[1] They made a number of comments, most of which were also discussed and addressed during the review process.

In our study, we aimed to investigate the minimum effective doses (MEDs) of succinylcholine and rocuronium to provide adequate control of muscle activity during induced seizure activity with ECT based on defined clinical criteria. We applied creative use of the randomized crossover design combined with up and down dose adjustment, because the 2 NMBAs have short half-lives, much reducing the risk of carryover effects between each treatment. Needless to say, randomized controlled crossover experiments are especially important in health care given that adequate power can sometimes be achieved with a relatively small number of patients. Our randomized clinical trial was a repeated-measures design, in which the same measures were collected multiple times in each subject. Our crossover design helped to achieve proper "balance" with all subjects receiving a similar number of treatments with both NMBAs.

The Dixon's Up and Down method that was used in our study estimates the median and standard error of the ED50 for a population and not for each subject. Dr Kopman's comments are inconsistent with the use of Dixon's method along with the fact that ED50 is a population measure.[2] It is illogical to discuss the ED50 for an individual. In our study, an optimal dose for each individual was estimated, and these individual estimates from multiple subjects were then used to calculate the ED50 for the population. Although the number of measurements per individual was partly reduced because of the crossover design of the study, well-validated methods (bootstrap resampling and mixed modeling) were used to account for both intraindividual and interindividual variabilities in the analysis. In addition, through exploration of the existing data and those from our pilot studies of 10 subjects, we narrowed the starting dose of each NMBA (0.4 and 0.8 mg/kg for rocuronium and succinylcholine, respectively) to achieve ideal control of the induced motor activity with minimal titration required, hence reducing the required ECT sessions in each subject to identify the actual MED50 by approximately 30% to 40%.[3]

Dr Kopman also seems surprised that an "intubating dose" of rocuronium would be insufficient to provide optimal conditions for ECT in some patients. Would not the dose of rocuronium needed to provide total body relaxation intuitively be expected to exceed the dose needed to relax the laryngeal muscles? Rocuronium doses of up to 1.2 mg/kg intravenously are commonly used for intubation when shorter onset time and potentially increased probability of successful intubation might be desired (ie, rapid sequence induction).[4,5] Furthermore, it is well known that anesthetics potentiate the effects of NMBAs, and the duration and dose of anesthetics used for intubation of a patient and for ECT are therefore not comparable.[6] Moreover, ECT and the induced seizure can result in an excessive release of acetylcholine into the neuromuscular junction, which can potentially interfere with the neuromuscular effects of the administered NMBA (ie, reducing the effect and duration of rocuronium). In our study, the MED90 of rocuronium (0.57 mg/kg) is the 90th percentile of doses resulting in adequate seizure activity, demonstrating that only 10% of population might need a higher dose to achieve this endpoint. Our estimated MED99 (99th percentile) is, nevertheless, only slightly higher (0.6 mg/kg), meaning that almost all patients will achieve adequate muscle relaxation for ECT with a dose of 0.6 mg/kg rocuronium.

Dr Kopman's comments on the recovery time after administration of rocuronium are similar to those on its effective ECT dose. The estimated recovery time to train of four (TOF) 0.9 in our study is simply the average of recovery times of subjects who had optimized induced seizure activity. First, comparing the average recovery time after 0.41 mg/kg (MED50) rocuronium in our study with 0.6 mg/kg in other studies is irrelevant. In addition, volatile anesthetics are used in many of the previously mentioned studies but not during ECT.[6] Considering that the median of applied doses (0.4 mg/kg) might only provide a comparable estimate under similar conditions, whereas ECT and intubation are 2 different clinical conditions, the comparison of results is therefore not necessarily conclusive. Interestingly, the recovery times in our study are comparable with what was reported by Lederer et al[7] and Turkkal et al[8] but was longer than what was reported by Wright et al,[9] as explained in the manuscript. Again, this observed difference may imply that during induced convulsions, the release of acetylcholine into the neuromuscular junction may reduce the duration of the induced neuromuscular blockade from rocuronium.[10]

With regard to Dr Kopman's comments on the criteria for assessing the quality of induced seizures in our study, it is important to note that such assessment is by necessity clinical, because no alternative techniques exist. Are similar clinically

subjective approaches not applied for the assessment of intubating conditions?[11,12] Both psychiatrists involved in the study have >40 years combined experience in ECT practice and have used standard and well-defined criteria for the assessment of the ECT quality. We agree that future research that addresses the letter writers' question of "what degree of neuromuscular block is required to prevent traumatic injury from an induced seizure" would be valuable. However, it is perhaps of greater clinical value to optimize the quality and adequacy of seizure and the efficacy of the ECT treatment. Accordingly, it is more prudent to define the MED of NMBAs under the optimum defined seizure quality.[13,14]

We would like to emphasize that, contrary to studies for intubation condition, few studies have systematically and objectively investigated different NMBAs during ECT. We not only believe that our results provide important clinical implications in this context, but also hope that they inspire other investigators to conduct relevant research within this important area of clinical practice.

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REFERENCES

1. Mirzakhani H, Guchelaar HJ, Welch CA, et al. Minimum effective doses of succinylcholine and rocuronium during electroconvulsive therapy: a prospective, randomized, crossover trial. *Anesth Analg*. 2016;123:587–596.
2. Dixon WJ. Staircase bioassay: the up-and-down method. *Neurosci Biobehav Rev*. 1991;15:47–50.
3. Dixon WJ, Massey FJ. *Introduction to Statistical Analysis*. 4th ed. New York, NY: McGraw-Hill, 1983:426–441.
4. Kirkegaard-Nielsen H, Caldwell JE, Berry PD. Rapid tracheal intubation with rocuronium: a probability approach to determining dose. *Anesthesiology*. 1999;91:131–136.
5. Heier T, Caldwell JE. Rapid tracheal intubation with large-dose rocuronium: a probability-based approach. *Anesth Analg*. 2000;90:175–179.
6. Paul M, Fokt RM, Kindler CH, Dipp NC, Yost CS. Characterization of the interactions between volatile anesthetics and neuromuscular blockers at the muscle nicotinic acetylcholine receptor. *Anesth Analg*. 2002;95:362–367.
7. Lederer W, Reiner T, Khuenl-Brady KS. Neostigmine injected 5 minutes after low-dose rocuronium accelerates the recovery of neuromuscular function. *J Clin Anesth*. 2010;22:420–424.
8. Turkkal DC, Gokmen N, Yildiz A, et al. A cross-over, post-electroconvulsive therapy comparison of clinical recovery from rocuronium versus succinylcholine. *J Clin Anesth*. 2008;20:589–593.
9. Wright PM, Caldwell JE, Miller RD. Onset and duration of rocuronium and succinylcholine at the adductor pollicis and laryngeal adductor muscles in anesthetized humans. *Anesthesiology*. 1994;81:1110–1115.
10. Denker A, Rizzoli SO. Synaptic vesicle pools: an update. *Front Synaptic Neurosci*. 2010;2:135.
11. Kopman AF, Klewicka MM, Neuman GG. Reexamined: the recommended endotracheal intubating dose for nondepolarizing neuromuscular blockers of rapid onset. *Anesth Analg*. 2001;93:954–959.
12. Naguib M, Samarkandi A, Riad W, Alharby SW. Optimal dose of succinylcholine revisited. *Anesthesiology*. 2003;99:1045–1049.
13. Minelli A, Abate M, Zampieri E, et al. Seizure adequacy markers and the prediction of electroconvulsive therapy response. *J ECT*. 2016;32:88–92.
14. Bumb JM, Aksay SS, Janke C, et al. Focus on ECT seizure quality: serum BDNF as a peripheral biomarker in depressed patients. *Eur Arch Psychiatry Clin Neurosci*. 2015;265:227–232.

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Does the Device Matter in Goal-Directed Fluid Therapy?

To the Editor

I read with interest the debate on the role of goal-directed fluid therapy (GDFT) in the context of enhanced recovery after surgery (ERAS) protocols.[1,2] A meta-analysis on this topic has been published in the time between acceptance and publication of these articles in *Anesthesia & Analgesia*.[3] The pooled analysis suggested that ERAS pathways and improved perioperative care of surgical patients have lessened the impact of GDFT on postoperative outcomes. This raised the question of whether GDFT was beneficial in an ERAS setting. However, there was huge variation between clinical trials in the method of deploying GDFT. Notably, esophageal Doppler monitoring was used in 9 of 10 (90%) ERAS pathway trials but in only 3 of 13 (23%) trials conducted in a traditional care setting.

The discussion in this journal highlighted the different technologies used to measure stroke volume and cardiac output and how there is poor agreement between monitors. However, this factor appears to be more important than previously thought. A recent study found that different devices varied widely in their accuracy and sensitivity to detect a statistically significant change in stroke volume.[4] The LiDCOrapid (LiDCO, London, UK) was able to detect this change after a 2.5% blood loss, the USCOM 1A (USCOM, Sydney, NSW, Australia) at 7.5%, and the CardioQ esophageal Doppler (Deltex Medical, Chichester, West Sussex, UK) and Vigileo FloTrac at (Edwards Lifesciences, Irvine) 12.5%. Mean stroke volume at baseline also varied from 90.8 to 138.9 mL depending on the device used. This was despite being deployed in young, healthy volunteers without the physiologic derangements of surgery, which may compound device-related inaccuracies.

To date, systematic reviews of perioperative GDFT have all failed to consider the actual method of delivery as a distinct category of analysis. As such, studies using a multitude of different devices have been included in pooled analysis. It is clear that GDFT needs to be considered in relation to the method of delivery and devices are not interchangeable. In addition, it is important to remember that national guidelines in the United Kingdom recommend esophageal Doppler monitoring and not GDFT in general. It would be misleading, as has been done, to challenge this using evidence from non-esophageal Doppler monitoring trials. Device variability is only part of the high degree of heterogeneity, which exists between study groups and within studies. The added nuance that these monitors may not all be equally able to accurately and reliably track changes in stroke volume makes the controversies surrounding perioperative GDFT even harder to untangle. Large-scale randomized controlled trials that tackle