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Effects of conventional *vs* high-dose rocuronium on the QTc interval during anesthesia induction and intubation in patients undergoing coronary artery surgery: a randomized, double-blind, parallel trial

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Abstract

Myocardial ischemia, as well as the induction agents used in anesthesia, may cause corrected QT interval (QTc) prolongation. The objective of this randomized, double-blind trial was to determine the effects of high- *vs* conventional-dose bolus rocuronium on QTc duration and the incidence of dysrhythmias following anesthesia induction and intubation. Fifty patients about to undergo coronary artery surgery were randomly allocated to receive conventional-dose (0.6 mg/kg, group C, n = 25) or high-dose (1.2 mg/kg, group H, n = 25) rocuronium after induction with etomidate and fentanyl. QTc, heart rate, and mean arterial pressure were recorded before induction (T0), after induction (T1), after rocuronium (just before laryngoscopy; T2), 2 min after intubation (T3), and 5 min after intubation (T4). The occurrence of dysrhythmias was recorded. In both groups, QTc was significantly longer at T3 than at baseline [475 *vs* 429 ms in group C (P = 0.001), and 459 *vs* 434 ms in group H (P = 0.005)]. The incidence of dysrhythmias in group C (28%) and in group H (24%) was similar. The QTc after high-dose rocuronium was not significantly longer than after conventional-dose rocuronium in patients about to undergo coronary artery surgery who were induced with etomidate and fentanyl. In both groups, compared with baseline, QTc was most prolonged at 2 min after intubation, suggesting that QTc prolongation may be due to the nociceptive stimulus of intubation.

Key words: QTc; Rocuronium; Induction; Intubation

Introduction

Effects of coronary vascular disease (e.g., ischemia, scar tissue, and reduced ejection fraction) may lower the cardiac depolarization threshold and cause corrected QT interval (QTc) prolongation. A delay in cardiac repolarization may create an electrophysiological environment that favors the development of cardiac arrhythmias, most notably torsade de pointes (1). Therefore, knowledge of the effects of drugs on the QTc is important, especially for patients with coronary ischemic disease (1-3).

An initial large bolus of an intermediate-acting neuromuscular blocker (e.g., rocuronium) is often given to obtain neuromuscular blockade (NMB) for rapid sequence intubation (4,5). This method is advantageous in cardiac surgery patients because an initial large single bolus of NMB has been shown to minimize postoperative residual muscle paralysis (6-8). At a dose of 1.2 mg/kg, rocuronium, the NMB agent with the fastest onset of action, increases heart rate and might help reduce thoracic rigidity, which might otherwise result if opioids are given during induction (9,10). The mild vagolytic effect of rocuronium is also an advantage in cardiac surgery (9,10).

The objective of this randomized, double-blind, parallel trial was to compare the effects of high single- and conventional-dose rocuronium NMB on QTc and hemodynamics in patients undergoing elective coronary artery bypass grafting under fentanyl and etomidate anesthesia.

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Patients and Methods

Patients

Ethical approval for this randomized, double-blind, parallel trial was granted by our university hospital's Ethics Committee (No. 00572010). Patients with a EuroSCORE (European System for Cardiac Operative Risk Evaluation score) of less than 6 (i.e., predicted medium risk) and about to undergo elective coronary artery revascularization surgery were invited to participate in the study. Those granting written informed consent were randomly allocated to one of two groups using sealed envelopes. Group H patients (high-dose) received 1.2 mg/kg and group C (conventional dose) patients received 0.6 mg/kg rocuronium for neuromuscular blockade during induction of anesthesia. The patients, intubating physician, and electrocardiogram (ECG) reader were blinded to group allocation. Patients with morbid obesity, anticipated difficult airway (Mallampati score $\geqslant$3), an abnormal ECG (atrial fibrillation or bundle branch block), neuromuscular disease, congestive heart failure, autonomic dysfunction, electrolyte disturbances, congenital long QT syndrome (in the patient or in a family member), or on medications known to prolong the QTc (tricyclic antidepressants, antidysrhythmics, β-adrenergic antagonists, calcium channel blockers), or with ventricular tachycardia, ventricular extrasystole, or a history of known allergy to drugs were excluded from participation. Patients having hemodynamic instability requiring resuscitation during anesthesia and those whose intubation was difficult were excluded from data analysis (11).

Monitoring

Patients received 5 mg diazepam orally 1 day before surgery. Routine operating room monitoring included arterial oxygen saturation (pulse oximetry), cardiac rhythm (leads II and V_5), end-tidal carbon dioxide, and index of consciousness (IoC-view, Morpheus Medical, Spain). An IV was placed in each forearm for crystalloid (Isolyte S®, a balanced electrolyte solution, Eczacibaşi-Baxter, Turkey) infusion. A radial artery catheter was placed and serum electrolytes (K^+, Ca^{2+}, Mg^{2+}) were measured. In the operating room, patients were monitored before induction and continually until 5 min after intubation with a 7-lead Holter electrocardiogram (DM Software, Stateline, USA). The IoC-view monitor recorded the EEG from 3 surface electrodes [middle forehead (+), left forehead (ref), and over the left zygomatic bone (–)]. The IoC is a unitless scale ranging from 99 (awake) to 0 (isoelectric EEG, coma) with a target range of 60-40 recommended by the manufacturer for surgical anesthesia. The IoC was measured and recorded at 4 study periods described below. Neuromuscular function was evaluated using a Tofguard® SX acceleromyograph (Organon Teknika NV, Belgium), which is fully compliant with Good Clinical Practice guidelines (11). Electrodes for ulnar nerve stimulation were placed at the wrist on the radial side of the flexor carpi ulnaris muscle and 2-3 cm proximal to the distal electrode. The acceleration transducer used to monitor neuromuscular function was placed on the volar side of the distal phalanx of the thumb with no preload to the thumb. The arm was not used for administration of anesthetic agents. After loss of consciousness, supramaximal train-of-four (TOF) electrical stimulation was applied every 15 s, with a square wave stimulus set at a current of 50 mA and a duration of 0.2 ms, and the evoked response of the adductor pollicis muscle was monitored. When the TOF ratio (T4/T1) was zero (i.e., when the depth of neuromuscular block was completely disrupted), direct laryngoscopy was initiated followed by tracheal intubation in 1 min. Intubation quality was evaluated as good, medium, or poor (11). Neuromuscular monitoring was continued until 5 min after intubation. Body temperature at baseline was measured via the tympanic membrane.

Anesthesia and study periods

General anesthesia was induced as follows: intravenous fentanyl (6 μg/kg) was administered over 4 min. Then, 0.15 mg/kg etomidate was injected and followed by subsequent doses of 0.05 mg/kg (if needed) until loss of responsiveness (LOR).

LOR was defined as the moment of loss of eyelash reflex combined with the absence of response to verbal or mild tactile stimulation. At that moment, patients were considered to be unconscious and received either 0.6 mg/kg (group C) or 1.2 mg/kg rocuronium (group H). Ventilation was controlled to maintain end-tidal CO_2 at 35-40 mmHg with a fresh gas flow of 6 L/min (100% oxygen) via face mask, either breathing spontaneously or by receiving manually assisted ventilation. Following rocuronium administration, patients were completely ventilated.

ECG data were transferred to a computer and analyzed by a senior cardiologist blinded to allocation group. The QT interval was measured manually in each lead from the beginning of the QRS complex to the end of the T wave. The QT, QRS, and RR intervals were measured and then QTc values were calculated according to Bazzet's formula [$QT/(RR^{1/2})$]. At least three consecutive cycles were measured for each lead. A QTc longer than 450 was regarded as long (12). Dysrhythmias were also recorded.

The study periods were: T0 = baseline, 1 min before administration of induction drugs; T1 = immediately after completion of initial etomidate/fentanyl doses (approximately 4 min after the start of induction); T2 = 2 min after rocuronium administration, just before laryngoscopy; T3 = 2 min after intubation, and T4 = 5 min after intubation. In order to minimize the cardiac rhythm artifacts, the patients remained untouched during the study periods except as needed to perform face-mask ventilation and intubation.

Statistical analysis

Data analysis was performed using Statistics for Windows® v6.0 (StatSoft Inc., USA). Student's *t*-test was used for intergroup comparisons of parameters with normal

distributions (means ± SD). The Mann-Whitney U test was used for intergroup comparisons of parameters without a normal distribution (median, lower and upper quartile values). Repeated measurements were analyzed with the Friedman analysis of variance (ANOVA) between variables at baseline and those at different postoperative times within each group. Intragroup comparisons of the dependent variables measured at specific times were compared with Wilcoxon's matched pairs test and then corrected with the Bonferroni method. Fisher's exact chi-square test was used to compare categorical variables between the two groups. A P value <0.05 was considered statistically significant. The initial sample size analysis revealed that 17 patients would be required in each group in order to show a 20 ms difference (with an estimated standard deviation of 20 ms) in QTc, with a power of 0.80 at an alpha level of 0.05.

Results

Fifty-four patients granted informed consent and were enrolled in the study. Fifty patients completed the study according to the protocol. Four patients were excluded from data analysis: 2 because of a problem with the Holter device, 1 because of the technical problems with the TOF monitor, and 1 with poor intubation due to a vocal cord nodule. Demographic and clinical characteristics of the participants are reported in Table 1. The patients had normal (<55%) and mild (<45-54%) ejection fractions, as measured by transthoracic echocardiography using the Simpson method. The proportions in each group were similar, with 10 (40%) in group C and 12 (48%) in group H having a normal ejection fraction. The other patients in each group (15 in group C and 13 in group H) had mildly impaired ejection fractions. The mean rocuronium dose was 46 ± 7 mg in group C patients and 102 ± 8 mg in group H patients. The mean time to a TOF ratio of 0 in group H (88 ± 9 s) was significantly shorter than that in group C (116 ± 5 s; Table 1). No patients had unexpected difficult intubations.

The mean QTc times in groups C and H were similar at baseline (P = 0.08, Table 2). Six patients in group C and 7 patients in group H had long QTc intervals (range 461 to 583 ms). Within both groups, the mean QTc changed significantly during the study period (P = 0.0001 for group C and P = 0.009 for group H). In group C, the mean QTc was significantly longer at T3 (2 min after intubation) than that at baseline (T0), after the induction agent was given (T1), and after rocuronium administration (T2), (P = 0.001, P = 0.001, and P = 0.0003, respectively; Table 2). The mean QTc intervals in group H were also significantly longer at 2 min after intubation (T3) than at baseline (T0), and after the induction agent was given (T1), (P = 0.005, P = 0.0001, respectively), but not after rocuronium administration (T2, P = 0.2). Sixteen patients in group C and twelve patients in group H had an increase in QTc of >10% at T3 compared

Table 1. Patient characteristics, drug requirements, intubation times, and number of coronary anastamoses.

	Group C (n = 25)	Group H (n = 25)
Age (years)	60 ± 10	62 ± 9
Sex, male/female (n)	19/6	21/4
BSA (m^2)	1.9 ± 0.4	2.0 ± 0.3
Ejection fraction (%)	52 ± 4	51 ± 6
EuroScore	4.9 ± 1.3	5.5 ± 0.8
Stenosis ⩾50% in the left main coronary (n)	4	5
Co-morbid diseases/chronic medications (n)		
Diabetes mellitus	5	5
Hypertension	13	11
Hyperlipidemia	3	2
Chronic obstructive lung disease	4	3
ACE inhibitor	4	2
Angiotensin II blocker	8	7
Induction medications		
Etomidate (mg)	15 ± 2	14 ± 3
Fentanyl (mg)	0.4 ± 0.1	0.4 ± 0.1
Rocuronium (mg)	46 ± 7	102 ± 8
Time to TOF zero after rocuronium administration (s)	116 ± 5	88 ± 9
Intubation quality (good/medium)	25/0	25/0
Number of coronary anastomoses	2.3 ± 0.5	2.4 ± 0.2

Data are reported as means ± SD. Group C: conventional-dose rocuronium (0.6 mg/kg); group H: high-dose rocuronium (1.2 mg/kg). Ejection fraction was measured by transthoracic echocardiography, using the Simpson method. Stenosis was detected angiographically. BSA: body surface area; TOF: train-of-four.

Table 2. Corrected QT intervals (QTc), heart rate and mean arterial pressure at various times in groups C (n = 25) and H (n = 25).

	T0	T1	T2	T3	T4	P
QTc (msn)						
Group C	429 (395-446)	428 (409-449)	430 (411-443)	475 (458-506)*	442 (425-449)	0.0001#
Group H	434 (423-456)	430 (408-454)	444 (418-467)	459 (418-487)**	440 (418-456)	0.009#
Heart rate (bpm)						
Group C	81 (69-92)	75 (67-81)	71 (62-78)*	88 (76-101)*	81 (69-92)	0.00001#
Group H	82 (78-87)	79 (76-82)	77 (63-85)**	86 (77-98)**	77 (69-80)	0.00003#
Mean arterial pressure (mmHg)						
Group C	99 (88-108)	93 (87-104)	79 (70-90)*	92 (76-106)*	77 (67-80)*	<0.001#
Group H	93 (82-107)	88 (75-100)	76 (68-90)**	85 (76-97)**	78 (68-91)**	<0.001#

Data are reported as median and lower and upper quartile values. Group C: conventional-dose rocuronium (0.6 mg/kg); group H: high-dose rocuronium (1.2 mg/kg); T0: before induction; T1: after induction with etomidate/fentanyl; T2: after rocuronium, just before laryngoscopy; T3: 2 min after intubation; T4: 5 min after intubation. #P values were determined using the Friedman ANOVA test. QTc: *Wilcoxon test with Bonferroni correction, group C: T3 *vs* T0, T1 and T2 (P = 0.001, P = 0.001 and P = 0.0003, respectively). **Wilcoxon test with Bonferroni correction, group H: T3 *vs* T0 and T1 (P = 0.005, P = 0.0001, respectively). There were no significant differences between groups for QTc (Mann-Whitney U test, T0, T1, T2, T3 and T4: P>0.1). Heart rate: *Wilcoxon test with Bonferroni correction (group C): T2 *vs* T0 (P = 0.0004) and T3 *vs* T2 (P = 0.0007). **Wilcoxon test with Bonferroni correction (group H): T2 *vs* T0 and T3 *vs* T2 (P = 0.03, P = 0.01, respectively). There were no significant differences between groups for heart rate (Mann-Whitney U test, T0, T1, T3 and T4: P>0.1; T2: P>0.05). Mean arterial pressure: *Wilcoxon test with Bonferroni correction (group C): T2 and T4 *vs* T0 (P = 0.001, P = 0.0001, respectively) and T3 *vs* T2 (P = 0.04). **Wilcoxon test with Bonferroni correction (MAP, group H): T2 and T4 *vs* T0 (P = 0.0001, P = 0.02, respectively) and T3 *vs* T2 (P = 0.01). There were no significant differences between groups for mean arterial presure (Mann-Whitney U test, T0, T1, T3 and T4: P>0.1; T2: P>0.05).

with baseline (T0, P = 0.2). Mean QTc intervals were not significantly different between group H and group C at any time point (P>0.05, Mann-Whitney U test; Table 2).

Within-group multiple comparisons revealed that mean heart rates in groups C and H varied significantly with time (P = 0.00001 and P = 0.00003, respectively; Table 2). In both groups, the mean heart rate was significantly lower after rocuronium (T2) compared with baseline (T0; P = 0.0004, P = 0.03, respectively) and higher 2 min after intubation (T3) compared to T2 (P = 0.0007 and P = 0.01, respectively). The overall mean heart rates (i.e., the mean of the rates measured at all time points) in groups C and H were not significantly different (Table 2).

Mean arterial pressures are reported in Table 2. In both groups, the mean arterial pressure fell significantly after rocuronium (T2) and 5 min after intubation (T4) compared with baseline (T0, P = 0.01 and P = 0.0001 for group C, P = 0.0001 and P = 0.02 for group H). In both groups, mean arterial pressure was significantly higher 2 min after intubation (T3) than after rocuronium administration (T2; P = 0.04 for group C and P = 0.01 for group H). The overall mean arterial pressures (i.e., the mean of the pressures measured at all time points) in groups C and H were not significantly different (P>0.05, Mann-Whitney U test; Table 2).

The incidence of dysrhythmias was similar in group C (28%) and group H (24%) (P = 0.5, Fisher exact two-tailed test; Table 3). In both groups, dysrhythmias appeared 2 min after intubation (T3) and continued during the following minutes. At T3, one patient in group C had nonsustained ventricular tachycardia and two patients had ST depression. In group H, three patients had premature atrial contractions and two patients had premature ventricular contractions (PVCs) at the beginning of the case that continued until 5 min after intubation. Two patients with PVCs in each group had prolonged QTc intervals 2 min after intubation. No dysrhythmia in any patient required therapy.

In both groups, the loC scale was significantly higher at baseline (T0) than at all other time points. The loC scale was significantly lower in group H (mean 56, range 55-58) than in group C (51, range 50-51) 2 min after rocuronium

Table 3. ECG abnormalities observed in groups C and H.

	T0	T1	T2	T3	T4
Group C (n = 25)					
PVC				4	4
Non-sustained VT				1	1
ST depression				2	2
Group H (n = 25)					
PVC	1	1	1	2	2
PAC	2	2	2	3	3
Sinoatrial block				1	1

Data are reported as number. Group C: conventional-dose rocuronium (0.6 mg/kg); group H: high-dose rocuronium (1.2 mg/kg); T0: before induction; T1: after induction with etomidate/fentanyl; T2: after rocuronium, just before laryngoscopy; T3: 2 min after intubation; T4: 5 min after intubation; PVC: premature ventricular contraction; VT: ventricular tachycardia; PAC: premature atrial contraction. The incidence of dysrhythmias (28% in group C and 24% in group H) was similar (P = 0.5, Fisher's exact two-tailed test).

Table 4. IoC scale (EEG) in groups C and H.

	T0	T1	T2	T3	T4	P
Group C	95 (93-97)*	61 (60-63)*	56 (55-58)	59 (59-61)*	50 (49-53)	0.0001#
Group H	95 (94-96)**	60 (60-62)**	51 (50-51)**	50 (49-51)**	44 (44-46)	0.0001#

Data are reported as median and lower and upper quartile values. IoC is a unitless scale ranging from 99 (awake) to 0 (isoelectric EEG, coma) with a target range of 60-40 recommended by the manufacturer for surgical anesthesia. Group C: conventional-dose rocuronium (0.6 mg/kg); group H: high-dose rocuronium (1.2 mg/kg); T0: before induction; T1: after induction with etomidate/fentanyl; T2: after rocuronium, just before laryngoscopy; T3: 2 min after intubation; T4: 5 min after intubation. #Friedman ANOVA test. *Wilcoxon test with Bonferroni correction, group C: T0 *vs* T1, T2, T3, and T4; T1 *vs* T2, T3, and T4; T3 *vs* T4 (P = 0.00001). **Wilcoxon test with Bonferroni correction, group H: T0 *vs* T1, T2, T3 and T4; T1 *vs* T2, T3, and T4; T2 *vs* T3 and T4; T3 *vs* T4 (P = 0.00001). Groups C and H were significantly different at T2, T3 and T4 (P = 0.0001, Mann-Whitney U test).

administration (T2, immediately before laryngoscopy; P = 0.0001, Table 4). The IoC scale was significantly lower in group H 2 min after laryngoscopy (T3) compared with group C (Table 4). The between-group difference in IoC measurement was maintained until T4, 5 min after intubation.

In a *post hoc* power calculation based on the test statistic comparing QTc intervals between the groups at T0 *vs* T3, this study achieved an actual power of 0.93 with 25 patients in each group.

Discussion

In this study, the effects of NMB with high (1.2 mg/kg) and conventional (0.6 mg/kg) single-dose rocuronium on QTc were similar in patients undergoing coronary artery revascularization surgery while under fentanyl and etomidate anesthesia. In both groups, the greatest prolongation of QTc compared with baseline occurred 2 min after intubation, but the QTc returned to baseline 5 min after intubation. Our findings suggest that the stimulation of intubation itself (rather than the dose of rocuronium used) may have caused the QTc prolongation. In both groups, mean heart rate was significantly increased, and mean arterial pressure was significantly decreased, before and after rocuronium compared with baseline, but these changes did not have negative clinical effects. Dysrhythmias were observed 2 and 5 min after intubation. Patients receiving the higher dose of rocuronium had fewer dysrhythmias than those receiving the conventional dose, but the difference in occurrence was not statistically significant.

A dose of 1.2 mg/kg is typically the highest rocuronium dose used in clinical practice, and was found to be the best dose to prevent electromyographic responses to intubation when compared with lower doses (0.3, 0.6, and 0.9 mg/kg) during general anesthesia with propofol (13). Therefore, we expected that high-dose rocuronium (1.2 mg/kg) would produce a weaker sympathetic response to intubation and have less of an effect on QTc intervals compared with the conventional lower dose (0.6 mg/kg). The only study of the effects of high-dose rocuronium on QTc during induction was conducted by Puhringer et al. (14) in American Society of Anesthesiologists (ASA) status I-III patients during non-cardiac surgery. As in this study, they observed no effect of rocuronium alone on QTc prolongation.

Intubation conditions are related more closely to the degree and time of onset of NMB in the laryngeal adductors, diaphragm, and masseter muscles than in the adductor pollicis muscle (15). Monitoring NMB at different muscles may provide additional information that can be used to effectively prevent hemodynamic responses to intubation despite good or excellent intubation conditions (15-17).

Neuromuscular blocking agents decrease stretch receptor activity in the muscles and thus suppress stimulation input to the arousal centers in the brain (afferentation theory). According to this theory, NMB agents suppress the bispectral index (BIS) and cardiovascular responses to nociceptive stimulation (13,18). In the present study, we intubated patients when they lost responsiveness after having received fentanyl and etomidate, which corresponded to a mean IoC of 55 in our study. The IoC correlated well with BIS, and we encountered no unexpected difficult intubations at this level of anesthesia. Studies state that a BIS value higher than 40 may not provide ideal conditions for intubation, and intraoperative airway complications may occur more frequently due to more pronounced laryngeal reflexes (19,20). The need to maintain hemodynamic stability during induction in patients with coronary artery disease leads us to not seek a low BIS value before intubation. Although high-dose rocuronium provided deeper anesthesia than conventional-dose rocuronium, adequate sympathetic blockade (as measured by hemodynamic values and length of QTc) was not obtained in the high-dose group. Others have reported that rocuronium administration did not affect BIS during steady-state propofol anesthesia in the absence of nociceptive stimulation (18). However, with nociceptive stimulation (laryngoscopy), the increase in BIS in patients who received rocuronium (0.6 mg/kg) was significantly lower than in patients who did not (saline) (18). We performed intubation when the TOF ratio reached zero to prevent the sympathetic response to stimulus before intubation and the large interindividual variation in neuromuscular depression that can occur after administration of NMB agents (15).

In our study, QTc intervals were longer than baseline

at 2 min after intubation and were independent of rocuronium dose, i.e., both doses of rocuronium failed to block the hemodynamic response to intubation. Preexisting myocardial injury in patients about to undergo cardiac surgery may also result in long QT intervals (2,3). QTc prolongation with rocuronium may be related to the extent of coronary artery disease, the extent of myocardial ischemia, and/or the extent of collateral circulation. Approximately 45% of our patients had altered depolarization thresholds at baseline. In our study population, the proportion of patients having long QTc was similar in both groups. We observed ST depression, ventricular extrasystoles, and sustained ventricular tachycardia 2 min after intubation. Dysrhythmias occurred with similar frequency in both groups, but a study with a larger number of patients should be done to determine these frequencies more precisely. Although the proportions of patients with long QTc were similar in the two study groups, future studies of rocuronium effects conducted in larger numbers of coronary artery disease patients will be useful to determine its adverse effects.

Limitations of our study are the small study group sizes and the lack of a placebo group that was not given rocuronium. We believe that the use of larger doses of non-NMB agents in adult patients with a history of cardiac ischemia would be likely to result in clinically unsafe side effects.

In conclusion, intubation provoked increases in QTc, heart rate, and MAP following conventional- and high-dose rocuronium given during induction and intubation of patients about to undergo coronary artery surgery. Anesthesia was induced with etomidate and fentanyl. Dysrhythmias occurred at similar rates in both dosage groups. In both groups, QTc was most prolonged, compared to baseline, 2 min after intubation, suggesting that the QTc prolongation may have been a response to the nociceptive stimulus of intubation. Further controlled studies are needed to assess depolarization thresholds and QTc after high-dose bolus rocuronium in patients with myocardial ischemia.

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