Effects of High-Dose Rocuronium on the QTc Interval During Anaesthesia Induction in Patients Undergoing Coronary Artery Bypass Graft Surgery

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Objective: Existing myocardial damage in coronary artery disease patients causes prolonged QT syndrome. The primary objective of this trial is to explore the effects of different doses of the muscle relaxant agent rocuronium (0.6 mg kg⁻¹ and 1.2 mg kg⁻¹) on QTc following anaesthetic induction. The second objective is to determine the incidence and kinds of arrhythmias.

Methods: In this prospective and randomized trial, patients undergoing elective coronary artery revascularization surgery were included in one of two groups. Both groups took the same anaesthetic induction agents: midazolam and fentanyl. Rocuronium was administered in Group 1 (n=20) with dose of 0.6 mg kg⁻¹ and in Group 2 (n=20) with a dose of 1.2 mg kg⁻¹ for muscle relaxation. Heart rate, average arterial pressure and QTc were recorded before induction (T0), after induction (T1), after muscle relaxant (T2), and 2 minutes (T3) and 5 minutes after intubation (T4).

Results: QTc was significantly longer 2 minutes after intubation (in Group 1 and Group 2, respectively, 447.9±28.3 and 466.1±37.8 ms) than at the beginning (respectively, 426.9±25.7, 432.0±35.5 ms) (p<0.01). In the intergroup comparison, average QTc values were similar in all trial periods (p>0.05). The prevalence of arrhythmias in between Group 1 (35%, n=7) and Group 2 (15%, n=3) was similar (p=0.06). Arrhythmias were recorded 2 minutes after intubation in both groups (n=10, 25%).

Conclusion: In patients undergoing coronary artery revascularization surgery, rocuronium doses of 0.6 mg kg⁻¹ and 1.2 mg kg⁻¹ prolong the QTc interval after intubation. Cardiac arrhythmias related to long QTc arising after intubation should be taken into consideration.

Key Words: Rocuronium, QTc, coronary artery disease

Introduction

Ischemia, and pre-existing myocardial injury and low ejection fraction due to scar tissue lead to prolongation of QT interval in patients with coronary artery disease (1-3). This condition lowers the threshold after depolarization, which is a critical factor for initiating the cardiac rhythm "torsade de pointes" and trigger the events leading to arrhythmia in long QT interval syndrome (4). Mortality rates due to sudden syncope and cardiac arrest increase by 2-5 folds in ischemic cardiac disease patients with long QT interval syndrome (1-3). These circumstances along with the QT interval prolonging effect of induction agents, intubation and hemodynamic conditions may form a basis to severe cardiac arrhythmias during anaesthesia induction (1-6).

In cardiac surgery, while the use of neuromuscular blockers under intense opioid anaesthesia is questionable due to their residual effects, they are necessarily used for providing smooth intubating conditions with stable hemodynamics. Administration of a single high dose of non-depolarizing neuromuscular blocking agent with intermediate onset of action at baseline is considered as a concept in the use of neuromuscular blocking agents in cardiac surgery (7, 8). Rocuronium, frequently used in recent years, is a non-depolarizing neuromuscular blocking agent with intermediate onset of action, which allows for rapid intubation with high doses and can be reversed independent from the number of receptors it blocks. Rapid sequence intubation dose of rocuronium (1.2 mg kg⁻¹) is preferred as it leads to a mild increase in heart beat rate, takes the airway that may be difficult due to chest wall rigidity after high opioid induction in cardiac surgery rapidly under control and as its residual effects are lower due to its activity duration (7, 9). Compared to the other lower doses of rocuronium beginning from 0.3 mg kg⁻¹, a dose of 1.2 mg kg⁻¹ was determined to be the optimal dose that suppresses the electromyographic response to

intubation (10). It was reported that in cases with poor left ventricular function that would undergo coronary artery bypass graft surgery, rocuronium provided a better suppression on the hemodynamic response to intubation, in comparison to other neuromuscular blocking agents (11). To our knowledge, there are no studies in the literature evaluating the effects of any dose of rocuronium on QTc.

The primary aim of this study is to evaluate the effects of two different doses (0.6 mg kg^{-1} and 1.2 mg kg^{-1}) of rocuronium, a neuromuscular blocking agent, on QTc interval after anaesthesia induction with midazolam and fentanyl in patients undergoing coronary artery revascularization, and the secondary aim is to determine the frequency and nature of arrhythmias developed in these cardiac patients.

Methods

This study was performed in the Cardiovascular Surgery operating rooms of Celal Bayar University by the approval of Clinical researches Ethics committee (dated August 2009 number: 0210), between April 2010 and April 2012, as a prospective and double-blind study. The study included 40 cases between the ages of 40 and 75 years that would undergo elective coronary artery revascularization surgery, with low (1-2) or intermediate (3-5) EURO score, after their written informed consents were obtained. Patients with hereditary or acquired long QT interval syndrome or a family history of long QT interval syndrome or a suspicious clinical history, those diagnosed as having severe liver, kidney failure and neuromuscular disease by clinical and laboratory findings, patients with abnormal ECG (atrial fibrillation, right or left bundle branch block), autonomic dysfunction, electrolyte disturbances, those receiving drugs known to prolong the QT interval (tricyclic antidepressants, antiarrhythmics, beta blocker agents, calcium canal blockers), those having signs of difficult intubation in preoperative assessment (mallampati score ≥ 3 , cervical deformities), those with haemodynamic instability, and patients who were intubated before surgery were excluded from the study. Requirement of resuscitation for impaired haemodynamic during anaesthesia induction was accepted as the criterion for withdrawal of the patient from the study.

One night before the surgery, all cases were premedicated with 5 mg diazepam orally. In the operating room, after standard monitoring, including SpO_2 , ECG and NIBP, the electrodes of a 7-channel HOLTER device (DM Software, NV, USA) was placed on the chest in order to record the study data. Heart rhythm was continuously recorded by the device. Recording was discontinued 5 minutes after intubation and surgery was started. In the operating room, vascular access was achieved on both arms by inserting 18-20 gauge cannula and infusion of balanced electrolyte solution (Isolyte S, Eczacıbaşı, Turkey) at a rate of $10\text{-}15 \text{ mL kg}^{-1} \text{ hour}^{-1}$ was initiated. Before induction, 2 mg kg^{-1} of IV midazolam (Dormicum, Roche) was administered. Invasive arterial pressure,

central venous pressure, depth of anaesthesia (BIS, IoC-View, Morpheus medical) and muscular relaxation (TOF-Guarda® SX, Organon) of the patients were monitored.

Before anaesthesia induction, the patients were assigned to one of the two groups by sealed envelope method. Both groups received fentanyl (Fentanyl citrate, Meditera) at a dose of $4 \mu\text{g kg}^{-1}$ and midazolam (Dormicum, Roche) at a dose of 0.1 mg kg^{-1} intravenously. After hypnotic effect was confirmed by loss of eyelash reflex and obtaining BIS values ≤ 60 on BIS monitor, Group 1 received a bolus dose of 0.6 mg kg^{-1} rocuronium (Esmeron, Organon), and Group 2 received a bolus dose of 1.2 mg kg^{-1} rocuronium. Patients were ventilated with 100% O_2 . A train of four (TOF) ratio $\leq 5\%$ on neuromuscular transmission monitor was accepted as the appropriate intubation time. The time between the administration of neuromuscular blocking agent to TOF $\leq 5\%$ was recorded as the intubation duration. After intubation, the quality of intubation was evaluated as good, intermediate and poor and was recorded. The patients were ventilated with 50% O_2 +50% air mixture after intubation. Heart beat rate (HR) and mean arterial pressure (MAP) were recorded at baseline before induction (T0), after induction (loss of eyelash reflex and a BIS ratio of 60%, (T1), after rocuronium, after the use of neuromuscular blocking agents when a TOF ratio of $\leq 5\%$ was achieved (T2), 2 minutes (T3) and 5 minutes (T4) after laryngoscopy and intubation. At the same measurement points, study periods were marked on the continuous recording by pushing the "EVENT" button on the Holter device. Holter recordings were evaluated by a cardiology specialist blinded to the study groups after termination of the study. The mean durations of randomly selected 2 RR interval and QT interval during 1 minute were recorded on each time interval marked on the recording. A heart rate-corrected QT interval (QTc) was calculated by Bazett's formula ($\text{QTc} = \text{QT}/\text{RR}^{1/2}$). A QTc longer than 440 msec was evaluated as long QTc (12). The arrhythmias developed were defined and recorded.

Statistical analysis

Data were evaluated using Statistica for Windows® v6.0 (Stat-Soft Inc., Tulsa, USA) statistical program. The distribution characteristics of the variables were assessed using the Kolmogorov-Smirnov test. Data are presented as mean $\pm$ standard deviation. Comparisons between the groups were performed using the Student-t test for variables showing normal distribution, Mann-Whitney U test for variables showing non-normal distribution and Chi-square test for categorical variables. Intra-group multiple comparisons were performed by Friedman test, and Wilcoxon test with Bonferroni correction was used for paired comparisons. Statistical significance level was accepted at $p = 0.05$. Predictive power of the test statistics was calculated as 0.81, when the difference between mean QTc measured at baseline and T3 was accepted to be significant at a p value of 0.05.

Results

The characteristics of the cases are given in Table 1. The mean rocuronium dose consumed was 46.3 ± 8.9 mg in Group 1, and 90.3 ± 6.4 mg in Group 2. The mean duration of intubation was significantly shorter in Group 2 than that of Group 1 (97.7 ± 13.3 sec. and 112.5 ± 12.6 sec., respectively; $p < 0.001$). Quality of intubation was similar in the groups (Table 2). The mean midazolam and fentanyl doses are given in Table 2.

The mean changes observed in the heart rate of the groups at the measurement time points are presented in Table 3. Intra-group comparisons in Group 1 and Group 2 revealed a statistically significant difference ($p < 0.001$). When the dependent variables measured at different time points was compared using paired comparisons within the groups using Wilcoxon test, and the significance level was corrected by Bonferroni test, the mean HR recorded after the use of induction agents (T1) (67.1 ± 10.7 beats min^{-1}) and after the use neuromuscular blocking agent (T2) (65.7 ± 10.2 beats min^{-1}) was significantly lower than the baseline (T0) values (76.3 ± 13.2 beats min^{-1}) in Group 1 ($p < 0.001$). The mean heart rate recorded after neuromuscular blocking agent (T2) was significantly lower than the baseline HR (T0), HR recorded after induction (T1) and 2 minutes after intubation (T3) ($p < 0.01$) in Group 2 (Table 3). Inter-group comparison revealed no significant difference between the groups in terms of mean heart rate ($p > 0.05$) (Table 3).

Mean arterial pressure measured in the study groups are presented in Table 3. Intra-group comparisons in the groups revealed a statistically significant difference ($p < 0.0001$). When dependent variables were compared by paired comparisons within the groups, the mean arterial pressure measured after the use of induction agents (T1), after the use of neuromuscular blocking agent (T2) and at 5 minutes after intubation (T4) were significantly lower in comparison to mean arte-

Table 1. Characteristics of the study groups

Demographic data	Group 1 n: 20	Group 2 n: 20
Age (years)	64.2 ± 7.1	61.8 ± 8.4
Gender (F/M, n)	5/15	6/14
BSA	1.7 ± 0.3	1.6 ± 0.4
EF %	56.2 ± 4.4	55.2 ± 6.3
Euroscore	5.0 ± 1.3	5.0 ± 1.5
Concomitant disease	(n)	(n)
HT	9	8
Hyperlipidaemia	5	6
COPD	2	2
DM	3	2
Drug use	(n)	(n)
ACE inhibitor	8	6
AT2	2	4

Data are presented as mean $\pm$ standard deviation. BSA: body surface area; EF: ejection fraction; HT: hypertension; COPD: Chronic obstructive pulmonary disease; DM: diabetes mellitus; ACE: angiotensin converting enzyme inhibitor; AT2: angiotensin 2 receptor blocker

Table 2. Intubation duration and intubation quality and mean drug consumption in the groups

	Group 1 n: 20	Group 2 n: 20	p
Intubation duration (TOF ≤ 5 sec)	112.5 ± 12.6	97.7 ± 13.3	$< 0.001^{\S}$
Intubation quality (good/intermediate)	18 / 2	20 / 1	0.1
Midazolam (mg)	6.1 ± 0.5	5.8 ± 0.9	
Fentanyl (mg)	0.36 ± 0.1	0.37 ± 0.1	

$^{\S}p < 0.05$: significance with student's t test. Data are presented as mean $\pm$ standard deviation. TOF: Train of four

Table 3. Inter-group and intra-group comparisons of mean heart rate (HR, beats min^{-1}) and mean arterial pressure (MAP, mmHg) measured at different time points in Group 1 and Group 2

	T0	T1	T2	T3	T4	p
HR						
Group 1	76.3 ± 13.2	$67.1 \pm 10.7^*$	$65.7 \pm 10.2^*$	73.3 ± 14.5	70.7 ± 13.6	$< 0.001^{\#}$
Group 2	77.8 ± 14.9	74.4 ± 11.0	$66.8 \pm 14.4^{\S}$	$79.2 \pm 13.1^{\S}$	70.3 ± 15.6	$< 0.0001^{\#}$
*CBG	0.7	0.09	0.5	0.2	0.7	
MAP						
Group 1	90.9 ± 10.5	$84.1 \pm 12.4^*$	$72.9 \pm 9.7^*$	$85.3 \pm 13.6^*$	$75.3 \pm 13.0^*$	$< 0.0001^{\#}$
Group 2	95.7 ± 11.6	$91.4 \pm 10.5^{\S}$	$76.2 \pm 11.1^{\S}$	$90.6 \pm 14.5^{\S}$	$73.6 \pm 12.1^{\S}$	$< 0.0001^{\#}$
*CBG	0.2	0.1	0.4	0.4	0.3	

$^{\#}$ Friedman test. * Wilcoxon test with Bonferroni correction (MAP, Group 1): comparison of T0 and T1 ($p < 0.01$) and comparison of T0 and T2 ($p < 0.001$), comparison of T0 and T4 ($p < 0.01$), comparison of T1 and T2 ($p < 0.01$), comparisons of T2 and T3 and T3 and T4 ($p < 0.03$). § Wilcoxon test with Bonferroni correction (MAP, Group 2): comparison of T0 and T1 ($p = 0.03$); comparisons of T0 and T2 and T0 and T4 ($p < 0.001$), comparison of T1 and T2 ($p < 0.01$), comparisons of T2 and T3 and T3 and T4 ($p < 0.001$). MAP: mean arterial pressure, mmHg; *CBG: comparison between the groups; Mann-Whitney U test. T0: baseline values; T1: after induction; T2: after rocuronium administration; T3: 2 minutes after laryngoscopy; T4: 5 minutes after laryngoscopy

Table 4. Comparison of mean QTc durations (msec) at different points between the groups

	T0 (msec)	T1 (msec)	T2 (msec)	T3 (msec)	T4 (msec)	p
Group 1 (n:20)	426.9±25.7	428.4±42.7	434.3±25.4	447.9±28.3*	434.5±23.1	<0.01 [#]
Group 2 (n:20)	432.0±35.5	430.4±44.3	426.2±42.4	466.1±37.8 ^s	450.1±44.9	
*CBG	0.2	0.1	0.7	0.4	0.4	<0.0001 [#]

[#]Friedman test; * Wilcoxon test with Bonferroni correction (Group 1): comparison of T0 and T3 (p<0.01). ^sWilcoxon test with Bonferroni correction (Group 2): comparison of T0 and T3 (p=0.01); comparison of T1 and T3 (p=0.02), comparison of T2 and T3 (p<0.02). *CBG: comparison between the groups; Mann-Witney U test; T0: baseline values; T1: after induction; T2: after rocuronium administration; T3: 2 minutes after laryngoscopy; T4: 5 minutes after laryngoscopy

rial pressure measured at baseline (T0) in both Group 1 and Group 2 (p<0.03) (Table 3). Mean arterial pressure measured at 2 minutes after intubation (T3) was significantly higher than that of measured before intubation (T2) in both groups (p<0.03) (Table 3). Also, both in Group 1 and in Group 2, mean arterial pressure measured at 5 min after intubation (T4) was significantly lower than the values at 2 min after intubation (T3) (p<0.03) (Table 3). Inter-group comparisons revealed no statistically significant difference in the mean arterial pressures of the groups (p>0.05) (Table 3).

The mean QTc values at baseline were similar in Group 1 and Group 2 (Table 4). Baseline QTc interval was long in 8 cases in Group 1, and in 10 cases in Group 2 (range, 445 msec -477 msec). Intra-group comparisons revealed significant differences in Group 1 and Group 2 (p<0.01 and p<0.0001, respectively). When the dependent variables measured at measurements time points were compared within the groups, mean QTc values at 2 minutes after intubation (T3) were found to be significantly longer compared to baseline values in both Group 1 and Group 2 (T0) (Table 4). In inter-group comparisons, there was no significant difference between the groups in terms of mean QTc values (p>0.05) (Table 4).

The types and frequency of rhythm disorders in the study groups observed at different measurement time points are shown in Table 5. Arrhythmia frequency was similar in Group 1 (35%, n=7) and Group 2 (15%, n=3) (p=0.06). Arrhythmias (n=10, 25%) developed in the time period until 2 minutes after intubation in both groups and continued during the study period. In Group 1, 1 of the cases developed nonsustained ventricular tachycardia (noncontinuous, 3 or more consecutive ventricular premature beats, self-terminating within 30 seconds). ST depression was observed 2 minutes after intubation in 2 cases in Group 1. Two cases in Group 2 had premature atrial contractions at baseline, which continued during the study period without addition of a new arrhythmia.

Among patients with cardiac rhythm disturbances, 2 cases in Group 1 and 2 cases in Group 2 had long QTc after intubation (p=0.4). On the other hand, 5 patients in Group 1 and 3 cases in group 2 did not have long QTc after intubation. Arrhythmia developed during the study period did not cause hemodynamic problems and not required any treatment.

Table 5. Types of arrhythmias developed at different time points during the study according to study groups

	T0	T1	T2	T3	T4
Group 1 (n:20)					
VPB (n)				4	4
Nonsustained VT(n)				1	1
ST depression				2	2
Group 2 (n:20)					
VPB (n)				2	2
APB (n)	2	2	2	2	2
SA block (n)				1	1

VPB: ventricular premature beats; VT: ventricular tachycardia; APB: atrial premature beats; SAB: sinoatrial block; T0: baseline values; T1: after induction; T2: after rocuronium administration; T3: 2 minutes after laryngoscopy; T4: 5 minutes after laryngoscopy

Discussion

This study, in which rapid sequence intubation dose of rocuronium (1.2 mg kg⁻¹), a neuromuscular blocking agent, was compared with a dose of 0.6 mg kg⁻¹, in patients undergoing coronary artery revascularization under midazolam and fentanyl anaesthesia, found that QTc interval was not significantly changed by both doses. With both doses of rocuronium, QTc duration at 2 minutes after intubation was significantly prolonged in comparison with the baseline value. Duration of QTc interval returned to baseline values at 5 minutes after intubation in both Group 1 and Group 2. Arrhythmias developed at 2 minutes after intubation and continued during the study period. Rocuronium at a dose of 1.2 mg kg⁻¹ caused lower frequency of arrhythmia; however, there was no statistically significant difference between the groups.

Rapid sequence intubation dose of rocuronium, which is 1.2 mg kg⁻¹, is preferred as it leads to a mild increase in heart rate, takes the airway, which may be difficult due to chest wall rigidity after opioid induction in cardiac surgery, rapidly under control, and has lower residual effects (7). In comparison to the other lower doses of rocuronium beginning from 0.3 mg kg⁻¹, a dose of 1.2 mg kg⁻¹ was determined to be the optimal dose that suppresses the electromyographic response to intubation (10) Likewise, in our study, rocuronium at a dose of 1.2 mg kg⁻¹, was expected not to prolong QTc after intubation. In our study, both 1.2 mg kg⁻¹ and 0.6 mg kg⁻¹

doses of rocuronium led to similar changes in QTc interval during intubation. This study is the first that has evaluated the effects of rocuronium intubation doses on QTc. There are a limited number of studies that have examined the effects of different doses sugammadex, an agent used for reversing the effects of Rocuronium, on QTc (13, 14).

In ASA I-II patients undergoing extra-cardiac surgery, the effects of using depolarizing and non-depolarizing neuromuscular blocking agents with induction agents on QT and hemodynamic changes, have been widely studied (9, 15-17). There are also various studies on cardiac patients (2, 3, 18, 19). In our study, both 1.2 mg kg⁻¹ and 0.6 mg kg⁻¹ intubation doses of rocuronium, prolonged the QTc interval after 2 minutes of intubation or in other words, rocuronium at both doses was not able to prevent the prolongation of QTc interval during intubation. The QT interval returned to baseline values in 2 minutes. Similar to our study, when thiopentone or etomidate has been used together with vecuronium in coronary artery patients, QT dispersion is not changed; however, QT dispersion after intubation is prolonged (2). Contrary to our study, anaesthesia induction using fentanyl and vecuronium in coronary artery patients statistically significantly prolonged the QTc interval, and by the addition of hypnotics (etomidate, midazolam and propofol) the duration of QTc was further prolonged, while intubation shortened the QTc interval (3). Another study, in which morphine, midazolam and thiopentone were used along with vecuronium (0.1 mg kg⁻¹) or rocuronium (0.6 mg kg⁻¹) in cases with poor left ventricular ejection fraction, found that rocuronium provided better intubation conditions than vecuronium and haemodynamic changes were similar with both agents (18).

Intubation itself raises the heart rate, blood pressure and catecholamine levels and lead to prolonged QTc interval and prominent U waves (19). In the present study, independent from the dose of rocuronium administered, the duration of QTc was prolonged after intubation. Rocuronium, at both doses, did not attenuate the response to intubation. Again, pre-existing myocardial damage in cardiac surgery patients may also cause long QT interval (1-3). Overall, 45% (n=18) of the present cases undergoing coronary artery revascularization had a prolonged QTc interval at baseline.

Laryngoscopy and intubation, causing catecholamine release from adrenal medulla and adrenergic nerve ends increase heart rate and systemic arterial pressure and lead to arrhythmias (10). The arrhythmias that were observed in the present study including ST depression, ventricular premature beats and nonsustained ventricular tachycardia, were arrhythmias which may lead to severe haemodynamic impairment in ischemic heart disease cases. All arrhythmias observed in our cases developed in the period until 2 minutes after intubation. The rate of arrhythmias after intubation was lower in the group which received rocuronium at a dose of 1.2 mg kg⁻¹ in our study; however, the difference between the study

groups was not statistically significant (p=0.06). We are in the opinion that, new studies with large number of patients will clear the statistical relation between arrhythmia incidence and rocuronium intubation dose. In addition, although the distribution of cases with long QTc was similar between the groups in our study, another controlled study including coronary artery patients with long QTc evaluating the effects of high doses of rocuronium on QTc, will be valuable to show the specific aspects of our study.

In our study, fentanyl (4 µg kg⁻¹) and midazolam (0.1 mg kg⁻¹) were the drugs that were both used in the two study groups. These agents did not alter QTc interval during anaesthesia induction in both groups; however, HR and MAP of the cases decreased after induction and neuromuscular blocking agent use. The decrease in heart rate and mean arterial pressure is due to suppression of adrenergic stimuli by these agents (20, 21). It has been reported that fentanyl (2 µg kg⁻¹), when used together with propofol and cisatracurium in ASA I-II cases, inhibits QTc prolongation immediately developed after intubation more effectively than remifentanyl (22). The difference in patient characteristics and induction agents may have led to the difference in our outcomes. Similar to our study, in ASA I-II cases without cardiac disease, anaesthesia induction using midazolam (0.4 mg kg⁻¹) or propofol (2 mg kg⁻¹) did not lead to prolongation of QTc, but significant QT prolongation was observed after suxamethonium use and intubation (16).

Conclusion

Conclusively, both 0.6 mg kg⁻¹ and 1.2 mg kg⁻¹ doses of rocuronium led to prolonged QTc interval after intubation in patients undergoing coronary artery revascularization during midazolam and fentanyl induction. We suggest that the fact that arrhythmias associated with long QTc interval may develop after intubation by both doses of rocuronium should be taken into account.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Celal Bayar University Clinical Research Ethics Committee.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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