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Evaluation of QT Interval of Patients Using Muscle Relaxants Under General Anesthesia, Randomized Clinical Trial

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Research Article

History

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ABSTRACT

Objective: The aim of the study was to investigate the effects of rocuronium, mivacurium, and atracurium on arrhythmia markers, QT interval, and QT dispersion (QTd).
Method: Ninety patients scheduled for septorhinoplasty were randomly assigned to one of three groups of 30. During the induction of anesthesia, muscle relaxants of 0.6 mg/kg rocuronium in Group R, 0.2 mg/kg mivacurium in Group M, and 0.5 mg/kg atracurium in Group A were employed. Mean blood pressure (MAP), heart rate (HR), and electrocardiogram (ECG) values were measured before induction of anesthesia (T0), immediately after induction of anesthesia (T1), at 1 minute (T2), 5 minutes (T3), 10 minutes (T4) and 15 minutes (T5) after muscle relaxant administration, and QT, corrected QT (QTc), QTd and corrected QTd (QTcd) intervals were recorded.
Results: When the groups were compared in terms of QTcd values, the difference between mivacurium and atracurium was significant in terms of T5 values, and atracurium (T5) QTcd was found to be shorter ($p<0.05$). Group M had 5 of the 6 measures with pathological QTc prolongation.
Conclusions: Because the prevalence of pathological QTc is greater in mivacurium, further clinical trials should be conducted to challenge the use of mivacurium in individuals with a long QT interval.

Keywords: Atracurium, electrocardiography, mivacurium, rocuronium, hemodynamics, qt interval.

Genel Anestezi Altında Kas Gevşetici Kullanılan Hastaların QT İntervalinin Değerlendirilmesi, Randomize Klinik Çalışma

Süreç

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ÖZ

Amaç: Genel anestezi indüksiyonunda kullanılan kas gevşeticilerden roküronyum, mivaküryum ve atraküryum'un aritmi belirteçleri olan QT intervali ve QT dispersiyonu (QTd) üzerine etkilerini araştırmak amaçlandı.
Yöntem: Çalışmada septorinoplasti planlanan 90 hasta rastgele 30'ar kişilik 3 gruba ayrıldı. Anestezi indüksiyonunda kas gevşetici ajan olarak Grup R'de 0,6 mg/kg roküronyum, Grup M'de 0,2 mg/kg mivaküryum ve Grup A'da 0,5 mg/kg atraküryum kullanıldı. Anestezi indüksiyonu öncesinde (T0), anestezi indüksiyonundan hemen sonra (T1), kas gevşetici uygulamasından sonraki 1. dakikada (T2), 5. dakikada (T3), 10. dakikada (T4) ve 15. dakikada (T5) ortalama kan basıncı (OKB), kalp atım hızı (KAH), ve aynı zamanlarda elektrokardiyogram (EKG) kaydı alınarak QT, düzeltilmiş QT (QTc), QTd ve düzeltilmiş QTd (QTcd) intervalleri kaydedildi.
Bulgular: Gruplar QTcd değerleri yönünden karşılaştırıldıklarında T5 değerleri açısından mivaküryum ile atraküryum arası fark önemli bulunmuş; atraküryum (T5) QTcd si daha kısa tespit edilmiştir ($p<0.05$). Patolojik QTc uzaması görülen 6 ölçümün 5'i Grup M'de idi.
Sonuç: Patolojik QTc görülme sıklığı mivaküryumda daha yüksek bulunduğundan QT intervali uzun olan hastalarda mivaküryum tercihi daha çok klinik çalışma ile sorgulanmalıdır.

Anahtar sözcükler: Roküronyum, mivaküryum, atraküryum, elektrokardiyografi, hemodinami, qt interval.

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Introduction

Cardiac arrhythmias are frequently encountered complications in patients under anesthesia and are commonly blamed for mortality. Many medications and factors, including electrolyte imbalances, prolonged congenital or acquired QT syndrome, sympathetic nervous system activation, and general and local anesthetics, can induce arrhythmias in anesthesia patients [1, 2].

Acquired QT prolongation can occur as a result of cardiac or nervous system diseases, heat, electrolyte, endocrine, and metabolic distortions, or the use of pharmaceutical drugs [3, 4]. It has been reported that a long QT interval may be responsible for ventricular arrhythmias and unexpected demise [5, 6, 7]. According to heart rate, a corrected QT (QTc) time exceeding 440 msn is considered pathological [8]. It is unusual for the QTc interval to be longer than 440 ms in men and 450 ms in women [9]. The QT interval represents the time it takes for the ventricle to repolarize on an electrocardiogram (ECG). Prolonged QT intervals can be utilized to help determine cardiac repolarization anomalies and arrhythmia risk [5].

Anesthesia induction, laryngoscopy, and endotracheal intubation lead to a significant stimulation of sympathoadrenal activity. As a result of sympathetic stimulation, hypertension, tachycardia, and arrhythmia may occur. Tachycardia increases myocardial oxygen demand while decreasing diastolic filling, thus preventing efficient coronary flow. According to several publications, there is a direct relationship between elevated catecholamine levels in the plasma during sympathetic activity and the QT interval [10, 11]. The effects of inhalation and intravenous anesthetic agents on the QT interval have been studied in both national and international research. However, the effects of muscle relaxants, which are commonly used in anesthesia and surgery, on the QT interval have not been studied in our country. In contrast, the impact of only 1 or 2 muscle relaxant agents was examined in 1 or 2 studies published abroad. This study will investigate the effects of routinely administered muscle relaxants on the risk of arrhythmia in anesthetized patients. The aim of the study is to examine the effects of muscle relaxants (such as rocuronium, mivacurium, and atracurium, etc.) that are commonly used in anesthesia to provide laryngoscopy and an appropriate surgical environment on QT interval and QT dispersion (QTd), which are arrhythmia reagents.

Material and Methods

Ninety patients with ASA I-II between the ages of 18 and 50 who were scheduled for septorhinoplasty under general anesthesia were included in the study after receiving approval from the local ethics committee with decision number 2017-02/07. This research was designed in accordance with the Helsinki Declaration.

Patients with known allergies and sensitivities to these drugs, any known cardiac disease, anticholinergic, antiarrhythmic, vasopressor, vasodilator, and hypotensive drugs, electrolyte imbalance, unstable hemodynamics, and patients with acquired or congenital long QT syndrome were excluded from the study. Furthermore, patients whose consent could not be obtained or whose consent was not given by their relatives were not included in the study. Patients who had hemodynamic instability and required endotracheal tube replacement during the study, and those who required anticholinergic, antiarrhythmic, vasopressor, and vasodilator drugs, were excluded from the study even if they were included.

Randomization was made by using closed envelop method. The whole procedures for general anesthesia and measurements were made by the same anesthesist who is blind for all groups.

Vascular access was established, and a 0.9% NaCl infusion was started at 10 ml/kg/h for the first hour, followed by 5 ml/kg/h for the next hour. For preoxygenation, 100% O2 (oxygen) was applied for 3 minutes. In our clinic, standardly 1 mcg/kg fentanyl, and 2-3 mg/kg propofol were given intravenously (iv) for anesthesia induction. Muscle relaxants of 0.6 mg/kg rocuronium in Group R, 0.2 mg/kg mivacurium in Group M, and 0.5 mg/kg atracurium in Group A were employed. For maintenance, 1.5-2.5% sevoflurane in 50% O_2/nitrogen oxide (N_2O) mixture was used. Following standard anesthesia induction, a muscle relaxant agent (rocuronium, mivacurium, or atracurium) was used to provide adequate depth of anesthesia and muscle relaxation, and mechanical ventilation was used to provide respiratory support to patients who had been intubated with the appropriate endotracheal tube. Following that, anesthesia was maintained.

The patients who were operated under general anesthesia were taken to the operating table, and after respiratory and cardiac monitoring were provided, 12-lead ECGs were taken, as well as systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MAP), heart rate (HR), and peripheral oxygen saturation (SpO_2) values. These values were taken as the baseline (T0). The same measurements were taken immediately after anesthesia induction (T1), and at the 1st minute (T2), 5th minute (T3), 10th minute (T4), and 15th minute (T5) after muscle relaxant administration. During the procedure, ECG (ST-T change, arrhythmia, etc.) changes were also recorded.

ECG recordings were performed at a height of 1 mV and a speed of 25 mm/s. The longest QT distance was measured among all leads in the ECG recordings by two anesthetists who did not know the groups, and the RR distance was measured in the same lead. Bazet's formula was used to calculate the QTc (corrected QT) distance:

QTc=QT interval / √ RR interval

The values of calculated QT, corrected QT (QTc), QT dispersion (QTd), and corrected QT dispersion (QTcd) were recorded. Male patients with QT and QTc intervals greater than 440 ms and female patients with QT intervals greater than 450 ms were classified as pathological. QTd and QTcd intervals of 30-60 msn were regarded as normal. Rather than these durations, QTd and QTcd measurements were thought to be pathological.

When the parametric test assumptions in the data evaluation are met by loading the data from our study into

the SPSS (Ver:22;0) program, the analysis of variance (Kolmogorov-Smirnov), Tukey Test, and Chi-Square test was used to evaluate the data obtained by counting, and the error level was set at 0.05 by stating our data in the tables as the arithmetic mean, standard deviation, number of individuals, and percentage.

Results

The present study included 90 patients. 41 of the patients were female, while 49 were male. Group R had 17 females and 13 males, Group M had 10 females and 20 males, and Group A had 14 females and 16 males. Mean age values were 27.86 ± 7,54 in Group R, 28.13 ± 9,11 in Group M, 27.26 ± 8,54 in Group A (p>0.05).

When the HR values at T1, T3, T4, and T5 were compared, it was discovered that the difference between the groups was statistically significant (p=0.01, p=0.01, p=0.01). When MAP values from different times were compared, the difference between groups was found to be insignificant (p>0.05).

When the (T0)QT, (T1)QT, (T2)QT measurements of the groups were compared, the difference between groups was found to be non-significant (p>0.05). When the (T3)QT, (T4)QT, (T5)QT measurements of the groups were compared, a significant (p0.05) difference was found (Table 1).

When the (T0)QTc, (T1)QTc, (T2)QTc, (T3)QTc, (T4)QTc, (T5)QTc measurements of the groups were compared, the difference between groups was found to be insignificant (p>0.05) (see Figure 1).

When the (T0)QTd, (T1)QTd, (T2)QTd, (T3)QTd, (T4)QTd, (T5)QTd measurements of the groups were compared, the difference between groups was found to be insignificant (p>0.05) (Figure 2).

When the (T0)QTcd, (T1)QTcd, (T2)QTcd, (T3)QTcd, (T4)QTcd measurements of the groups were compared, the difference between groups was found to be insignificant (p>0.05). When the (T5)QTcds were compared, a significant difference (p<0.05) was found (Figure 3).

When the (T5)QTcd values of the groups were compared in pairs, the difference between Mivacurium and Atracurium was found to be significant (p<0.05), while the difference between the other groups was found to be insignificant (p>0.05) (Figure 3).

When the QT measurements taken at different times in Group R, Group M, and Group A were compared, the difference in measurements was found to be significant (p<0.05) (Table 2).

When the QTc measurements taken at different times in Group R, Group M, and Group A were compared, the difference in measurements was found to be significant (p<0.05) (Table 3).

Table 1. Demographic data of the patients.

Demographic data		Group R	Group M	Group A	p
Age (year) (mean±SD)		27.86 ± 7.54	28.13 ± 9,11	27.26 ± 8.54	p>0.05
Gender (Female/Male)	n	17 / 13	10 / 20	14 / 16	p>0.05
	%	56.7 / 43.3	30 / 70	46.7 / 56,3	
ASA	I	18 (%60)	26 (%86.7)	19 (%63.3)	p>0.05
	II	12 (%40)	4 (%13.3)	11 (%26.7)	
Surgery type	Rhinoplasty	16 (%53,3)	21 (%70.0)	16 (%53.3)	p>0.05
	Septoplasty	14 (%46.7)	9 (%30.0)	14 (%46.7)	

p>0.05: statistically insignificant, SD: standard deviation, n: number of the patients, ASA: American Society of Anesthesiologists risk classification

Table 2. Intragroup comparison of QT interval values measured at different times.

		HR		MAP			
Time of measurement	Groups	Mean (/minute)	SD(±)	Mean (mmHg)	SD(±)	p for HR	p for MAP
T0	Group R	82.16	10.46	93.63	9,73	0.098	0.666
	Group M	81.13	11.13	94.90	9,14		
	Group A	76.73	8.97	95.93	10.66		
T1	Group R	86.60	11.92	90.33	10.85	0.001*	0.560
	Group M	87.66	11.57	87.13	13.32		
	Group A	78.13	12.38	87.93	11.47		
T2	Group R	82.96	15.15	81.80	10.42	0.353	0.264
	Group M	84.23	13.74	77.96	11.68		
	Group A	79.43	10.47	82.60	12.75		
T3	Group R	83.36	13.08	86.33	13.01	0.001*	0.888
	Group M	87.13	13.66	86.33	15.37		
	Group A	77.00	10.17	84.76	13.04		
T4	Group R	82.86	13.66	86.43	11.73	0.001*	0.628
	Group M	88.70	15.62	89.63	14.52		
	Group A	75.90	14.08	88.46	12.52		
T5	Group R	83.43	14.48	81.30	10.78	0.001*	0.178
	Group M	85.36	12.14	83.26	12.21		
	Group A	72.76	13.25	86.73	10.79		

*p<0.05: statistically insignificant, SD: standard deviation, HR: heart rate, MAP: mean arterial pressure

Table 3. Intragroup comparison of QTc values measured at different times.

Time of measurement	Groups	Mean (millisecond)	SD (±)	p
T0	Group R	368.86	15.78	0.154
	Group M	367.46	19.34	
	Group A	375.36	14.56	
T1	Group R	371.56	22.44	0.073
	Group M	364.63	25.41	
	Group A	378.46	21.12	
T2	Group R	383.56	27.13	0.386
	Group M	379.46	25.05	
	Group A	388.13	19.79	
T3	Group R	383.30	21.29	0.049*
	Group M	376.63	27.42	
	Group A	390.83	18.58	
T4	Group R	387.13	21.62	0.004*
	Group M	374.80	27.93	
	Group A	395.63	21.41	
T5	Group R	387.43	25.89	0.002*
	Group M	377.93	24.66	
	Group A	401.13	21.63	

SD: standard deviation

Table 4. Intragroup comparison of QT interval values measured at different times.

Groups	Time of measurement	Mean (millisecond)	SD(±)	p
Group R	T0	368.86	15.78	0.001*
	T1	371.56	22.44	
	T2	383.56	27.13	
	T3	383.30	21.29	
	T4	387.13	21.62	
	T5	387.43	25.89	
Group M	T0	367.46	19.34	0.001*
	T1	364.63	25.41	
	T2	379.46	25.05	
	T3	376.63	27.42	
	T4	374.80	27.93	
	T5	377.93	24.66	
Group A	T0	375.36	14.56	0.001*
	T1	378.46	21.12	
	T2	388.13	19.79	
	T3	390.83	18.58	
	T4	395.63	21.41	
	T5	401.13	21.63	

SD: standard deviation

Table 5. Intragroup comparison of QTc values measured at different times.

Groups	Time of measurement	Mean (millisecond)	SD (±)	p
Group R	T0	404.96	10.42	0.001*
	T1	413.83	18.27	
	T2	419.66	17.02	
	T3	422.63	15.72	
	T4	424.03	13.48	
	T5	424.16	13.38	
Group M	T0	403.03	20.22	0.001*
	T1	408.16	22.31	
	T2	418.36	25.97	
	T3	423.30	21.49	
	T4	421.16	25.13	
	T5	418.56	20.43	
Group A	T0	405.30	12.97	0.001*
	T1	409.30	19.43	
	T2	421.43	13.93	
	T3	420.73	12.59	
	T4	422.70	13.70	
	T5	423.46	15.11	

SD: standard deviation

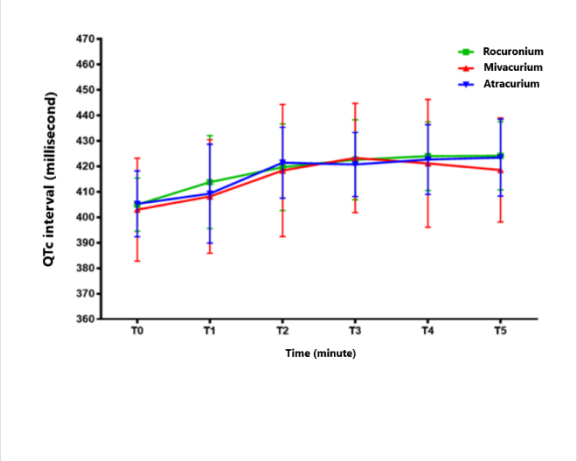

Figure 1. QTc intervals of the groups according to time

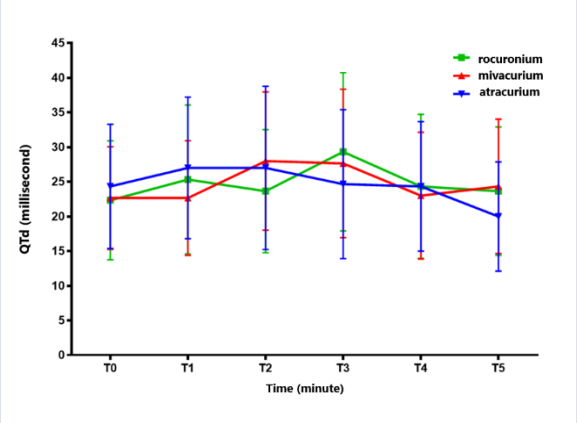

Figure 2. QTd values of the groups according to time.

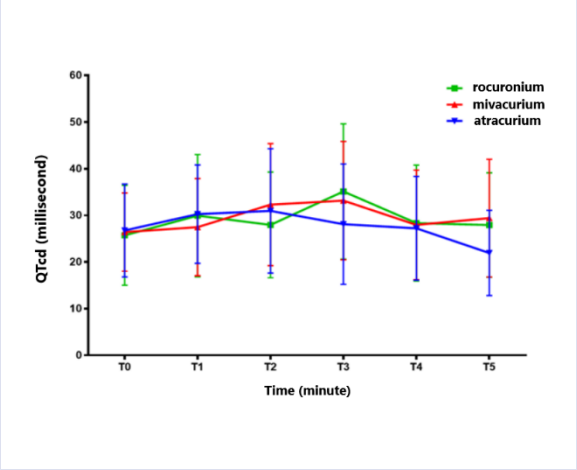

Figure 3. QTcd values of the groups according to time

When the QTd and Qtcd values from Group R, Group M, and Group A were compared, the difference between the groups was found to be insignificant (p>0.05).

QT;

The presence of QT prolongation (pathological) was not observed in all groups (100%).

Those who have pathological QTc prolongation;

(T2) QTc;

The presence of QTc prolongation (pathological) was not observed in Group R. (100%). The presence of QTc prolongation (pathological) was observed in one individual in Group M (3.3%). The presence of QTc prolongation (pathological) was not observed in group A.

(T3) QTc;

The presence of QTc prolongation (pathological) was observed in one individual in Group R (3.3%). The presence of QTc prolongation (pathological) was observed in two individuals in Group M (6.7%). The presence of QTc prolongation (pathological) was not observed in group A.

(T4) QTc;

The presence of QTc prolongation (pathological) was not observed in Group R. (100%). The presence of QTc prolongation (pathological) was observed in one individual in Group M (3.3%). The presence of QTc prolongation (pathological) was not observed in group A.

(T5) QTc;

The presence of QTc prolongation (pathological) was not observed in Group R. The presence of QTc prolongation (pathological) was observed in one individual in Group M (3.3%). The presence of QTc prolongation (pathological) was not observed in group A.

Those who have pathological QTd prolongation;

(T2) QTd;

The presence of QTd prolongation (pathological) was not observed in Group R. The presence of QTd prolongation (pathological) was not observed in Group M. The presence of QTd prolongation (pathological) was observed in one individual in Group A (3.3%).

(T3) QTd;

The presence of QTd prolongation (pathological) was observed in one individual in Group R (3.3%). The presence of QTd prolongation (pathological) was not observed in Group M. The presence of QTd prolongation (pathological) was not observed in Group A.

Those who have pathological QTcd prolongation;

(T2) QTcd;

The presence of QTcd prolongation (pathological) was observed in one individual in Group R (3.3%). The presence of QTcd prolongation (pathological) was observed in one individual in Group M (3.3%). The presence of QTcd prolongation (pathological) was observed in two individuals in Group A (6.7%).

(T3) QTcd;

The presence of QTcd prolongation (pathological) was observed in two individuals in Group R (6.7%). The presence of QTcd prolongation (pathological) was not observed in Group M and Group A.

There was no arrhythmia in the baseline ECGs of any of the patients in the study. Sinus arrhythmia was observed in T1 ECGs in three patients in Group R, but not in the other groups (p0.05). Sinus arrhythmia was observed in 1 patient in Group A in T2, 1 patient in Group M in T3, and 1 patient in Group M in T4, but these findings were not statistically significant (p>0.05). Sinus arrhythmia was observed in 3 patients in Group M in T5, which was statistically significant (p<0.05).

Discussion

QT, QTc, QTd, and QTcd values were measured at six different times in patients receiving rocuronium, mivacurium, and atracurium as muscle relaxants under general anesthesia, and the relationship between these values and ventricular dysrhythmias was attempted to be determined. The presence of QT prolongation did not reach pathological limits in any of the patients as a result of the study. In six patients, QTc prolongation was found to be pathological (5 in Group M, 1 in Group R). In two patients, the QTd value was found to be pathological (1 in Group R, 1 in Group A). In six patients, the QTcd value was found to be pathological (3 in Group R, 2 in Group A, 1 in Group M). Despite these facts, no patient developed ventricular dysrhythmia. Intraoperative sinus arrhythmia developed in 8 people who were not the same as the people who had pathological QTc, QTd, and QTcd prolongation, despite the fact that their baseline ECGs showed no arrhythmia. The intraoperative normal rhythm was restored in these patients without the need for any intervention or treatment, and there were no perioperative cardiac complications. There was no study in the literature that looked at the effects of three muscle relaxants on QT intervals. That's why the present study is so significant

There are studies looking into the effects of sedative agents other than muscle relaxants such as midazolam, dexmedetomidine, opioids, and volatile anesthetics on QT [12, 13, 14, 15]. In their study on the effects of propofol, midazolam, and dexmedetomidine used for sedation in the intensive care unit on the QT interval, Avci et al. concluded that midazolam and dexmedetomidine prolong the QT interval and that propofol infusion can be used more safely in the intensive care unit in terms of QT prolongation [12].

In the study conducted by Safaeian et al., one group of pediatric patients received propofol anesthesia induction, while the other group received sevoflurane anesthesia induction. Sevoflurane was found to prolong the QT in the measurements, whereas propofol was found to be safer in terms of QT prolongation in anesthesia induction [13]. Chang et al. revealed that anesthesia induction with propofol and fentanyl is safe in terms of the risk of QT interval prolongation [15]. Following these studies in the literature, we used propofol and fentanyl in the induction of anesthesia in the individuals included in the study, which have minimal effects on the QT interval.

Agdanli et al. examined the effects of high dose rocuronium on QTc during anesthesia induction in patients undergoing coronary artery surgery, using midazolam and fentanyl as induction agents. Individuals in Group 1 were intubated with 0.6 mg/kg rocuronium and 1.2 mg/kg rocuronium in Group 2. Before induction (T0), after induction (T1), after rocuronium (T2), at 2 minutes (T3), and 5 minutes after intubation, HR, MAP, and QTc values were recorded (T4). Agdanli et al. revealed that the mean QTc values after intubation (T3) were significantly longer than the initial (T0) values in Groups 1 and Group 2 (16). Similarly, the mean QTc value after intubation (T3) in the rocuronium group was found to be significantly longer than the baseline (T0) value ($p<0.05$) in the present study.

When the arrhythmias in Groups 1 and 2 in the study of Agdanli et al. are compared to the rocuronium group in our study, while Agdanli et al. found ventricular tachycardia, ventricular premature beat, premature atrial premature beat, and sinoatrial block in their study, we only found sinus arrhythmia. This difference may be due to the different surgical procedures, the different induction agents, the fact that the individuals in our study group had coronary artery disease, even though the individuals in our study group did not have any comorbidities, and the presence of long QT in baseline ECGs at a rate of 45% (T0) at baseline and including patients on medication [16].

Gursoy et al. In the study titled Investigation of Cardiac Effects of Pancuronium, Rocuronium, Vecuronium, and Mivacurium in Isolated Rat Atrium; Pancuronium increased heart rate in a dose-dependent manner when compared to the control group, particularly at higher concentrations, but vecuronium, rocuronium, and mivacurium did not [17]. The effects of rocuronium and mivacurium on heart rate increase were found to be statistically insignificant in our study, as they were in the studies of Gursoy et al.

There are some limitations about this present study. First of all studying the isolated effects of muscle relaxant agents in a clinical setting is impossible. Anesthetic induction agents and volatile anesthetics may also have an effect on the hemodynamics and ECG measurements. So this was the first problem of our study because of its natural design. Second, the number of patients of this study may not be enough for making a certain judgement to change in routine clinical practice.

There have been few clinical studies on the effects of rocuronium on the QT and QTc intervals. There has only been one clinical study on the effect of atracurium on QT and QTc. In the literature review, no clinical study on the effect of mivacurium on QT and QTc was found. The present study is the first study to compare the effects of rocuronium, atracurium, and mivacurium on QT and QTc.

Conclusion

As a result of this study, which included patients with normal ECG limits, 5 of the 6 measurements with pathological QTc prolongation were obtained from patients who used mivacurium. Another significant finding was that the number of patients with intraoperative sinus arrhythmia was statistically significant in the mivacurium-treated group. More clinical studies should be conducted to question the use of mivacurium in the selection of muscle relaxant drugs in clinical practice, particularly during the administration of general anesthesia to patients with Long QT syndrome.

Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Disclosure: The authors declare that this study received no financial support.

The study has been conducted after the Local Ethics Committee issued a decision dated 14.02.2017 and numbered 2017-02/07.

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