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Original Article / *Özgün Makale*

Anesthesia induction regimens may affect QT interval in cardiac surgery patients: A randomized-controlled trial

Kardiyak cerrahi hastalarında anestezi indüksiyon rejimleri QT intervalini etkileyebilir: Randomize kontrollü çalışma

Şule Dede, Zeliha Aslı Demir, Eda Balcı

Department of Anesthesiology and Reanimation, Health Sciences University, Ankara City Hospital, Ankara, Türkiye

ABSTRACT

Background: The aim of this study was to investigate the effects on QT interval of the propofol-ketamine combination and the midazolam-fentanyl combination in anesthesia induction for cardiac surgery.

Methods: Between September 2020 and June 2021, a total of 95 cardiac surgery patients (80 males, 15 females; mean age: 57±9.1 years; range, 26 to 76 years) were included. The patients were divided into two groups as Group PK (propofol-ketamine, n=50) and Group MF (midazolam-fentanyl, n=45). The 12-lead electrocardiographic and hemodynamic measurements were performed at three time points: before anesthesia induction, after anesthesia induction, and after endotracheal intubation. The measurements were evaluated with conventional Bazett's formula and a new model called index of cardio-electrophysiological balance.

Results: The evaluated QTc values of 95 patients after anesthesia induction were significantly prolonged with the Bazett's formula and the index of cardio-electrophysiological balance in Group PK (p=0.034 and p=0.003, respectively). A statistically significant QTc prolongation was observed with the index of cardio-electrophysiological balance after laryngoscopy and endotracheal intubation in Group PK (p=0.042). Hemodynamic parameters were also higher in Group PK.

Conclusion: Our study shows that the propofol-ketamine combination prolongs the QTc value determined by the Bazett's formula and the index of cardio-electrophysiological balance model. Using both QTc measurement models, the midazolam-fentanyl combination has no prolongation effect on QTc interval in coronary surgery patients.

Keywords: Cardiac anesthesia, electrocardiography, enhanced recovery after surgery, fentanyl, ketamine, long QT syndrome, midazolam, propofol.

ÖZ

Amaç: Bu çalışmada kalp cerrahisinde anestezi indüksiyonunda propofol-ketamin kombinasyonu ve midazolam-fentanil kombinasyonunun QT intervali üzerindeki etkileri araştırıldı.

Çalışma planı: Eylül 2020-Haziran 2021 tarihleri arasında toplam 95 kalp cerrahisi hastası (80 erkek, 15 kadın; ort. yaş: 57±9.1 yıl; dağılım, 26-76 yıl) çalışmaya alındı. Hastalar Grup PK (propofol-ketamin, n=50) ve Grup MF (midazolam-fentanil, n=45) olmak üzere iki gruba ayrıldı. Üç zaman noktasında 12 derivasyonlu elektrokardiyografik ve hemodinamik ölçümler yapıldı: anestezi indüksiyonu öncesi, anestezi indüksiyonu sonrası ve endotrakeal entübasyon sonrası. Ölçümler klasik Bazett formülü ve kardiyoelektrofizyolojik denge indeksi adı verilen yeni bir model ile değerlendirildi.

Bulgular: Doksan beş hastanın anestezi indüksiyonu sonrası Bazett formülü ve kardiyoelektrofizyolojik denge indeksi ile değerlendirilen QTc değerleri, Grup PK'de anlamlı olarak daha uzundu (sırasıyla p=0.034 ve p=0.003). Grup PK'de laringoskopi ve endotrakeal entübasyon sonrası kardiyoelektrofizyolojik denge indeksi ile istatistiksel olarak anlamlı QTc uzaması görüldü (p=0.042). Hemodinamik parametreler de Grup PK'de daha yüksek izlendi.

Sonuç: Çalışmamız, propofol-ketamin kombinasyonunun Bazett formülü ve kardiyoelektrofizyolojik denge indeks modeli ile hesaplanan QTc değerini uzattığını göstermektedir. Her iki QTc ölçüm yöntemi ile midazolam-fentanil kombinasyonunun koroner cerrahi hastalarında QTc aralığını uzatmada herhangi bir etkisi izlenmemiştir.

Anahtar sözcükler: Kardiyak anestezi, elektrokardiyografi, cerrahi sonrası hızlandırılmış iyileşme, fentanil, ketamin, uzun QT sendromu, midazolam, propofol.

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Correspondence: Eda Balcı, MD. SBÜ, Ankara Şehir Hastanesi, Anesteziyoloji ve Reanimasyon Kliniği, 06800 Çankaya, Ankara, Türkiye.
Tel: +90 533 - 629 77 60 e-mail: edaaksoy84@gmail.com

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Anesthesia induction is one of the most critical parts of perioperative anesthesia management in cardiac surgery cases. In addition to the desired anesthetic-analgesic effects of each selected agent, these agents also have undesirable side effects. Conventionally administered intravenous anesthesia agents include both opioids and benzodiazepines. Opioids have many side effects that limit their use in the perioperative period, such as respiratory depression, delayed recovery, gastrointestinal system depression, and nausea-vomiting.[1] Midazolam, following many years of use, has recently been shown to have a substantial side effect known as postoperative delirium, a condition experienced by 57% of patients after cardiac surgery.[2] Currently, developing surgical and anesthetic techniques represent attempts to reduce postoperative complications and improve patient outcomes.[3,4]

The present study focuses on propofol and ketamine. The propofol and ketamine combination is one of the most preferred anesthesia induction combinations in enhanced recovery after surgery (ERAS) and opioid-free anesthesia (OFA) protocols. Propofol is superior in many respects to benzodiazepines: it takes effect quickly, provides high-quality amnesia, facilitates airway manipulation, and has potent anti-inflammatory and antioxidant properties and, more importantly, delirium is not a typical side effect. Ketamine use in cardiac surgery has received attention in recent years due to its strong analgesic effects, as well as its ability to suppress the inflammatory response caused by cardiopulmonary bypass.[5] In recent years, ketamine has been a popular analgesic drug used instead of opioids to avoid the side effects of the latter in modern fast-track protocols. A known effect of ketamine is that it stimulates the sympathetic system, causing an increase in blood pressure and heart rate (HR), which may compensate for hypotension due to other hypnotic agents used. Several studies have shown that propofol's systemic vascular resistance-lowering effects can be balanced with the sympathomimetic effects of ketamine.[6] A concern germane to the anesthesia in use is measuring its hemodynamic effects, which is another focus of this study.

It is known that drugs used during anesthesia and analgesia management affect QT interval.[7] While many formulas are used for the QT calculation, the most preferred is Bazett's formula ($QTc=QT/\sqrt{RR}$).[8] Besides, a new model called the index of cardio-electrophysiological balance (iCEB=QT/QRS) is used to detect drug-induced long QT syndrome (LQTS) and Torsades de Pointes (TdP), drug-induced QT shortening and their associated non-TdP-like ventricular tachycardia (VT), and ventricular fibrillation (VF).[9,10] While other studies have investigated the effects of anesthetics on QT interval, they were carried out in non-cardiac surgery and/or with healthy patients.[11,12]

In the current study, we hypothesized that propofol might blunt ketamine's sympathomimetic effects on hemodynamics and QT interval in cardiac anesthesia induction. We, therefore, aimed to compare the propofol-ketamine (PK) and midazolam-fentanyl (MF) combination in terms of QT interval during cardiac anesthesia induction.

PATIENTS AND METHODS

This prospective, parallel-group, randomized-controlled study was conducted at Ankara City Hospital, Yüksek İhtisas Cardiac Center between September 2020 and June 2021. Adult patients undergoing elective open coronary surgery were included with equal randomization (1:1). The allocation sequence was concealed from the two researchers in sequentially numbered stapled envelopes. Randomization took place at the preoperative assessment area by an investigator with no clinical involvement in the trial, and the information was given to the other investigator who would process the protocol. Eligible participants were all adults aged 18 or over who would undergo open coronary surgery. Patients with any of the following were excluded: re-do and emergency surgeries, preoperative arrhythmia, history of LQTS, allergies specific to known drugs, increased intracranial pressure, preoperative electrolyte disorders, and patients who were unwilling to participate in the study. Complications during anesthesia induction or endotracheal intubation (such as difficult intubation, allergic reaction), newly developed arrhythmias, failure in anesthesia induction with planned drugs, and the need for additional or different drugs were also excluded. A total of 100 coronary surgery patients were included in this study. Five patients were excluded from the study due to multiple laryngoscopy attempts and the need for additional medication. Finally, 95 patients (80 males, 15 females; mean age: 57±9.1 years; range, 26 to 76 years) were enrolled. The patients were divided into two groups as Group PK (n=50) and Group MF (n=45) (Figure 1).

The primary endpoint of the study was the time required to reach the desired number of patients. Patients who met the eligibility criteria in the study were evaluated in terms of demographic data, comorbidities,

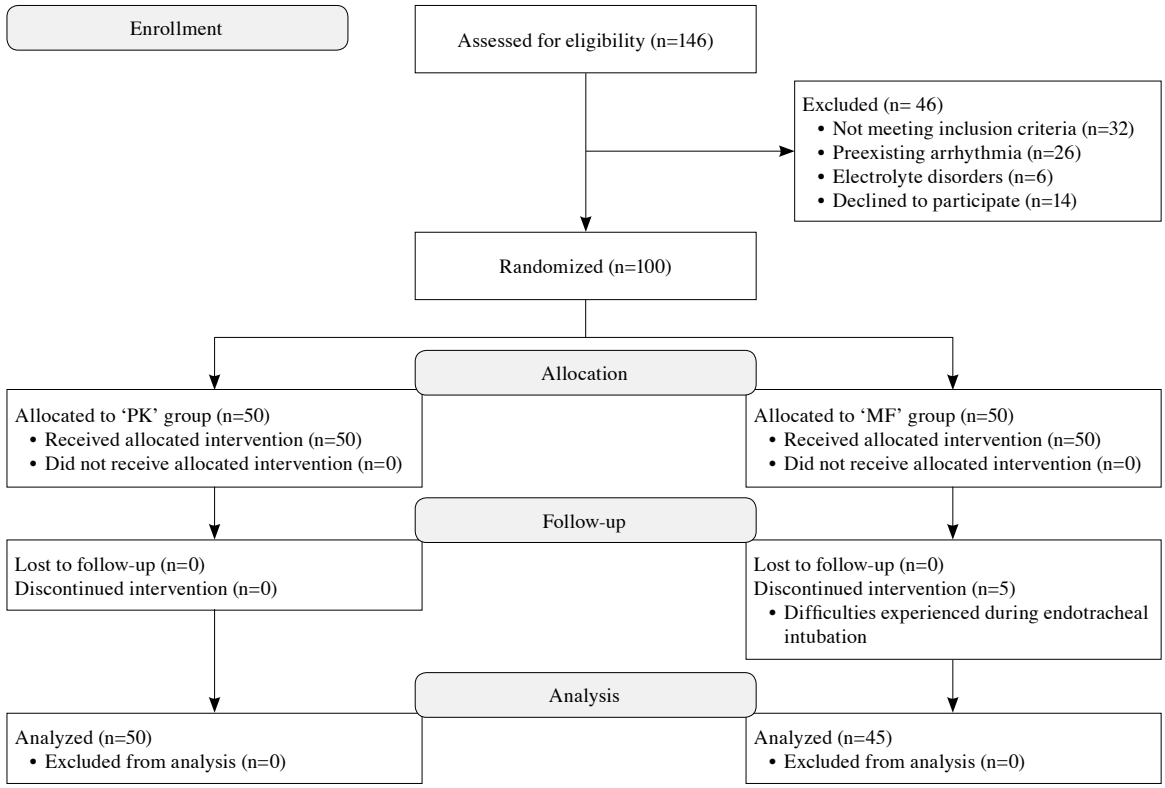

Figure 1. CONSORT diagram.
PK: Propofol-ketamine; MF: Midazolam-fentanyl.

medications, preoperative fasting blood sugar, sodium, potassium, magnesium, and calcium values.

The groups were determined according to the anesthetic agents used in anesthesia induction. Group PK patients were administered propofol and ketamine for anesthesia induction, while Group MF patients were administered midazolam and fentanyl for anesthesia induction.

All patients were taken to the operating room and monitored with electrocardiography (ECG), pulse oximetry bispectral index (BIS™, Covidien, MN, USA), and invasive arterial catheter. After 2 min of preoxygenation, a 12-lead ECG (GE Healthcare MAC 2000) was performed, and simultaneously the patients' systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), HR, oxygen saturation (SpO_2) and BIS values were recorded (first measurement). After 2 to 2.5 mg kg^{-1} propofol and 1 mg kg^{-1} ketamine were administered in the induction of anesthesia in Group PK patients, when the BIS value reached 40 to 50, ECG was performed and simultaneous SAP, DAP, MAP, HR, and BIS values were recorded (second measurement). After the administration of 0.15 mg kg^{-1} midazolam and 10-15 μg kg^{-1} fentanyl in the induction of anesthesia in Group MF patients, when the BIS value reached the range of 40 to 50, the ECG was repeated and simultaneous SAP, DAP, MAP, HR, and BIS values were recorded (second measurement). Then, 0.8 mg kg^{-1} rocuronium was administered to both groups, and 2 min later, the patients were intubated, and appropriate mechanical ventilator settings were made with 50% oxygen/air mixture. After 2 min of intubation, ECG recording was repeated, simultaneous SAP, DAP, MAP, HR, and BIS values were re-recorded (third measurement). Sevoflurane was administered after the third measurement. After this stage, a central venous catheter was inserted, and surgery was initiated.

The corrected QT (QTc) and QRS distances were calculated automatically on the calibrated ECG device in all ECG recordings performed in both patient groups. The QTc assessment measurements were made on leads II and V5. The primary outcome of this study was the prolongation of the QTc according to Bazett's

formula[8] from baseline. The secondary outcome was to evaluate the feasibility of the corrected iCEB (iCEBc) method in anesthesia practice.

Statistical analysis

The study power and sample size calculation were performed using the G*Power version 3.1.9.7 software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). Accordingly, the values were as follows: n1=50, n2=45, α=0.05, effect Size (d)=0.67; power=90%.

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). The chi-square (χ^2) test was used to compare qualitative data. Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The suitability of the data to the normal distribution was evaluated using the Kolmogorov-Smirnov test, skewness-kurtosis, and graphical methods (histogram, Q-Q Plot, Stem and Leaf, Boxplot). In the study, in the evaluation of the quantitative data showing normal distribution, the independent samples t-test (t-test in independent groups) and repeated measures analysis of variance (ANOVA) were used to compare repeat measurements. In cases where there was a difference in multiple comparisons, the post-hoc Tukey honestly significant difference test was used to find the source of the difference. A *p* value of <0.05 was considered statistically significant.

RESULTS

There was no significant difference between the groups in terms of demographic and preoperative characteristics (Table 1).

In the intergroup comparisons in terms of hemodynamic parameters, SAP, DAP, MAP, and HR were higher in the second and third measurement periods in Group PK patients (p<0.001 for all). In the intragroup comparisons, a statistically significant difference was observed in both groups (Table 2).

In Group PK patients, the mean QTc value according to Bazett's formula (449.6±21.6) was longer in the second measurement period compared to that of Group MF (439.8±22.7) (p=0.034). In the first and third measurement periods, there was no statistically

Table 1. Demographic variables, comorbidities, and laboratory parameters of the study population

	Group PK (n=50)			Group MF (n=45)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			55.8±8.2			59.0±9.9	0.088†
Sex Male	42	84		38	84		1.000*
Weight (kg)			81.9±12			83±11.5	0.645†
Hypertension	37	74		31	68.9		0.746*
Diabetes mellitus	19	38		18	40		1.000*
Chronic obstructive pulmonary disease	9	18		6	13.3		0.733*
Coronary artery disease	39	78		35	77.8		1.000*
Cerebrovascular disease	4	8		6	13.3		0.510*
Thyroid disease	3	6		6	13.3		0.300*
Renal disease	5	10		6	13.3		0.853*
Smoking	34	68		32	71.1		0.916*
COVID-19 history	3	6		2	4.4		1.000*
Blood glucose (mg/dL)			134.1±61.9			124.6±52.5	0.427†
Sodium (mEq/L)			139.1±2.4			139.2±2.6	0.942†
Potassium (mEq/L)			4.3±0.3			4.4±0.4	0.230†
Calcium (mg/dL)			9.4±0.4			9.4±0.6	0.560†
Magnesium (mg/dL)			1.9±0.2			1.9±0.2	0.700†

PK: Propofol-ketamine; MF: Midazolam-fentanyl; SD: Standard deviation; * Chi-Square test, † Independent Samples t test.

Table 2. Comparison of SAP, DAP, MAP, and HR between and within the groups

	Group PK (n=50)	Group MF (n=45)	
	Mean±SD	Mean±SD	*p**
SAP 1st measurement	171.8±24.1	166±25	0.253
SAP 2nd measurement	123.1±21.1	106.4±20.9	**<0.001**
SAP 3rd measurement	152±22.1	127.3±30.1	**<0.001**
p value†	**<0.001**	**<0.001**	
Difference	All	All	
DAP 1st measurement	83.6±9.9	80.2±11.6	0.133
DAP 2nd measurement	67.9±10.9	57.9±11.4	**<0.001**
DAP 3rd measurement	82.4±11.9	71.2±15.7	**<0.001**
p value†	**<0.001**	**<0.001**	
Difference	2nd measurement with 1st and 3rd measurement	All	
MAP 1st measurement	112.5±12.2	108.4±13.7	0.119
MAP 2nd measurement	85.8±13	74.0±14	**<0.001**
MAP 3rd measurement	105.3±13.8	88.9±19.8	**<0.001**
p value†	**<0.001**	**<0.001**	
Difference	All	All	
HR 1st measurement	78.3±12.4	78±12	0.898
HR 2nd measurement	79.9±13.4	70.3±11	**<0.001**
HR 3rd measurement	92±13.9	80.5±15.9	**<0.001**
p value†	**<0.001**	**<0.001**	
Difference	3rd measurement with 1st and 2nd measurement	2nd measurement with 1st and 3rd measurement	

SAP: Systolic arterial pressure; DAP: Diastolic arterial pressure; MAP: Mean arterial pressure; HR: Heart rate; PK: Propofol-ketamine; MF: Midazolam-fentanyl; SD: Standard deviation; * Independent Samples t test; † Repeated Measures ANOVA.

significant difference between the groups in QTc values according to Bazett's formula (461.6±20.5, 456.4±27.4, respectively) (p=0.297) (Figure 2, Table 3).

There was a statistically significant difference between all Bazett QTc values in Group PK. The first measurement was 440.9±23.9, the second measurement 449.6±21.6, and the third measurement 461.6±20.5 (p<0.001) (Figure 2, Table 3).

In Group MF, the mean Bazett QTc value in the third measurement period was higher than in other periods as the first measurement was 439.3±24.8, the second measurement 439.8±22.7, and the third measurement 456.4±27.4 (p<0.001) (Figure 2, Table 3).

The mean iCEBc values revealed significant differences between groups. While the whole first measurement period was similar (Group PK 4.9±0.6, Group MF 4.8±0.5, p=0.186), iCEBc values were significantly higher in the second measurement (5.0±0.5) and third measurements (4.7±0.5) in

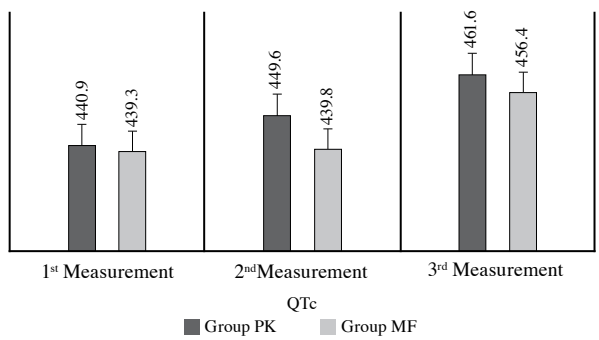

Figure 2. Comparison of QTc between groups.
QTc: Corrected QT; PK: Propofol-ketamine; MF: Midazolam-fentanyl.

Table 3. Comparison of Bazett QTc and iCEBc between and within the groups

	Group PK (n=50)	Group MF (n=45)	
	Mean±SD	Mean±SD	*p**
Bazett QTc 1st measurement	440.9±23.9	439.3±24.8	0.752
Bazett QTc 2nd measurement	449.6±21.6	439.8±22.7	**0.034**
Bazett QTc 3rd measurement	461.6±20.5	456.4±27.4	0.297
p value†	**<0.001**	**<0.001**	
Difference	All	3rd measurement with 1st and 2nd measurement	
iCEBc 1st measurement	4.9±0.6	4.8±0.5	0.186
iCEBc 2nd measurement	5.0±0.5	4.7±0.5	**0.003**
iCEBc 3rd measurement	5.2±0.5	5.0±0.6	**0.042**
p value†	**<0.001**	**<0.001**	
Difference	3rd measurement with 1st and 2nd measurement	2nd and 3rd measurements	

iCEBc: Corrected index of cardio-electrophysiological balance; PK: Propofol-ketamine; MF: Midazolam-fentanyl; SD: Standard deviation; * Independent Samples t test; † Repeated Measures ANOVA.

Group PK (p=0.003 and p=0.042, respectively) (Figure 3, Table 3).

In addition, in the intragroup comparisons, the mean iCEBc values calculated in the third measurement (5.2±0.5) period were higher than the first (4.9±0.6) and second measurements (5.0±0.5) in Group PK (p<0.001) (Figure 3, Table 3).

The intragroup comparisons in Group MF revealed that the mean iCEBc values calculated in the second measurement (4.7±0.5) and third measurement (5.0±0.6) periods were significantly different (p<0.001) (Figure 3, Table 3).

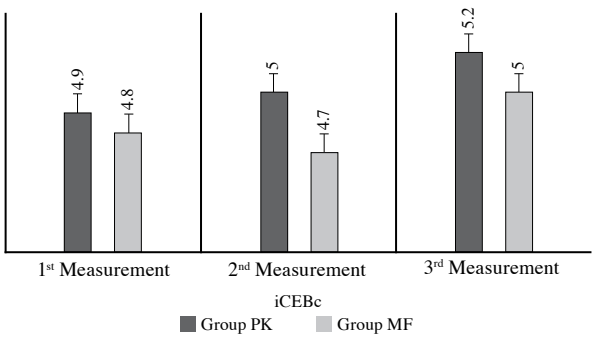

Figure 3. Comparison of iCEBc between groups.

iCEBc: Corrected index of cardio-electrophysiological balance; PK: Propofol-ketamine; MF: Midazolam-fentanyl.

DISCUSSION

This study evaluated the effects of two different anesthesia induction techniques on QT interval in patients undergoing coronary surgery. As the measurement times progressed in both groups, QTc prolongation was found according to the two measurement methods. After anesthesia inductions, Bazett's formula and iCEBc measurements were significantly longer in the PK group. After laryngoscopy and endotracheal intubation, iCEBc measurements were significantly longer in the PK group, while Bazett's formula revealed no significant difference.

Cardiac arrhythmias are frequently encountered in the perioperative period and are often held responsible for mortality. Congenital or acquired LQTS, many drugs including anesthetics, electrolyte imbalances, and sympathetic nervous system activation can cause arrhythmia.[7,13] The diagnosis of LQTS can be made by genotyping; however, 30% of patients with LQTS have a normal phenotype and a normal QT interval and, thus, they remain undiagnosed until they encounter a trigger.[14] These patients are potential carriers of LQTS, and 70% of them have a normal QTc interval until exposure to a triggering drug. Unfortunately, the operating room environment provides the most suitable conditions for these symptoms to manifest. In patients admitted for surgery, there may be the use of prescribed drugs that may cause adverse effects by prolonging cardiac repolarization. Therefore, attention

was paid to the fact that the patients selected in our study did not have electrolyte disturbances and did not have a history of QT prolongation or related drug use. Existing cardiac disease and myocardial damage in cardiac surgery patients may also cause long QT intervals. Considering that the anesthetics and/or the applications in anesthesia practice are the same in patients undergoing non-cardiac surgery and in patients undergoing cardiac surgery, evaluating arrhythmogenic effects in patients with cardiac disease is a useful implementation.

Prolongation of QT interval by the agents used during anesthesia induction is considered critical in mortality and morbidity.[13] It has been suggested that a significant prolongation of QTc is observed in 80% of patients undergoing non-cardiac surgery due to the cumulative effect of agents administered under general anesthesia.[15] The widespread opinion regarding the effects of propofol on QTc is that propofol does not significantly affect QTc in patients with LQTS and healthy adults and is, thus, suitable for use in this group of patients.[7] A study examining the relationship between the use of propofol as a single dose of 0.2 to 5 mg kg^{-1} in anesthesia induction and QT interval found that this dosing did not prolong QTc and claimed that propofol was safe in patients with QTc prolongation.[16] Despite the need for further research on the relationship between ketamine and QT interval in humans, its use is not recommended in patients with known LQTS or those at high arrhythmia risk, since its sympathomimetic properties may cause TdP.[7,17,18] In our study, a significant prolongation in QTc was detected with Bazett's formula and the iCEBc model in patients administered the PK combination for anesthesia induction. As propofol does not have a negative effect on QTc and even shortens it, we suggest that the cause of this prolongation is ketamine. In our study, hemodynamic parameters (SAP, DAP, MAP, HR) as an indicator of the sympathomimetic effect were significantly higher in Group PK. In the light of these results and despite ketamine's many positive effects, a prudent application may be warranted with patients with LQTS or those considered to be at high risk for LQTS. Alternatively, other combinations may be preferable, particularly considering the relative dearth of studies on ketamine's use in cardiac surgery.

It has been suggested that midazolam does not affect QTc or electrical distribution and it can be safely used for premedication and induction of anesthesia in patients with LQTS or those at high risk.[17,18] Similarly, it is claimed that fentanyl does not affect repolarization time at clinical doses, does not prolong QT and QTc distance at 2 μg kg^{-1} doses, and reduces QT prolongation when used before laryngoscopy and endotracheal intubation.[12,19] The results of our study confirm the safety of these two agents on QT intervals in patients undergoing cardiac surgery.

It is impossible to evaluate the isolated effects of neuromuscular agents in human studies. However, it is also claimed that non-depolarizing neuromuscular blocking agents have minor autonomic effects and are not associated with QT and QTc prolongation.[7,9] Rocuronium, which is a non-depolarizing blocker, was used in both groups after the second measurement in our study, indicating that the observed changes can be attributed to anesthetic-analgesic drugs.

The American Heart Association (AHA) and the American Society of Cardiology (ASC) recommend using standardized methods for measuring QTc interval,[20] and the classical formula corrected for HR is Bazett's formula.[8] However, it is claimed that this formula gives false positive long QTc values at high HRs, whereas it gives false negative long QTc values at lower HRs.[20] Therefore, many ECG parameters have been developed to predict ventricular arrhythmias due to the unreliability of Bazett's formula.[20-22] While Bazett's formula is seen as a repolarization marker, the iCEBc model, which has become increasingly popular in recent years, shows the balance between depolarization and repolarization of the action potential.[10] The iCEBc model has been validated in humans in the presence of drug use, LQTS, and Brugada syndrome.[9] In addition to drug-induced QT prolongation and TdP, iCEBc can also be a guide in detecting conduction slowdowns, QT shortening, and the associated risk of non-TdP-like VT/VF, particularly induced by agents used in anesthesia management.[9,10] It is claimed that iCEBc increases after administering drugs that predispose to TdP, and decreases after administering drugs that increase the risk of non-TdP VT/VF.[10] At the bedside or during daily patient admission to the clinic, patients may need a rapid assessment of arrhythmia risk, and it is, therefore, recommended to include "QRS prolongation" and "iCEBc" in this initial risk classification, alongside the traditional QTc method.[23] According to Bazett's formula, values above 440 ms are considered prolonged QTc, but a threshold value has not yet been specified for iCEBc. Although there was no significant difference between the groups, Bazett values after laryngoscopy were above 440 ms in both groups. We cannot make this speculation for iCEB, as it is a relatively new parameter; there is no consensus as to which threshold value increases the risk of arrhythmia.

However, this issue may be clarified with further studies to be added to the literature.

Nonetheless, our study has some limitations. First, anesthesia induction agents cannot be evaluated individually in daily practice. Second, postoperative evaluation and long-term follow-up of the patients were not performed in arrhythmia development. Since the exact cut-off values for iCEBc measurements have not been determined yet, we cannot comment further on this issue. Besides, we did not perform intention to treat analysis.

In conclusion, our study shows that the propofol-ketamine combination prolongs the QTc value, as determined by both Bazett's formula and the index of cardio-electrophysiological balance model. Using both QTc measurement models, our observations confirm that the midazolam-fentanyl combination has no prolongation effect on QTc interval in cardiac surgery patients with heart disease. However, more extensive studies are needed to confirm the effects of agents used in anesthesia on electrocardiographic findings, cardiac function, and outcomes.

Ethics Committee Approval: Ethics approval for this study (ID: E1-1014) was approved by the local Ethics Review Board on 19/08/2020. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, literature review: Ş.D., Z.A.D.; Design: Ş.D., E.B.; Control/supervision, writing the article: Z.A.D.; Data collection and/or processing: Ş.D., E.B.; Analysis and/or interpretation: E.B., Z.A.D.; Critical review: Ş.D., E.B., Z.A.D.

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