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# The effects of propofol-ketamine combination on QTc interval in patients with coronary artery disease

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**Abstract**

The purpose of this study was to evaluate the effects of propofol-ketamine combination on QTc, T wave (Tp-e) interval, hemodynamics during the induction of anesthesia in patients with coronary artery disease (CAD) undergoing coronary artery bypass grafting (CABG). Patients were prospectively randomized, in a double blinded manner, to either the propofol group (Group P, n=41) or the propofol-ketamine combination group (Group PK, n=45). In both groups the drugs were infused at an IV dose of 2 mg/kg administered over 30 seconds. After that, 5µg/kg fentanyl and 0.1mg/kg vecuronium were administered and tracheal intubation was performed. ECG recordings were performed prior to induction of anesthesia (baseline, T1), 2 min after the beginning of study drugs (T2), 3 min after vecuronium (immediately before intubation, T3), and 30 s (T4), 1 min (T5) and 5 min (T6) after intubation. Eighty-six patients were evaluated in the study. The baseline QTc interval values were similar between the groups, In Group P, QTc interval increased significantly for T3-T6 in all periods according to baseline value. Also in Group P, QTc interval increased significantly in T4, T5, T6 according to T3. In group PK, QTc interval increased significantly in T3-T6 according to baseline value. Group PK increased significantly in T5 and T6 compared to T3. In both groups a statistically significant change was not found in Tp-e intervals of all periods. Following induction with propofol-ketamine combination, QTc interval did not increase, but it prolonged postintubation QTc interval just like propofol. Assuming that increased repolarization transmural dispersion (TDR) is a reliable indicator of risk of torsade de pointes (TdP), and lack of any change in Tp-e interval, in the presence of depressed hemodynamic response to intubation, we think that this combination can be safely used for the induction of anesthesia in patients with CAD undergoing CABG.

**Keywords:** Propofol; ketamine; QT interval; Tp-e interval

## Introduction

The prolongation of the QT interval can cause ventricular fibrillation as well as torsade de pointes (TdP) polymorphosis ventricular tachycardia. Clinical studies show that a more reliable predictor of TdP is the interval between the peak and the end of the T wave (Tp-e), the surface ECG marker of repolarization transmural dispersion (TDR) (1,2). It is known that patients with coronary artery disease (CAD) are prone to arrhythmias that occur in the perioperative period (3). Therefore, cardiovascular stability is an important prerequisite for any anesthetic agent used for anesthesia induction in patients undergoing coronary artery bypass grafting (CABG).

Ketamine use is recommended in hypovolemic patients or patients with cardiovascular instability because of its sympathomimetic effects (4). In the presence of CAD, increase in plasma catecholamine levels may prolong QT, and Tp-e interval in addition to hemodynamic effect of ketamine. Clinically relevant dosages for the induction of anesthesia with propofol have been reported as a very safe agent in induction of anesthesia regarding QT prolongation (5).

Hemodynamic advantages of ketamine-propofol combination in CABG have been reported (6). Besides in patients who had undergone CABG under this anesthetic combination, significantly lower rates of ventricular rhythm disorders were reported as

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evaluated by postoperative Holter electrocardiogram (ECG) monitorization (7). Sympathomimetic effects of ketamine may be greatly reduced by its combination with propofol, and also QT and Tp-e intervals may shorten.

The purpose of this study was to evaluate the effects of ketamine-propofol combination on QTc, Tp-e interval, hemodynamics during the induction of anesthesia in patients with CAD undergoing CABG.

## Materials and methods

### Study Design

The study protocol was approved by the ethics committee of Inonu University Medical Faculty and all patients provided written, informed consent prior to study. This study was performed in 86 patients scheduled for elective CABG. We excluded patients with unstable angina pectoris, persistent pacemaker, diabetes mellitus, severe atrioventricular block, chronic obstructive pulmonary disease and electrolyte imbalance, and patients receiving anti-arrhythmic and adrenergic beta-blocking agents. We also excluded patients with ejection fraction <40% and abnormal prolongation of the QTc interval (> 440 ms).

All routine heart medications were continued until the morning of the surgery. All patients were in sinus rhythm when they came to the operating room. Using a 16-G intracath, were cannulated veins on both arms after, each patient was monitored by 5-lead ECG, blood pressure, and SpO2. Premedication with 1-2 mg IV midazolam was administered. The left radial artery was cannulated using a 20-G intracath using local anesthesia. After 10 min of stabilization, the baseline values for the mean arterial pressure (MAP), heart rate (HR) and 12-lead standard ECG (paper speed of 50 mm.s¯1) were recorded.

Patients were prospectively randomized, in a double blinded manner, to either the propofol group (Group P, n=41) or the ketamine-propofol combination group (Group PK, n=45). Group allocations were based on computer generated codes. For Group P, propofol, 200mg, and for Group PK, ketamine-propofol combination was prepared (propofol, 200mg, and ketamine, 200mg mixed together) in 20 mL syringe. Study drugs were prepared and coded by a nurse anesthetist who did not take part in the care of patients. Staffs involved in patient management and data collection were unaware of group assignments. In both groups the drugs (propofol and ketamine-propofol were infused at an IV dose of 2 mg/kg administered over 30 seconds. After that, 5µg/kg fentanil and 0.1mg/kg vecuronium were administered and tracheal intubation was performed.

Induction of anesthesia and tracheal intubation were performed by two of the authors who were unaware of the group allocation. The patients' lungs were manually ventilated using 100% O2 (for 3 min) until intubation and then were ventilated mechanically. If tracheal intubation took more than 40 s, the patient was to be excluded from the study. ECG recordings were performed prior to induction of anesthesia (baseline, T1), 2 min after the beginning of study drugs (T2), 3 min after vecuronium (immediately before intubation) (T3), and 30 s (T4), 1 min (T5) and 5 min (T6) after intubation.

### Outcome Parameters

QT interval and Tp-e interval were measured by an author (FE) who was unaware of group distribution. QT intervals were measured manually from the beginning of the QRS complex to the end of the T wave (defined as the intersection of the isoelectric line and the tangent of the maximum downstream limb of the T wave). Tp-e interval from the peak of the T wave to the end of the T wave. If there are U waves, we defined the end of the T wave as the lowest point of the curve between T and U waves. QT and Tp-e intervals, II. And in lead V5 it was calculated for four consecutive complete P-QRS-T cycles, and their II. Average QT interval for derivation and Tp-e interval for V5 were averaged. QT intervals were corrected according to the Friedericia formula with $QTc=QT/RR^{-1/3}$.

### Statistical Analysis

Statistical analysis was performed using SPSS for Windows, version 10.0 (SPSS Inc. Headquarters, Chicago, IL, USA). Assuming an alpha level of 0.05 and power of 0.80, a minimum of 21 patients in each group were required to detect a mean difference of 20ms and 22ms of Standard deviation for the QTc interval between two groups. Continuous variables were reported as mean ± standard deviation. Categorical variables were reported as number. Differences between groups were evaluated using the independent sampled t-test. Heart rate, blood pressure and QT measurements were analyzed using repeated-measures analysis of variance post Hoc multiple comparisons with Bonferroni test. Chi-square test were used for comparison of categorical variables between studied groups. A p value <0.05 was considered to be statistically significant. The results were expressed as numbers (n) or mean (SD).

## Results

Ninety-seven patients were included in the study. Eleven patients were excluded from the study because of shortage of ECG strip, six, for machinery breakdown, and five, for prolongation of the intubation time. The remaining 86 patients were evaluated for the study.

The patients were similar as for age, bodyweight, height, and gender (Table 1). In intergroup assessments, a statistically significant difference was not found as for MAP. In intragroup evaluations, MAP values of both groups were significantly lower at T2-T6 when compared with the baseline values (p<0.0001). In both groups, MAP, at T4-T5-6 significantly increased according to T3 period. In intergroup assessments, HR in Group PK was lower at T4 (P=0.029). In both groups, heart rate decreased according to baseline value in T3-T6 period. Compared to the T3 period, T5, T6 also increased significantly (Table 2).

**Table 1.** Demographic variables of patients. Values are mean (SD) or number (proportion).

| | Group P (n=41) | Group PK (n=45) |
|---|---|---|
| **Age; year** | 59.05±9.8 | 58.9±9.6 |
| **Gender; M: F** | 34/7 | 38/7 |
| **Weight; kg** | 76.4±9.4 | 75.6±12.5 |
| **Height; cm** | 165.8±10.3 | 166.7±11.2 |

The baseline QTc interval values were similar between the groups, and they were not statistically significantly different in T1-T6 periods. In Group P, QTc interval increased significantly for T3-T6 ($p < 0.0001$) in all periods except T2 according to baseline value. Also in Group P, QTc interval increased significantly in T4, T5, T6 according to T3. In group PK, QTc interval increased significantly (T3-T6) according to baseline value. Group PK increased significantly in T5 and T6 compared to T3 ($p < 0.0001$ for T5 and T6). In both groups a statistically significant change was not found in Tp-e intervals of all periods. There was no difference in Tp value in Group P Group PK was increased at T6 according to the baseline in Tp (Table 3)

The number of patients with QTc intervals>440ms were similar in both groups. There were no adverse events in either group.

**Table 2.** Haemodynamic variables

| | Group P - HR | | Group P - K HR | | Group P - MAP | | Group P - K MAP | |
|---|---|---|---|---|---|---|---|---|
| **T1** | 69.93 | 11.65 | 68.44 | 11.52 | 96 | 2.43 | 94.17 | 2.24 |
| **T2** | 68.63 | 11.81 | 65.64 | 10.51 | 68.29* | 2 | 70.28* | 1.72 |
| **T3** | 60.29* | 9.34 | 56.96* | 10.21 | 59.83* | 1.54 | 60.77* | 1.34 |
| **T4** | 62.59* | 10.69 | 57.82*♯ | 9.23 | 68.29*¥ | 2.35 | 69.08*¥ | 2.20 |
| **T5** | 63.90*¥ | 10.68 | 61.64*¥ | 10.73 | 70.71*¥ | 2.34 | 73.64*¥ | 2.27 |
| **T6** | 63.46*¥ | 9.61 | 61.82*¥ | 10.76 | 74.58*¥ | 2.31 | 75*¥ | 2.11 |

[T1: Baseline (before induction of anesthesia),T2: 2 min after the beginning of study drugs (postinduction), T3: before intubation, T4: 30 s , T5: 1 min and T6: 5 min after intubation].
*p<0.05 when compared with baseline
¥ p<0.05 when compared with T3
♯ p<0.05 when compared with Group P

**Table 3.** QT and Tp variables

| | Group P - QT | | Group P - KQT | | Group P - Tp | | Group P - K Tp | |
|---|---|---|---|---|---|---|---|---|
| **T1** | 412.1 | 16.42 | 407.9 | 13.8 | 90.73 | 16.30 | 89.77 | 15.29 |
| **T2** | 403.6 | 18.07 | 408.3* | 13.7 | 89.63 | 16.67 | 88.77 | 15.00 |
| **T3** | 415.5* | 17.24 | 416.5* | 14.8 | 90.85 | 16.69 | 90.88 | 15.60 |
| **T4** | 421.1*¥ | 16.82 | 420.1* | 14.3 | 90.85 | 15.96 | 91.15 | 15.58 |
| **T5** | 422.4*¥ | 18.12 | 424.5*¥ | 14.8 | 91.46 | 16.62 | 91.88 | 16.00 |
| **T6** | 423.8*¥ | 17.39 | 427.1*¥ | 14.9 | 91.46 | 16.24 | 92.28* | 16.32 |

[T1: Baseline (before induction of anesthesia),T2: 2 min after the beginning of study drugs (postinduction), T3: before intubation, T4: 30 s , T5: 1 min and T6: 5 min after intubation].
*p<0.05 when compared with baseline, ¥ p<0.05 when compared with T3

## Discussion

In our study, propofol-ketamine combination did not prolong post induction QTc interval in patients with CAD, however after intubation it prolonged QTc similar to propofol. Besides, in all periods, Tp-e intervals did not change, but hemodynamic response to intubation was depressed.

Some publications reported significant QT shortening effects of anesthesia induction with propofol at clinical doses, while in other articles, this effect was not demonstrated (8-11). However in patients with CAD, induction of anesthesia with propofol did not demonstrate any effect as evaluated at any measurement point (12). In our study, after propofol induction, QTc interval shortened. This finding may be related to measurements of QT intervals in different leads, diverse the HR correction formulas used to calculate QTc intervals or administration of analgesics before propofol injection. However, Tp-e interval did not change in consistent with other studies (2, 13).

Ketamine may cause myocardial damage in patients with CAD because of its sympathomimetic properties. In addition, reports have indicated that ketamine facilitated the induction of isoproterenol-refractory idiopathic ventricular tachyarrhythmias in one patient,

and in another patient injection with ketamine probably induced wide-complex dysrhythmias (14, 15). Theoretically, in patients with CAD or in patients with long QT syndrome use of ketamine as a single agent is not recommended. Therefore, we did not use ketamine as a single agent.

In our study, propofol-ketamine combination did not prolong post induction QTc interval. This effect may be due to compensatory sympatholytic effects of propofol against sympathomimetic effects of ketamine. However, following tracheal intubation, QTc intervals in both groups, increased according to baseline values. Ay et al. (18), regardless of the induction agents used, reported that QTc dispersion had increased during intubation period in patients with CAD when compared with those without. Also a study performed with another induction agent in a similar patient group, demonstrated prolongation of QTc interval with intubation (19). Ischemic heart disease and sympathomimetic effects together with multidrug (fentanyl, vecuronium) use in the induction of anesthesia may contribute to the prolongation of QTc interval induced by intubation. In our study, we did not evaluate QTc interval after fentanyl injection. However, one of the reasons for the post intubation prolongation of QTc interval in both groups according to baseline values may be attributed to the effects of induction agents and interaction of fentanyl with cardiac K channels (20). In addition, QTc prolonging effects of fentanyl in patients with CAD have been also reported (12). Any adverse effect of vecuronium use in patients with long QT syndrome has not been reported yet (21). However, unchanged Tp-e interval may suggest that these agents used in induction of anesthesia had a very low risk of TdP development (2).

In patients with ischemic heart disease or serious cardiac dysfunction, to prevent sympathomimetic effects associated with the use of ketamine as a single agent, its combination with a sedative or an analgesic can be recommended. In patients with CAD, higher incidence of sinus, and ventricular tachycardias during intubation caused by 4 mg/kg racemic ketamine or 2 mg/kg S-ketamine plus midazolam combination necessitated termination of the study (16). In our study we used propofol (2mg/kg IV) and ketamine (2mg/kg IV) combination for anesthesia induction. Doses mentioned above were preferred for tracheal intubation of ASA I-II patients undergoing spinal surgery (17). In CABG, from induction of anesthesia to post intubation period, combination with nearly similar doses had provided an improved hemodynamic stability (6). However in our study, hemodynamic effects of propofol-ketamine combination were similar to those of propofol. In addition, in both groups, sympathomimetic effect to intubation was prevented.

In conditions with known myocardial dysfunction, adverse cardiovascular effects of ketamine have been demonstrated (22, 23). Sympathoadrenergic and hemodynamic effects of S-ketamine and racemic ketamine are generally identical (24). Nagels et al. (25) reported that IV anesthesia performed by S-ketamine-propofol before bypass induced statistically significant increases in post intubation systolic arterial blood pressure, MAP and HR values. In addition to hypertension, especially tachycardias are unwanted side effects in patients with CAD (26). We added fentanyl to achieve better hemodynamic stability. This approach may be a limitation of our study.

For the measurement of QT intervals, frequently ECG recordings at lead II derivations are used. For the measurement of Tp-e interval, the most optimal derivation has not identified yet. TDR finds its optimal reflection in measurements from the left precordial leads (27). Whyte et al., stated that measurements of both QTc and Tp-e intervals from leads II and V5 were the most appropriate approaches. We also used these leads in our study.

The Bazette formula is commonly used HR correction in clinical practice. However, this method may be overcorrect in conditions of accelerated HR, and under correct in bradycardic states. Especially, during general anesthesia where HR varies within a wide spectrum, this method might lead to misinterpretation of QTc interval. Though a standard measurement for QTc interval corrected for HR is not available, Fridericia method is thought to be a much better approach (28).

In conclusion, following induction with ketamine- propofol combination, QTc interval did not increase, but it prolonged post intubation QTc interval just like propofol. Assuming that increased TDR is a reliable indicator of risk of TdP, and lack of any change in Tp-e interval, in the presence of depressed hemodynamic response to intubation, we think that this combination can be safely used for the induction of anesthesia in patients with CAD undergoing CABG.

**Conflict of interests**
*The authors declare that they have no competing interests.*

**Financial Disclosure**
*All authors declare no financial support.*

**Ethical approval**
*The study protocol was approved by the ethics committee of Inonu University Medical Faculty and all patients provided written, informed consent prior to study.*

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