# QTc Interval During Desflurane Anesthesia: The Effects of Intravenous Lidocaine Prior to Intubation

## Desfluran Anestezisi Sırasında QTc Aralığı: İntübasyondan Önce Uygulanan İntravenöz Lidokainin Etkileri

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**ABSTRACT Objective:** Prolongation of the corrected QT (QTc) interval is an important predictor for the risk of polymorphic ventricular tachycardia and ventricular fibrillation. Volatile inhalational anaesthetics and intubation may cause prologation in the QTc interval. Lidocaine can be useful in preventing intubation-related cardiovascular responses. The aim of this study was to investigate whether administration of intravenous (iv) lidocaine prior to intubation would prevent the prolongation of QTc interval occuring after tracheal intubation (TI) during desflurane anesthesia. **Material and Methods:** The study group included 82 patients, all admitted for elective surgery. Anesthesia induction was provided with midazolam (0.3 mg/kg). After loss of eyelash reflex, the anaesthetic circuit was filled with desflurane and oxygen, then manually controlled ventilation was started. Cisatracurium besylate (0.15 mg/kg) was administered for muscle relaxation. After administration of muscle relaxant, either 1.5 mg/kg iv lidocaine or placebo were administered to the patients in study group (n=41) and control group (n=41), respectively. Two minutes after the administration of drugs, TI was performed at first attempt. The electrocardiography (ECG) recordings were obtained at four occasions; before anesthesia induction, after reaching steady state concentration of end tidal desflurane, just after intubation and 10 minutes after intubation. The QTc intervals, QT dispersion (QTd) and QTcd ($QTc_{max}$-$QTc_{min}$) were calculated. **Results:** QTc interval was prolonged after anesthesia induction. After intubation, QTc interval was significantly prolonged and remained so for 10 more minutes. **Conclusion:** In this study, lidocaine could not prevent prolongation of the QTc interval occuring after TI during desflurane anesthesia.

**Key Words:** Lidocaine; desflurane; electrocardiography, ambulatory; intubation, intratracheal

**ÖZET Amaç:** Düzeltilmiş QT (QTc) aralığının uzaması, polimorfik ventrikül taşikardisi ve ventrikül fibrilasyonu için önemli bir öncül bulgudur. Uçucu inhalasyonel anestetikler ve intübasyon, QTc aralığının uzamasına neden olabilmektedir. Lidokainin, intübasyona bağlı olarak gelişen kardiyovasküler yanıtların önlenmesinde yararlı olduğu gösterilmiştir. Bu çalışmanın amacı, intübasyon öncesi intravenöz (iv) lidokain uygulamasının, desfluran anestezisi altındaki hastalarda trakeal intübasyon (TI) uygulamaları sonrası gelişen QTc aralığındaki uzamayı önleyip önleyemeyeceğini araştırmaktır. **Gereç ve Yöntemler:** Çalışma grubu elektif cerrahi için yatırılan 82 hastadan oluşmaktadır. Anestezi indüksiyonu midazolam (0.3 mg/kg) ile sağlandı. Hastalarda kirpik refleksinin kaybolmasından sonra, ilk olarak, anestezi devresi desfluran ve oksijen ile doldurudu, daha sonra, manuel olarak kontrol edilen ventilasyona başlandı. Kas gevşetici olarak cisatracurium besylate (0.15 mg/kg) uygulandı. Kas gevşetici uygulamasından sonra hastalara, çalışma grubunda (n=41) 1.5 mg/kg iv lidocaine, kontrol grubunda (n=41) iv placebo verildi. Bu uygulamadan iki dakika sonra tüm hastalar ilk denemede intübe edildi. Anestezi indüksiyonundan önce, desfluranın end tidal sabit durum konsantrasyonuna ulaştıktan sonra, intübasyondan hemen sonra ve intübasyondan 10 dakika sonra olmak üzere, dört ayrı dönemde hastalardan elektrokardiografik (ECG) ölçümler alındı. QTc aralıkları, QT dispersiyonu (QTd) ve QTcd ($QTc_{max}$-$QTc_{min}$) hesaplandı. **Bulgular:** QTc aralığının anestezi indüksiyonu sonrası uzadığı gözlendi. İntübasyon sonrası, QTc aralığı belirgin olarak uzamakta ve 10 dakika bu şekilde uzamış kalmaktadır. **Sonuç:** Bu çalışmada, lidokainin, desfluran anestezisi altındaki hastalarda TI sonrası gelişen QTc aralığındaki uzamayı önleyemediği gösterildi.

**Anahtar Kelimeler:** Lidokain; dezfloran; elektrokardiyografi, ambulatuar; entübasyon, intratrakeal



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The QT interval represents the duration of ventricular depolarisation and repolarisation. Abnormally long and short QT intervals have been shown to be associated with an increased risk for life threatening ventricular arrhythmias and sudden cardiac death. Prolongation of the QT interval may be congenital or acquired and is an important marker for malignant ventricular arrhythmias.[1,2]

Since QT interval has an inverse relationship with heart rate; bradycardia causes QT prolongation, whereas tachycardia shortens it. The measured QT intervals are generally corrected for heart rate (heart rate corrected QT value= QTc) in order to determine whether they are prolonged relative to baseline or not.[3] Clinical studies have suggested that the interlead variability of the QT interval in the standart electrocardiography (ECG) should be defined as the QT dispersion (QTd), reflecting regional differences in ventricular repolarization. QTd may be useful in the assessment of dysrhythmia risk and the efficacy of antidysrhythmic drugs. Increased dispersion of recovery time (QTd≥100ms) is believed to increase the risk for serious ventricular dysrhythmias.[4]

In anesthesia practice, various factors like drugs and inhalation agents, laryngoscopy and tracheal intubation, might cause prolongation in QTc interval.[5-7] The prolongation of ventricular repolarisation following laryngoscopy and intubation could be related to increased activity of the sympathetic system and increased catecholamine release. Administration of a potent opioid or β-adrenergic blocker is generally recommended for attenuating sympathoadrenal responses elicited following laryngoscopy and TI. Ganglionic blockers, antihypertensive agents, sodium nitroprusside, nitroglycerin, barbiturates, opioids, topical or iv lidocaine, and deep anesthesia are used for preventing the hemodynamic changes (tachycardia, blood pressure changes, arrhythmia) due to TI.[8-10]

Lidocaine, intravenously and locally (via transtracheal route or laryngotracheal spray), was found to be effective for inhibiting hemodynamic changes related to TI.[11,12] On the other hand, several studies have shown that administration of intravenous (iv) lidocaine is inefficient for attenuating the cardiovascular responses.[13,14]

In the following report, it was hypothesized that inhibitory effects of lidocaine on sympathetic system would prevent the prolongation of QTc interval due to TI during desflurane anesthesia.

## MATERIAL AND METHODS

Following approval from the Bioethical Committee of the Izmir Ataturk Training and Research Hospital, and written informed consents for study participation were obtained, 82 patients were recruited to take part in the study. Patients undergoing elective non-cardiac surgery, aged between 18 and 60 years, with ASA grade I with a preoperative QTc of < 440 ms. were enrolled in this randomized, double-blind trial. With the use of a computer generated block randomization, patients were allocated into the groups receiving either 1.5 mg/kg iv lidocaine (lidocaine group, n= 41) or saline (control group, n= 41). The other anaesthetic procedures were standardized in both groups. The patients were, not premedicated. Pulse oximetry, non-invasive blood pressure (NIBP) and concentration of inspired oxygen were monitorized in all patients besides the concentrations of end-tidal anaesthetic and carbon dioxide (AS/5 monitors; Datex Ohmeda, Bromma, Sweden).

Anesthesia induction was started with iv midazolam (0.3 mg/kg). After loss of eyelash reflex, the anaesthetic circuit was filled with desflurane (vol. 6%) and oxygen (94%-fresh gas flow of 8 $L.min^{-1}$) [(Suprane™; Baxter International Inc, Lessines, Belgium, ADU S/5™ (Datex Ohmeda), Aladin™ vaporizer (Datex Ohmeda)]. Controlled ventilation was started manually to maintain the end tidal $CO_2$ level within normal limits. After steady state concentration of end tidal desflurane reached 1 MAC (minimum alveolar concentration), cisatracurium besylate (0.15 mg/kg) was administered for muscle relaxation.

Immediately after administration of the muscle relaxant, lidocaine (1.5 mg/kg) was administered intravenously to the patients in the study group. Control group received same volume of 0.9% saline. All of these medications were admi-

nistered by a physician blinded to the study drugs. Two minutes after administration of these drugs, TI was performed at first attempt.

Twelve-lead 12-lead ECG was recorded with an ECG device (Cardiofax, ECG 9620L, Nihon Kohden, Tokyo, Japan). The ECG recordings were obtained before anesthesia induction (T0), after steady state concentration of end tidal desflurane reached 1 MAC (T1), just after intubation (T2), and 10 minutes after intubation (T3). Heart rate (HR), ECG, and NIBP were also recorded at the same time.

QT intervals were measured manually using a magnifier by a physician who was blinded to any other data on each individual patient. QT interval was determined as a mean value, derived from three consecutive cardiac cycles. It was measured from the beginning of the earliest onset of the QRS complex to the end of the T wave (the point that T wave returned to the isoelectric line). If U waves were present, the end of the T wave was taken as the nadir of the curve between the T and U waves. The mean value of QT interval was calculated from all derivations. The results were expressed in milliseconds.

QT correction for HR was calculated for each derivation using Bazett's formula ($QTc=QT.RR^{-1/2}$). QTd was calculated as the difference between maximal and minimal QT in each of the 12 ECG leads ($QT_{max}$-$QT_{min}$). QTcd was calculated similarly ($QTc_{max}$-$QTc_{min}$).

### STATISTICAL ANALYSIS

A power analysis based on our pilot study suggested that a minimum sample size of 38 patients per group would be required to detect a 15 ms difference in means (standard deviation: 79 ms) for the QTc interval in the anaesthetic groups (power of 96% at the $p<0.05$ level of significance) (NCSS-PASS 2000, Repeated Measures ANOVA Power Analysis).

The variables (related to QT and hemodynamic findings) were analysed by "repeated measure ANOVA" in respect to time lines (T0-T3) and the groups. When significant differences were found by ANOVA method, pairwise analyses were performed with Bonferroni test as post hoc method. Student's t-test was used for intergroup comparisons. A p value of $<0.05$ was considered significant. Data are expressed as mean ± standard deviation (SD).

## RESULTS

The patients' demographic data showed no significant differences between the groups (Table 1). Neither supraventricular nor ventricular dysrhythmias were observed during the study and no patient was excluded from the study.

Lidocaine administration before intubation resulted in stability of systolic and diastolic blood pressure values (p= 0.07, p= 0.124, respectively); but in the control group, blood pressures were increased after intubation and statistically significant changes were noted for systolic and diastolic blood pressure values (p= 0.001, p= 0.005, respectively) (Figure 1). Intergroup comparisons were statisti-

**TABLE 1:** Demographic characteristics of the study groups.

| | Lidocaine Group | Control Group | p |
|---|---|---|---|
| Age (years) | 46 ± 13 | 45 ± 14 | 0.78 |
| Weight (kg) | 70 ± 12 | 67 ± 11 | 0.19 |
| Sex M/F (n) | 16/25 | 15/26 | 1.0 |

Data are Mean ± SD

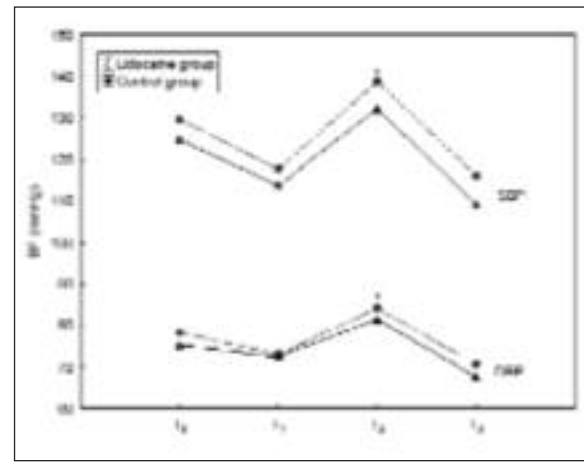

**FIGURE 1:** Systolic (SBP) and diastolic (DBP) blood pressure mean differences between groups at each time point. T0, before anesthesia induction; T1, after reaching steady state concentration of end tidal desflurane; T2, just after intubation; T3, 10 minutes after intubation.*p< 0.05 intragroup comparisons for T0 in control group. Intergroup comparisons were statistically insignificant at each time point (p> 0.05)

cally insignificant at each time point (p> 0.05). The heart rates recorded after induction and intubation were significantly increased in both groups (p= 0.001) (Figure 2).

Desflurane was associated with a statistically significant prolongation of QTc in both lidocaine and control group (p< 0.05) and this prolongation was also present 10 minutes after intubation. However, QTc prolongation in the lidocaine and control groups were similar throughout the study and there were no statistically significant differences. Compared with T0 and T1 values, the QTc intervals recorded after intubation (T2) were significantly prolonged in both groups (lidocaine group p<0.001 and control group p=0.003). QTc prolongations following intubation were similar in both groups with no statistically significant differences. Intergroup and intragroup comparisons for QTd and QTcd measurements throughout the study were statistically insignificant (Table 2, Figure 3).

## DISCUSSION

In the present study iv lidocaine administration prior to endotracheal intubation did not prevent the prolongation of QTc interval following intubation during desflurane anesthesia.

Sympathetic nervous system activation was observed when desflurane was added into the inspired gas just after induction of anesthesia. This activation has been noted whenever the concentration of inspired desflurane exceeds 5-7% (approximately 1.0 MAC). Rapid increase in the concentration of desflurane is associated with sympathetic activation, causing tachycardia and hypertension in humans.[15]

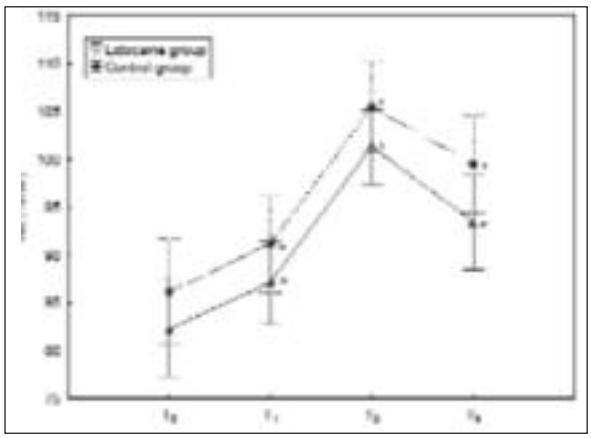

**FIGURE 2:** Mean and 95% confidence intervals of heart rate (HR) during study. T0, before anesthesia induction; T1, after reaching steady state concentration of end tidal desflurane; T2, just after intubation; T3, 10 minutes after intubation *p< 0.05 intragroup comparisons for T0.

**TABLE 2:** QT measurements.

| | | Lidocaine Group | Control Group | **p |
|---|---|---|---|---|
| QT | T0 | 362 ± 31 | 355 ± 32 | 0.32 |
| | T1 | 359 ± 26 | 354 ± 32 | 0.47 |
| | T2 | 348 ± 24 # | 345 ± 26 # | 0.52 |
| | T3 | 362 ± 32 | 356 ± 29 | 0.32 |
| QTc | T0 | 421 ± 15 | 421 ± 15 | 0.87 |
| | T1 | 430 ± 17 * | 431 ± 14 * | 0.79 |
| | T2 | 451 ± 17 # | 454 ± 18 # | 0.42 |
| | T3 | 448 ± 21 # | 453 ± 17 # | 0.18 |
| QTd | T0 | 19 ± 15 | 19 ± 11 | 0.93 |
| | T1 | 17± 13 | 22 ± 12 | 0.06 |
| | T2 | 20 ± 11 | 19 ± 11 | 0.62 |
| | T3 | 22± 10 | 18 ± 11 | 0.14 |
| QTcd | T0 | 31± 17 | 32 ± 17 | 0.66 |
| | T1 | 27 ± 18 | 32 ± 16 | 0.16 |
| | T2 | 31 ± 14 | 27 ± 14 | 0.18 |
| | T3 | 29± 13 | 26 ± 16 | 0.35 |

T0: Before anesthesia induction
T1: After reaching steady state concentration of end tidal desflurane
T2: Just after intubation
T3: 10 minutes after intubation
Data are Mean ± SD
*p< 0.05 intragroup comparisons for T0
# p<0.05 intragroup comparisons for T0 and T1
** p intergroup comparisons

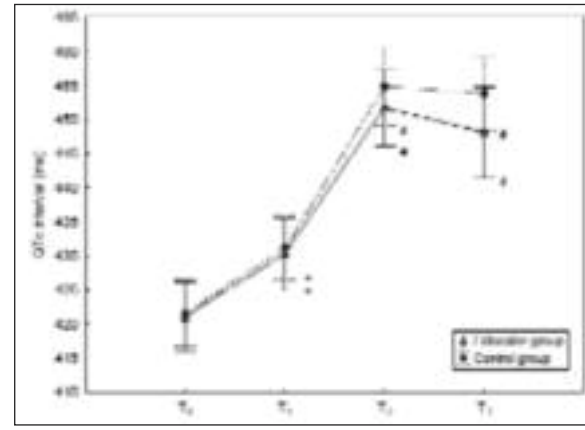

**FIGURE 3:** Mean and 95% confidence intervals of QTc interval during different time points. T0, before anesthesia induction; T1, after reaching steady state concentration of end tidal desflurane; T2, just after intubation; T3, 10 minutes after intubation; *p< 0.05 intragroup comparisons for T0; # p<0.05 intragroup comparisons for T0 and T1.

A second possible site for eliciting sympathoexcitatory responses might be within the central nervous system (CNS). The rapid increase in the partial pressure of desflurane in CNS could cause a disinhibition of central sympathetic outflow.[16]

Studies on ventricular papillary muscles of Guinea pigs revealed that desflurane related myocardial depression was due to decreased $Ca^{2+}$ influx, similar to the effects of isoflurane and sevoflurane. Desflurane causes depression in the delayed outward $K^{+}$ current which, in turn, is associated with significant lengthening in cardiac action potentials.[17]

Desflurane, similar to the other inhalation agents, affects the QTc interval by its irritating effects on respiratory tract, besides eliciting sympathoexcitatory responses and alterations in the cardiac ion channels.[15,17]

We determined that desflurane caused prolongation of QTc, which is previously reported by Yildirim and Owczuk.[18,19] The prolongation of QTc interval has started after induction of anesthesia, and may be due to symphatetic activation and the irritating effect of desflurane on respiratory tract. Owczuk also determined that the prolongation of QTc interval increased with intubation, as in the present study.[19] In our study, the prolongation of QTc did not return to normal values 10 min. after intubation, which may be due to desflurane effect. Owczuk stated that the significant QTc prolongation may be attributable to the direct effect of the anaesthetic on the myocardium.[19] However, that study terminated just after intubation and did not observe QT changes that might occur during the time period following intubation. Yildirim et al also found that the prolongation continued 10 min. after reaching a steady state of 1 MAC desflurane concentrations.[18] However, they didn't investigate the relation between prolongation of QTc and intubation.

The cardiovascular response associated with laryngoscopy and intubation is attenuated in some patients by iv administration of lidocaine (1.5 mg/kg) 1-3 min. prior to instrumentation. Then, we hypothesized that this effect of lidocaine may also prevent the prolongation of QTc interval which is caused by intubation. Ugur et al. showed that iv administration of lidocaine prior to intubation during sevoflurane anesthesia prevented the increase in sympathetic autonomic cardiac function.[20] However, Lin et al. stated that lidocaine 3 and 5 min prior to intubation was ineffective on autonomic regulation during tracheal intubation under the influence of induction agents used in general anesthesia.[14] They concluded that there was no evidence to indicate the effectiveness of iv lidocaine on the autonomic regulation during TI under the influence of induction agents used in general anesthesia. In some other studies, both iv and topical lidocaine were reported to fail in attenuating the sympathetic response against desflurane, and it was concluded that airway irritation was not the only cause of this phenomenon.[21,22]

In a recent study Owczuk et al. stated that lidocaine administration prevented prolongation of the QTc interval induced by laryngoscopy and tracheal intubation.[23] In contrast to Owczuk et al. findings of our study demonstrates that iv lidocaine prior to intubation cannot prevent the prolongation of QTc. In the present study, TI and lidocaine administration was performed during desflurane anesthesia which is known to prolong QTc and different results from Owczuk's study may be related to desflurane effects.

Yildirim et al. have detected prolongation of both QTd and QTcd in the desflurane group.[18] However, we have not detected QTd or QTcd prolongation with desflurane. QT dispersion was originally proposed to measure spatial dispersion of ventricular recovery times. Later, it was shown that QT dispersion did not directly reflect the dispersion of recovery times and that it resulted mainly from variations in the T loop morphology and the error of QT measurement. The reliability of both automatic and manual measurement of QT dispersion is low and significantly lower than that of the QT interval. The measurement error is of the order of the differences between different patient groups. The agreement between automatic and ma-

nual measurement is poor. There is little to choose between various QT dispersion indices, as well as between different lead systems for their measurement.[4] The difference between the present study and Yildirim et al.'s study for QTd and QTcd intervals may be due to the low reliability of measurements.

## CONCLUSION

We conclude that desflurane prolonged QTc interval, tracheal intubation increased this prolongation, and iv lidocaine 1.5 mg/kg given two minutes before intubation does not prevent intubation related QTc prolongation during desflurane anesthesia.

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