

The effect of adrenaline on desflurane-induced prolonged QTc interval: a randomized double-blind trial

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This article was presented in 46th the Turkish Anaesthesiology and Reanimation Congress

Abstract. – BACKGROUND AND AIM: We investigated the effect of adrenaline on desflurane-induced prolonged corrected QT (QTc) interval.

PATIENTS AND METHODS: Sixty-two adult patients scheduled for nasal surgery were included. Following intubation, packs soaked in physiological saline were used for Group C (control) and packs soaked in adrenaline (1/200,000, 5 ml) were used for Groups A1 and A2. Group A2 was given desflurane simultaneously with nasal packing; other groups were given desflurane following removal of the packs. QTc interval was evaluated at 9 periods, from prior to induction of anaesthesia to postoperative first hour.

RESULTS: QTc interval was significantly reduced in Groups A1 and A2 compared to Group C during packaging ($p < 0.001$, $p < 0.05$ respectively), while QTc interval gradually prolonged after desflurane administration ($p < 0.05$ in Groups C compared to Groups A1 and A2). Patients did not develop arrhythmia.

CONCLUSIONS: Our findings show that desflurane caused progressive prolongation of the QTc interval, and adrenaline shortened QTc interval only at application period of packs.

Key Words:

Desflurane, Adrenaline, QTc interval.

pointes”, which can cause sudden death¹⁻³. QT interval depends on heart rate; higher heart rate is associated with shorter QT interval¹. Therefore, in practice, QT interval is corrected according to heart rate (rate-corrected QT: QTc). Previous studies revealed that volatile anaesthetic agents (halothane, isoflurane, sevoflurane, desflurane) prolong QTc interval⁴⁻⁶. Owczuk et al⁵ suggested that desflurane caused prolongation of QTc interval from the first minute of application.

In nasal surgery, vasoconstrictors such as cocaine, phenylephrine and adrenaline are commonly used alone or in combination to reduce bleeding at the intervention area and to increase surgical comfort⁷. In our hospital, adrenaline (with or without lidocaine) is often infiltrated to a pack and used by surgeons by placing in the nasal cavity. Adrenaline prolongs QT interval both in patients with long QT syndrome (LQTS) and in normal patients^{8,9}.

In the present study, we investigated the effect of 1/200,000 adrenaline which was topically applied to the surgical area to control bleeding in nasal surgery under desflurane anaesthesia on desflurane-induced prolonged QTc interval.

Introduction

In electrocardiogram (ECG), the time from the onset of QRS complex to the end of T wave reflects electrical polarization and repolarization of left and right ventricles, and is termed QT interval. Congenital or acquired prolonged QT interval is a significant risk factor for the development of ventricular tachyarrhythmia such as “torsades de

Patients and Methods

Informed consent was obtained from each participants, and the study was approved by the Firat University School of Medicine Clinical Research Ethics Committee. Sixty-two adult patients of both genders from ASA I physical status who were scheduled for elective nasal surgery (septoplasty, rhinoplasty or septorhinoplasty) under general anaesthesia were included in this prospective,

randomized, externally controlled and double blind study. Patients with a history of allergy to drugs used; with QTc interval above 440 ms; those who had a cardiac disease; patients using drugs that are known to have effect on QTc interval; those with endocrine and metabolic diseases and fluid-electrolyte imbalance were excluded from the study. Data on the control group (Group C, n=22) was obtained from the specialization thesis of one of the Authors¹⁰. The remaining 40 patients were divided into adrenaline 1 (Group A1, n=20) and adrenaline 2 (Group A2, n=20) groups using a random number table.

Standard premedication, motoring and anaesthesia techniques were applied to all patients. The patients were premedicated with 0.05 mg.kg⁻¹ midazolam intramuscularly approximately 30 min before the induction of anaesthesia. ECG, noninvasive systolic arterial pressure (SAP), diastolic arterial pressure (DAP), heart rate (HR), peripheral oxygen saturation (SpO₂) and end-tidal carbon dioxide (ETCO₂) were continuously monitored in the operating room. HR, SAP, DAP and 12-lead ECG records were taken simultaneously before (baseline values) and immediately after induction of anaesthesia, immediately after tracheal intubation, immediately before the removal of nasal packs, at 5, 15 and 30 min of desflurane administration, after discontinuation of anaesthesia, and at 1st h postoperatively. QT intervals (from the onset of QRS complex to the end of T wave) were measured on ECG by a researcher who was blinded of the patient groups; rate-corrected QT interval (QTc) was calculated using the Bazett's formula ($QTc = QT / \sqrt{RR}$).

Anaesthesia was induced with 0.2 mg.kg⁻¹ etomidate, 1 µg.kg⁻¹ fentanyl and 0.1 mg.kg⁻¹ vecuronium bromide. After tracheal intubation, ventilation was mechanically maintained by adjusting ETCO₂ within normal values. The packs soaked in 5 ml physiological saline solution were used in the control group; the packs soaked in 5 ml 1/200,000 adrenaline solution were used in Group A1 and Group A2. The packs were placed in both nasal cavities for 5 min immediately after endotracheal intubation. Anaesthesia was maintained with 4-6% desflurane in 50% O₂ and 50% air, and 2 mg vecuronium bromide and 0.5-1.0 µg.kg⁻¹ fentanyl were given when needed. Desflurane was given to Group A2 at the same time by placing nasal packs, to Group C and Group A1 after removal of nasal packs. In Group C and Group A1, additional intravenous bolus etomidate was given when necessary until desflurane

administration. Anaesthetic administration was ended after the surgery; 0.03 mg.kg⁻¹ neostigmine and 0.01 mg.kg⁻¹ atropine sulfate were given intravenously to remove residual effect of muscle relaxation. Patients were monitored in the recovery room for 1 h following endotracheal extubation. Intraoperative bleeding at the surgical site was evaluated using the "Scale for Quality of Surgical Field" by a surgeon who performed the surgery and who was blinded of the content of the packs (Table I)¹¹. In addition, the amount of bleeding in gauze and compresses used during surgical intervention was calculated and added to the volume of blood in the aspirator to estimate the amount of bleeding (a saturated gauze was considered to hold 10 ml blood; one compress was considered to hold 100 ml blood).

Statistical Analysis

Data were statistically analyzed using SPSS (Statistical Package for Social Sciences for Windows Inc., version 15.0, Chicago, IL, USA). Chi-square test, one-way analysis of variance (ANOVA) and post-hoc Tukey's HSD (honestly significant difference) test were used for comparisons between groups. The Wilcoxon two-sample test was used for statistical analysis of intragroup comparisons. A value of $p < 0.05$ was considered significant.

Results

The study was successfully completed in all participants. Demographic characteristics, duration of anaesthesia and surgery of the groups were similar (Table II). Bleeding was significantly lower ($p < 0.001$) and quality of surgical field scale was lower ($p < 0.01$) in Group A1 and Group A2 compared to Group C (Table II).

Table I. Scale for Quality of Surgical Field¹¹.

Score	Status of the surgical field bleeding
5	Massive uncontrollable bleeding
4	Bleeding, heavy but controllable, that significantly interfered with dissection
3	Moderate bleeding that moderately compromised surgical dissection
2	Moderate bleeding, a nuisance but without interference with accurate dissection
1	Bleeding, so mild it was not even a surgical nuisance
0	No bleeding, virtually bloodless field

Table II. Demographic characteristics, duration of anaesthesia and surgery, surgical bleeding status of groups (mean $\pm$ SD).

	Group C	Group A1	Group A2
Age (years)	26.77 $\pm$ 4.87	27.60 $\pm$ 4.25	25.85 $\pm$ 5.00
Height (cm)	172.36 $\pm$ 14	170.70 $\pm$ 6.97	174.10 $\pm$ 8.66
Weight (kg)	74.72 $\pm$ 11.62	73.70 $\pm$ 7.98	78.10 $\pm$ 9.05
Gender (M/F)	13/9	13/7	14/6
Duration of anaesthesia (min)	70.22 $\pm$ 22.49	75.40 $\pm$ 20.28	73.35 $\pm$ 24.71
Duration of surgery (min)	53.40 $\pm$ 20.43	59.20 $\pm$ 22.63	55.60 $\pm$ 24.94
Bleeding (ml)	70.22 $\pm$ 8.79*	57.20 $\pm$ 6.56	58.00 $\pm$ 7.32
SQSF&	2.72 $\pm$ 0.45‡	1.95 $\pm$ 0.68	1.90 $\pm$ 0.78

&SQSF: Scale for Quality of Surgical Field. * $p < 0.001$ compared with Groups A1 and A2; ‡ $p < 0.01$ compared with Groups A1 and A2.

There was no statistically significant difference between the groups in terms of preanaesthetic haemodynamic parameters and QTc interval values (baseline values) ($p > 0.05$).

The observed changes in QTc interval were similar in all three groups excluding the period when nasal packs were placed (Figure 1). Both anaesthesia induction and tracheal intubation caused prolongation of QTc interval compared to baseline values, but was within normal values. On the other hand, before removal of nasal packs a minimal reduction occurred in QTc interval in Group C. However, statistically significant reduction occurred in Group A1 and Group A2 compared with Group C ($p < 0.001$ and $p < 0.05$, respectively). After removal of the packs, significantly increasing prolongation of QTc interval

was observed in all groups throughout desflurane administration ($p < 0.05$ in Group C compared to Groups A1 and A2 at 15th min). It was observed that QTc interval duration exceeded 440 ms in some cases of Group C and Group A1 at 30th min of desflurane application ($p < 0.001$ compared to baseline values in all groups). After discontinuation of anaesthesia, QTc interval reduced rapidly and reached baseline values at postoperative 1st h in all three groups. None of the patients developed arrhythmia during the study period.

Heart rate was higher in Group A1 and Group A2 than Group C in the presence of nasal packs and during desflurane administration (Figure 2). At the 4th and 5th periods in which the values were recorded, there was a statistically significant difference between the groups ($p < 0.05$ in

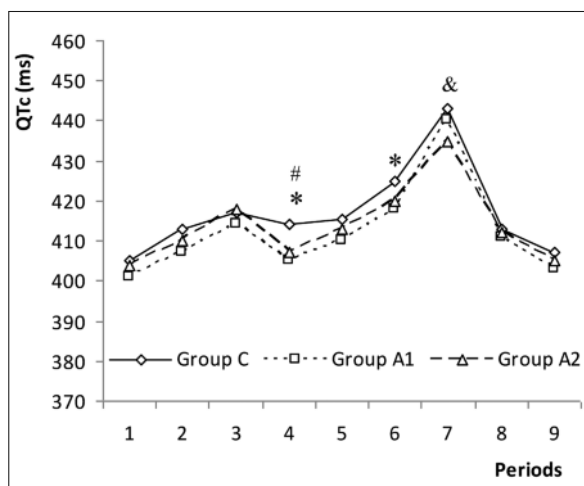


Figure 1. Changes in QTc interval. Periods: 1. Prior to induction of anaesthesia; 2. Immediately after induction; 3. Immediately after intubation; 4. Before removal of nasal packs; 5, 6, and 7. During desflurane administration 5th, 15th and 30th min; 8. 5 min after extubation; 9. Postoperative 1st h. * $p < 0.05$, # $p < 0.001$, & $p < 0.001$.

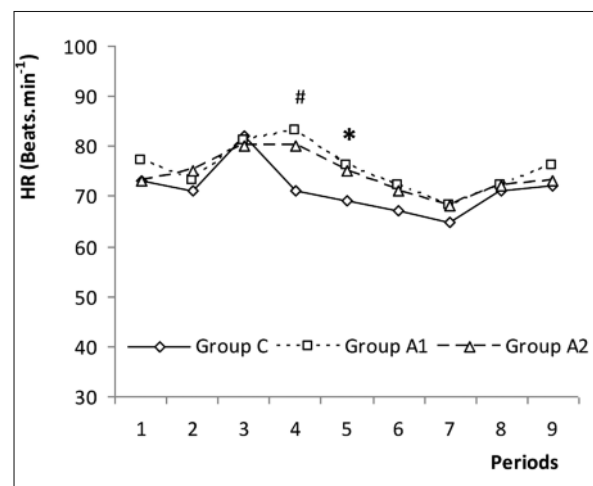


Figure 2. Changes in heart rate (HR). Periods: 1. Prior to induction of anaesthesia; 2. Immediately after induction; 3. Immediately after intubation; 4. Before removal of nasal packs; 5, 6, and 7. During desflurane administration 5th, 15th and 30th min; 8. 5 min after extubation; 9. Postoperative 1st h. # $p < 0.01$, * $p < 0.05$.

Groups A1 and A2 compared to Group C). During the 4th period, immediately before the removal of nasal packs, the SAP and DAP values of Group A1 and Group A2 were significantly higher than those of Group C ($p < 0.05$). Apart from this period, SAP and DAP values were similar in all three groups (Figures 3 and 4).

Discussion

It was reported that volatile and intravenous anaesthetics were associated with prolonged QTc interval^{4,6,12}. Previous studies showed that desflurane, which is a volatile anaesthetic, led to the prolongation of QTc interval when used to induce and to maintain anaesthesia^{5,6}. It had been suggested that desflurane significantly prolonged QTc interval more than sevoflurane^{13,14}. In this study, we detected prolonged QTc interval, which started with desflurane administration and tended to increase, even exceeding the normal upper-value 440 ms at 30th min of desflurane application in Group C and Group A1. Owczuk et al⁵ used desflurane to induce anaesthesia in adult patients undergoing elective surgical intervention, and detected prolonged but non-progressive QTc interval from the first minute of desflurane application. Yildirim et al⁶ gave 1 MAC either sevoflurane, isoflurane or desflurane in 100% O₂ to maintain general anaesthesia in adult patients.

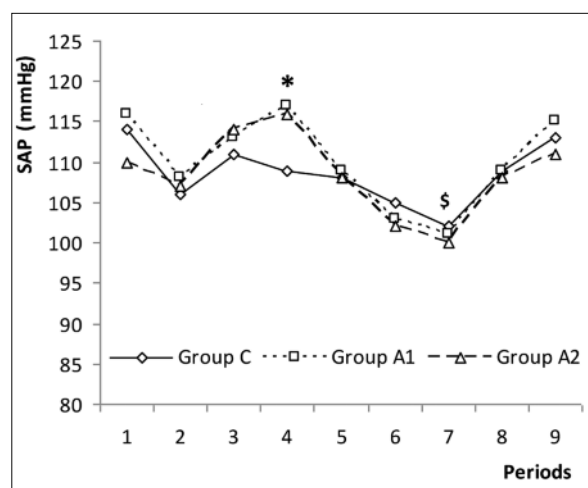


Figure 3. Changes in systolic arterial pressure (SAP). Periods: 1. Prior to induction of anaesthesia; 2. Immediately after induction; 3. Immediately after intubation; 4. Before removal of nasal packs; 5, 6, and 7. During desflurane administration 5th, 15th and 30th min; 8. 5 min after extubation; 9. Postoperative 1st h. * $p < 0.05$.

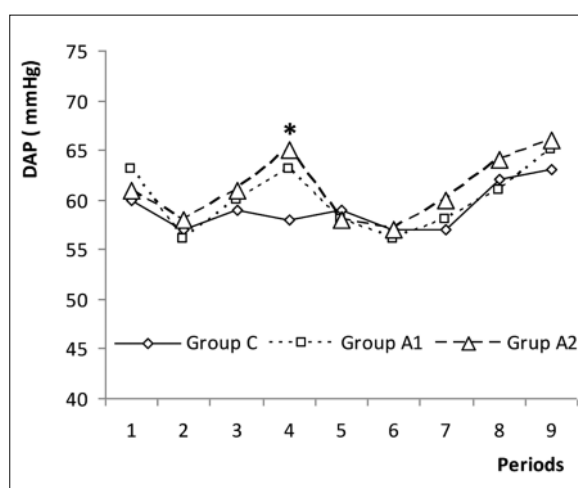


Figure 4. Changes in diastolic arterial pressure (DAP). Periods: 1. Prior to induction of anaesthesia; 2. Immediately after induction; 3. Immediately after intubation; 4. Before removal of nasal packs; 5, 6, and 7. During desflurane administration 5th, 15th and 30th min; 8. 5 min after extubation; 9. Postoperative 1st h. * $p < 0.05$.

They observed that all three volatile anaesthetic agents caused prolongation of QT, QTc and QTc dispersion. Examination of their findings showed that, in the desflurane and isoflurane group, QTc interval progressively lengthened similarly to the present study.

In nasal surgery, adrenaline, a sympathetic agonist, is frequently used alone or in combination with a local anaesthetic, by infiltration or topically during and after surgery to reduce bleeding at the intervention site. In this study, the use of nasal packs infiltrated with 5 ml 1/200,000 adrenaline solution for 5 min significantly reduced surgical bleeding. Both infiltration and topically-applied adrenaline can be absorbed into the systemic circulation¹⁵ and might cause temporary but significant hemodynamic changes, although the findings are controversial^{16,17}. Adrenaline prolongs QT interval both in individuals with LQTS and in normal patients^{7,8}. The "Adrenaline QT stress test" is emphasized to be a beneficial tool in detecting LQTS in suspected cases.⁹ However, we detected significantly shorter QTc interval although adrenaline nasal pack groups had higher SAP, DAP and HR values than the control group at the time of applying nasal packs. Research on healthy adults volunteers showed a correlation between sympathetic hyperactivity and desflurane^{18,19}. For this reason desflurane-induced prolonged QTc interval can be expected to be aggravated by the use

of adrenaline-soaked nasal packs. Contrary to the expectations, the use of nasal packs before or simultaneously with desflurane administration did not cause further prolongation of QTc interval; conversely, it was shortened when compared to post-intubation values, during the presence of nasal packs. This might be caused by the elevation in HR following the use of adrenaline-soaked packs, because increased HR is claimed to be correlated with shorter QT interval¹. The main reason of shortened QTc interval might be adrenaline-induced increased ventricular contractility. In an experimental study on mongrel dogs, Huang et al²⁰ found that shorter QT interval induced by efferent sympathetic neurons, was associated with strengthened ventricular contractility rather than heart rate. Like other volatile anesthetics, desflurane inhibits ventricular contractility²¹. However, the changes in QTc interval in the group with simultaneous use of desflurane with adrenaline soaked nasal packs were similar to those in the other group with adrenaline-soaked nasal packs with no desflurane. The effect of adrenaline on QT interval duration also depends on dosage. In our study, only 5 ml 1/200,000 adrenaline solution was used. Magnano et al⁸ reported that 0.05 and 0.10 $\mu\text{g.kg}^{-1}.\text{min}^{-1}$ epinephrine infusion shortened QT interval for 15 ± 11 ms and 21 ± 17 ms, respectively. When certain agents are used together or in succession, they might change their effects on QT interval. Kleinsasser et al²² claimed that propofol completely reversed sevoflurane-induced prolonged QTc in 15 min. In our study, although Group A2 was given desflurane that prolonged QTc interval, QTc interval did not lengthen during the presence of nasal packs might be associated with the effect of the small amount of adrenaline contained by the packs.

In addition to certain agents used for anaesthesia, direct laryngoscopy and tracheal intubation can also prolong QT interval and are known to cause high arterial blood pressure, increased HR and to prolong QTc interval due to increased sympathetic activity^{23,24}. In anaesthesia practice, to prevent haemodynamic response to laryngoscopy and tracheal intubation, induction drugs are generally used in combination with a synthetic opioid, beta-blocker agent or lidocaine²³⁻²⁶. Sometimes, adding a single agent (for example fentanyl) to induction drugs might not be sufficient. Kaneno et al²⁷ observed that, although they used intravenous 1.5 mg.kg^{-1} propofol combined with 2 $\mu\text{g.kg}^{-1}$ fentanyl to induce anaesthesia in adult patients, QT

and QTc interval significantly increased for 10 min during and after tracheal intubation. On the other hand, in patients who were given 0.04 $\text{mg.kg}^{-1}.\text{min}^{-1}$ infusion landiolol (a β_1 -adrenoceptor antagonist) following 0.125 mg.kg^{-1} loading, immediately before induction to this combination, QT and QTc interval was significantly lower than those who were not given landiolol. Etomidate is frequently preferred to induce anaesthesia in patients with cardiac disease, or in patients who are planned to undergo cardiac surgery, because it provides superior haemodynamic stability compared with propofol, thiopental and midazolam. Owczuk et al²³ administered 1.5 mg.kg^{-1} lidocaine or placebo following intravenous 20 mg etomidate and 0.1 mg fentanyl to induce anaesthesia in female patients undergoing elective surgical intervention. They investigated the effects of laryngoscopy and tracheal intubation on QT, QTc and transmural dispersion of repolarization (TDR) via Bazett's Formula, Fridericia's correction and Framingham Formula to correct QT interval. They reported no significant difference between groups in terms of TDR, and that unlike those who were give lidocaine, QT interval calculated according to all three formulae significantly prolongation in the placebo group. In our study, anaesthesia induction and tracheal intubation caused prolonged QTc interval in all three groups.

Conclusions

We detected prolonged QTc intervals, which started with desflurane administration and tended to increase, even exceeding 440 ms at 30th min of anaesthesia application. This might not cause a problem for healthy patients; however it can cause life-threatening arrhythmia in patients with congenital long QT syndrome. Our study shows that, prior to surgery, application of nasal packs soaked in 1/200,000 adrenaline (particularly simultaneously with desflurane administration) significantly controlled bleeding at the surgical site and also provided shorter desflurane-induced QTc interval. Since QTc interval continued to prolong in parallel to desflurane application time, we believe that patients under desflurane anaesthesia should be closely monitored for potential arrhythmias.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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