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Research Article

Effect of anthracyclines and isoflurane on QTc interval

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KEYWORDS

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Abstract *Background:* Anaesthetics and anthracyclines can affect the QT interval of the electrocardiogram (ECG). This study investigated whether the use of isoflurane in anthracyclines pretreated patients may induce or augment the QT prolongation to an arrhythmogenic level.
Materials and methods: Fifty-four female patients with breast cancer scheduled for mastectomy were included in the study, 27 received anthracyclines based chemotherapy before surgery, whereas 27 did not. All patients received a standardized balanced anaesthetic in which 0.5% end tidal concentration of isoflurane was used. The QT and corrected QT intervals (QTc) were measured before anaesthesia, after 1, 5, 15, 30, 60 min, respectively, following intubation and during recovery from anaesthesia.
Results: Statistically significant QTc prolongation was observed in patients who received anthracycline chemotherapy even prior to the administration of anaesthesia. The comparison of QTc interval at different intervals of isoflurane anaesthesia also showed a statistically significant difference between the two groups namely anthracycline treated group (study group) versus control group.
A sample size of 27 in each group was calculated in order to achieve a study power of 80% with type 1 error rate of 5%. For the purpose of calculation, values of QT and QTc interval (range, mean, standard deviation) from the study of Owczuk et al. were used. *t*-test and analysis of variance were employed using SPSS version 10. $P < 0.05$ was considered as statistically significant.
Conclusions: Anthracycline chemotherapy can produce significant prolongation of QTc interval. In addition, use of 0.5% end tidal concentration of isoflurane can further augment the QTc interval significantly.

1. Introduction

Chemotherapy forms an important adjuvant for the treatment of breast cancer. Anthracyclines especially doxorubicin is a commonly employed chemotherapeutic agent which can prolong the QT interval in susceptible individuals [1]. Isoflurane, one of the most commonly used inhalational anaesthetic agent for maintenance of anaesthesia, is also shown to prolong the QT interval [2]. Prolongation of the QT interval is associated

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with sinister arrhythmias [3,4]. In recipients of anthracyclines, dose dependent prolongation of the QT interval is a marker of post anthracyclines cardio toxicity [1,5,6]. Earlier studies have shown that Propofol, which was used for induction of anaesthesia, tends to shorten the QT interval [7,8]. The effect of increased heart rate on QT interval has been overcome by using correction of QT interval for heart rate (QTc) by (Bazett's [9,10] and Fridericia's formulae [11].

In this context, a study was conducted in our institute to investigate whether the addition of Isoflurane to the anaesthetic regimen in anthracycline pretreated patients would prolong the QT interval to an arrhythmogenic level and to assess the effect of isoflurane on the haemodynamic variables (blood pressure and heart rate) of the patients under study. Propofol was used as the induction agent, which may limit the QT prolongation produced by isoflurane.

2. Materials and methods

After obtaining approval from the institutional review board and ethics committee, 54 women aged 30–60 years of ASA (American Society of Anaesthesiologists) 1 and 2 statuses scheduled for mastectomy were enrolled in the study. Twenty-seven patients received anthracycline chemotherapeutic agents (study group) and 27 patients did not receive any such treatment before surgery (control group). Patients were excluded from the study if they received class 1 or 3 antiarrhythmics and had any history of heart disease, hypertension or any circulatory insufficiency. Patients receiving psychotropic or other drugs known to prolong the QT interval or having any preoperative electrolyte abnormalities, significant arrhythmias, or conduction disturbances in the preoperative ECG were also excluded. Diabetics included in the study were controlled with regular insulin if they were previously on oral hypoglycaemic agents.

All patients included in the study group underwent a detailed preanaesthetic check-up, a cardiology evaluation including echocardiography. The age, weight, baseline heart rate, systolic and diastolic blood pressures were noted. The preoperative ECG findings were recorded. Written informed consent was obtained from all the patients. They received tablet diazepam 0.2 mg/kg bodyweight and tablet ranitidine 150 mg the night before surgery and tablet ranitidine 150 mg and tablet metoclopramide 10 mg at 6.00 am on day of surgery following overnight fasting.

After the machine check and preparation of the operation theatre, an ECG was taken in the reception area and the time, blood pressure and the heart rate were noted. An intravenous access was secured, and fluid infusion started with 0.9% normal saline and then shifted to the operating room in a trolley. 1 mg of midazolam was given, and monitors were attached – ECG, non invasive blood pressure (NIBP), pulse oximetry (SPO2) and baseline values obtained in the multiparameter monitor. The electrodes for recording the lead 2 of ECG were also attached.

The patients were preoxygenated with 100% oxygen for 3 min and intravenous fentanyl 2 μg/kg bodyweight was given 5 min before laryngoscopy. General anaesthesia was induced with intravenous propofol 2 mg/kg bodyweight. The adequacy of mask ventilation was confirmed and vecuronium 0.1 mg/kg bodyweight was given and the time noted. Anaesthesia maintained with nitrous oxide oxygen mixture at a ratio of 2:1 at 6 l/min fresh gas flow. At 1.5 min after giving the relaxant intravenous lidocaine, 2% was given at a dose of 1.5 mg/kg body weight for stress response attenuation. Direct laryngoscopy with appropriate sized Macintosh blade was carried out and the trachea intubated with an appropriate sized cuffed oral endotracheal tube. The endotracheal tube was secured after confirming the position of the tube by auscultation and end tidal carbon dioxide (ETCO2). Soon after intubation, an ECG was obtained and anaesthesia was maintained using nitrous oxide oxygen in 2:1 ratio at fresh gas flow of 3 l/min and isoflurane in a concentration of 0.5% by volume. ECGs were obtained at 1 min of anaesthesia with isoflurane 0.5% and then at regular intervals of 5, 15, 30 and 60 min of anaesthesia. During the whole period of ECG recording, the end tidal isoflurane concentration was monitored in the anaesthesia workstation and was kept at 0.5%. Near the end of surgery, the isoflurane concentration was reduced and discontinued at beginning of skin closure. Following reversal of neuromuscular block with neostigmine 0.05 mg/kg body weight and glycopyrrolate 0.01 mg/kg bodyweight, trachea was extubated and another ECG-lead 2 was obtained in the recovery room.

The QT and corrected QT intervals (QTc) were measured before anaesthesia, after 1, 5, 15, 30, 60 min, respectively, following intubation and during recovery from anaesthesia. QTc were calculated using Bazett's [9,10] and Fridericia's formulae [11].

3. Results

All patients in the study group received adriamycin with 21 patients received 6 cycles and 6 patients received 5 cycles. The total cumulative dose received by the study patients ranged from 250 mg/m^2 to 300 mg/m^2 body surface area. The age and body weight were similar in both the groups ($p > 0.05$). The QT interval showed statistically significant differences even at baseline and subsequently at different intervals of anaesthesia between the study and control groups. In the study group (anthracycline group), significant prolongation of QT interval was observed. The mean (SD) baseline values of QT for control and study groups were 0.27 (0.03) and 0.37 (0.03) respectively (p-value = 0.001). In the control group, the mean values of QT interval at different time intervals of anaesthesia increased to 0.29 s, whereas the corresponding values in the study group increased to 0.42 s, which exceeded the normal value of 0.40 s. The augmentation of QT prolongation produced by isoflurane was proportional in both the control and study group (Table 1).

Similar to QT interval, QTc interval based on both Bazett's and Fridericia's formulae also showed statistically significant differences at baseline and subsequently at different intervals of anaesthesia between the study and control groups. The mean (SD) baseline values of QTc based on Bazett's formula for control and study groups were 0.30 (0.03) and 0.46 (0.05), respectively (p-value = 0.001). In the control group, the mean values of the QTc interval at different time intervals increased to 0.34 s, whereas the corresponding values in the study group increased to 0.48 s which exceeded the normal value of 0.44 s. Similar to QT interval, the augmentation of QTc prolongation produced by isoflurane was proportional in both the control and study group (Table 2).

Table 1 Comparison of QT at baseline and at different intervals of anaesthesia.

Time	Control group (n = 27)		Study group (n = 27)		p-Value
	Mean	SD	Mean	SD	
Baseline	0.27	0.03	0.37	0.03	0.001*
After induction and intubation	0.29	0.03	0.38	0.03	0.008*
After 1 min	0.29	0.03	0.39	0.03	0.0001*
After 5 min	0.28	0.03	0.40	0.03	0.0001*
After 15 min	0.28	0.03	0.41	0.03	0.0001*
After 30 min	0.29	0.03	0.41	0.03	0.0001*
After 60 min	0.29	0.04	0.42	0.03	0.0001*
Recovery	0.29	0.03	0.40	0.03	0.0001*

* Statistically significant at 0.01 level.

Table 2 Comparison of QTc based on Bazett's formula at baseline and at different intervals of anaesthesia.

Time	Control group (n = 27)		Study group (n = 27)		p-Value
	Mean	SD	Mean	SD	
Baseline	0.30	0.03	0.46	0.05	0.001*
After induction and intubation	0.34	0.04	0.48	0.04	0.007*
After 1 min	0.34	0.05	0.48	0.03	0.0001*
After 5 min	0.33	0.05	0.47	0.03	0.0001*
After 15 min	0.32	0.04	0.47	0.03	0.0001*
After 30 min	0.32	0.04	0.47	0.03	0.0001*
After 60 min	0.32	0.04	0.46	0.04	0.0001*
Recovery	0.32	0.04	0.47	0.04	0.0001*

* Statistically significant at 0.01 level.

The mean (SD) baseline values of QTc based on Fridericia's formula for control and study groups were 0.29 (0.03) and 0.43 (0.04), respectively (p-value = 0.001). In the control group, the mean values of the corresponding QTc intervals at different time intervals increased to 0.32 s, whereas the corresponding values in the study group increased to 0.45 s as against 0.48 s according to Bazett's formula. The augmentation of the QTc prolongation produced by isoflurane was proportional in both the control and study group using Fridericia's formula also (Table 3).

Table 4 summarizes the number of patients in whom the QTc value exceeded the reference value of 0.44 s during the course of study. There was a significant prolongation of QTc interval in the study group both before induction of anaesthesia, during anaesthesia and during recovery. Only 3.7% of control group patients had a prolongation of QTc after induction and intubation and after 1 min (1 patient). Only two patients showed an increase in QTc interval at 5 min of anaesthesia. The highest percentage of QTc prolongation occurred after induction and at 15 min of anaesthesia (81.5%). Table of distribution of prolonged QTc showed a consistently high percentage in the study group.

The baseline value of heart rate of patients in the study group was statistically significant ($p < 0.01$) as compared to the patients in control group. The mean (SD) baseline values of heart rate per minute for control and study groups were 77.9 (6.2) and 83.6 (9.3), respectively (p-value = 0.01). However, during the course of anaesthesia, there was no statistical difference between the heart rates in both the groups.

After induction and intubation, there were no significant differences between the two groups with regard to the systolic, diastolic and mean arterial pressures. No significant difference between the systolic, diastolic and mean arterial pressures between the two groups during the rest of the anaesthetic period (data not shown).

Table 3 Comparison of QTc based on Fridericia's formula at baseline and at different intervals of anaesthesia.

Time	Control		Study		p-Value
	Mean	Sd	Mean	Sd	
Baseline	0.29	0.03	0.43	0.04	0.001*
After induction and intubation	0.32	0.04	0.44	0.03	0.001*
After 1 min	0.32	0.04	0.44	0.03	0.001*
After 5 min	0.31	0.04	0.45	0.03	0.001*
After 15 min	0.30	0.04	0.45	0.03	0.001*
After 30 min	0.31	0.04	0.45	0.03	0.001*
After 60 min	0.31	0.04	0.45	0.03	0.001*
Recovery	0.31	0.04	0.44	0.03	0.001*

Table 4 Distribution of prolonged QT interval (QTc > 0.44).

Time	Control group		Study group	
	No. of patients	Percentage	No.of patients	Percentage
Baseline	0	0.0	18	66.7
After induction and intubation	1	3.7	22	81.5
After 1 min	1	3.7	21	77.8
After 5 min	2	7.4	21	77.8
After 15 min	0	0.0	22	81.5
After 30 min	0	0.0	20	74.1
After 60 min	0	0.0	19	70.4
Recovery	0	0.0	22	81.5

4. Discussion

The main finding of this study was that patients who have received anthracyclines based chemotherapy (study group) were more prone to develop prolongation of QT interval during administration of isoflurane anaesthesia compared to the control group. The QT interval shortens with increasing heart rate [12]. Therefore, heart rate corrected QT interval or 'QTc' is used to study the cardiac depolarization. QTc is the QT interval that would be observed in the same ECG if the heart rate was 60 beats per minute, i.e. R–R interval is 1 s [13]. Many methods have been developed to calculate QTc. In practice, the QT interval is expressed as a 'corrected QT (**QTc**)' dividing the QT interval by the square root of the R–R interval (interval between ventricular depolarization). QTcB = QT/$\sqrt{}$RR interval (Bazett's formula) [9,10] where QTc is the QT interval corrected for heart rate, and RR is the interval from the onset of one QRS complex to the onset of the next QRS complex. According to Fridericia's formula [11], QTc is obtained by dividing the QT interval by the cube root of RR interval, i.e. QTcF = QT/cube root of RR interval. In the present study, we used both the formulae to overcome the effect of increased heart rate on QT interval. They assume an exponential relationship between QT and RR interval. This was in accordance with the International Conference on Harmonization (ICH) document published in 2005 (E 14 Clinical evaluation of QT/QTC Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmics Drugs) [14]. This allows an assessment of the QT interval that is independent of heart rate. Normal corrected QTc intervals are less than 0.44 s and considered to be prolonged if more than 0.44 s, based on the reports of Owczuk et al. [15]. This confirms other studies quoting QTc prolongation as a marker of postanthracycline cardio toxicity [5,6,16,17]. This was in contrast to the finding of Owczuk et al. [15] who found no statistical difference in the QT intervals between the two groups. The study population in the present study received a higher total dose of anthracyclines than that of the study of Owczuk et al. [15], and this may account for the difference in baseline QT intervals seen between the two studies. Larsen R L et al. [5] reports the prolongation of QT interval after a cumulative dose of anthracyclines of 282 mg/m^2 body surface area.

In the present study, the QTc at different intervals of isoflurane anaesthesia based on both the formulae also showed a statistically significant difference between the two groups. The increase in QTc interval from baseline occurred for both the control and the study groups but for the control group it was statistically insignificant. The mean QTc in the study group ranged from 0.46 to 0.48 s based on Bazett's formula. However, according to Fridericia's formula, the corresponding values ranged only from 0.43 to 0.45. This is due to difference in the formula as Bazett's formula used square root of RR interval, whereas the Fridericia's formula used the cube root of RR interval. Even though Fridericia's formula showed less difference, at some points of time, the QTc prolongation was more than the reference value of 0.44 s based on studies from Khan [3] and Wisely and Shipton [18].

The finding of statistically prolonged QTc interval in the study group was consistent with that from the study of Owczuk et al. [15] The QTc values were more prolonged in the present study than the study of Owczuk et al. [15]. Michaloudis et al. [2] reported that Isoflurane anaesthesia statistically prolongs the QTc interval. The increase in QTc interval after laryngoscopy and intubation can be attributed to the increased plasma concentrations of catecholamines. This finding has been made by Yee et al. [19] which proposed that the increase in QT interval after intubation might be due to an increase in catecholamines which increases the after load of the heart. In the present study, no value of QTc exceeded the 0.6 s which is suggested as the level for significant arrhythmia generation.

In a study of the time dependent cumulative effects of three inhalational anaesthetics on QTc interval by Karagoz et al. [20], it was found that although 1% isoflurane produced higher QTc values than halothane and sevoflurane, none of them produced critical value of 0.44 s. In the present study, significant increase in QTc interval was observed although only 0.5% isoflurane was used.

The baseline heart rate in the present study was higher for the study group of patients. The range of heart rate for the study population was 74–93 beats per minute. This is in contrast to the control group whose heart rates ranged from 71 to 83 beats per minute. Booker et al. [9] reviewed that the QT interval varies with heart rate, lengthening with bradycardia and shortening with increased rates. This was not observed in the present study. In this study, the baseline heart rate of the study population was higher and the baseline QT was also prolonged. But after induction of anaesthesia, the QT further prolonged and the heart rate decreased.

The main limitation of the present study was the use of propofol for induction of anaesthesia, which was cited by Kleinsasser et al. [7] in their study to significantly shorten the QT but not the QTc interval. The finding of Kleinsasser et al. [7] has been reinforced in the study done by Paventi et al. [8]. Saarnivaara et al. [21] found a shortening of QTc interval with

the use of propofol. One observation made from the present study was that the use of propofol could have mitigated undue prolongation of the QTc interval to the arrhythmogenic potential of 0.6 s.

In the present study, although QTc is prolonged, the use of combination of anaesthetic agents such as propofol and isoflurane might have helped to prevent generation of arrhythmias. During no point of time of anaesthesia, any significant arrhythmia was observed. The only arrhythmia that occurred during anaesthesia with no statistical significance was an occasional extra systole observed in two patients who received anthracycline chemotherapy. The heart rates and mean arterial blood pressures showed no significant change during anaesthesia.

In conclusion, anthracyclines especially doxorubicin produce statistically significant QTc prolongation. The use of isoflurane for maintenance of anaesthesia in such patients further augments the QTc prolongation. Hence, if at all used its use for maintenance of anaesthesia in such patients should be carefully monitored and kept below 1% for patient safety. The augmentation of QTc prolongation produced by isoflurane is proportional in both the control and study groups.

Conflict of interest

None.

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