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Research Article

Effect of Short-Term Use of Sevoflurane on QT Interval in Children Undergoing Eye Surgery

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ABSTRACT

Studies have shown that taking anesthesia drugs can increase QT interval. We investigated the effect of short-term use of sevoflurane on QT and QTc intervals in the early stages of anesthesia and in children. In this prospective cohort study, 52 patients aged 2-14 years, were enrolled. Children were randomly divided into two groups: Sevoflurane (S) and control (sodium thiopental, P). In the intervention group, anesthesia induction using sevoflurane was continued for 10-15 minutes and the sevoflurane level was adjusted so that the end-expiratory concentration remained constant at 3%. In group P (control group), anesthesia was induced with 5 mg/kg sodium thiopental. ECGs were taken at 0, 5, 10, and 15 minutes after induction of anesthesia and compared between both groups. QT measurement in lead II in the four times showed that the two groups were not significantly different from each other, and all values obtained were in the normal range and less than 0.44. Measurement of QT in lead V5 showed that the QT interval between groups increased 10 and 15 minutes postoperatively in both groups, and this increase was more in group P than the S group. In group S, QT values in 10 and 15 minutes compared to time 0 and 5 were associated with an increase of about 0.01 seconds and the increase was not significant. Short-term use of sevoflurane does not increase QT and QTc levels in children undergoing surgery without intubation and need for muscle relaxants.

Keywords: Sevoflurane, Thiopental, QT interval, Arrhythmia

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INTRODUCTION

Based on their effect on the electrical activity of the heart, anesthesia drugs can cause or eliminate arrhythmias in patients under anesthesia (Hanci V, *et al.*, 2010). Drug reactions with one or more cardiac ion channels can increase the action potential at the cellular level by delaying myocardial repolarization (Kang J, *et al.*, 2006).

QT and QT intervals are the electrocardiogram indicators of ventricular repolarization (Hanci V, *et al.*, 2010). The QT interval in the ECG, defined as the beginning of the QRS complex to the end of the T wave, is in fact a period of ventricular systole or ventricular depolarization and repolarization, the changes of which are of particular importance during the induction of anesthesia (Higashijima U, *et al.*, 2010; Whyte SD, *et al.*, 2005). Since the increase and decrease of heart rate affects the size of the QT (the higher the heart rate, the shorter the interval and vice versa), so scientists use the corrected QT value (QT_c=Corrected QT interval=QT/√ RR (sec) (Kim ES and Chang HW, 2011; Booker PD, *et al.*, 2003).

An increase in QT_c of more than 440 m/sec during induction of anesthesia and surgery is clinically significant. Numerous medications such as anesthetics, antipsychotics, antidepressants, antibacterial, and antiviral drugs, antihistamines, and antiarrhythmics can increase QT and QT_c. The QT interval is affected by autonomic tone, heart rate, catecholamines, sex, and circadian rhythm (Kweon TD, *et al.*, 2008; Kazanci D, *et al.*, 2009; Silay E, *et al.*, 2005).

Sevoflurane is an anesthetic that increases the QT interval. Studies have shown that the use of sevoflurane in induction and maintenance of anesthesia increases the QT and QT_c interval in children, women, and men by blocking potassium KvLQT1/mink and Kv4.3 heart valves (Higashijima U, *et al.*, 2010; Kazanci D, *et al.*, 2009; Silay E, *et al.*, 2005; Han DW, *et al.*, 2010).

Increased QT interval can be associated with life-threatening arrhythmias such as torsade de pointes tachycardia, ventricular fibrillation, asystole, syncope, seizure-like attacks, and even sudden death (Kleinsasser A, *et al.*, 2000; Oji M, *et al.*, 2013; Ugur B, *et al.*, 2006). Many other anesthetic drugs, including sodium thiopental, succinylcholine, halothane, sevoflurane, isoflurane, and desflurane, increase QT interval. Acquired increase in QT and QT_c can increase the risk of sudden cardiac death, especially in patients with a history of long QT syndrome (Yildirim H, *et al.*, 2004; Gürkan Y, *et al.*, 2013).

To the best of our knowledge, most existing studies on sevoflurane have examined the effect of taking this and other anesthetic drugs on the induction and maintenance of anesthesia. We investigated the effect of short-term use of sevoflurane on QT and QT_c intervals in the early stages of anesthesia and in children who do not require intubation and use of muscle relaxants during surgery.

MATERIALS AND METHODS

In this prospective cohort study, after the approval of the study protocol in the Ethics Committee of Shiraz University of Medical Sciences (Code: IR.SUMS.MED.REC.1395.39), and after determining the sample size using statistical formulas, 52 patients aged 2-14 years, in class I according to the classification of the American Society of Anesthesiologists (ASA) who had referred to Khalili Hospital in Shiraz, Iran for elective eye surgery, were enrolled. Informed consent for participation was obtained from their parents. To avoid daily changes in the autonomic cardiac system, only patients who underwent surgery from 8 am to 12 noon were included. Block randomization method was used to select individuals and group them using a random list taken from the site "http: www.randomization.com".

The exclusion criteria were as follows: Use of any medication that affects the QT interval, including many anesthetics, antipsychotics and antidepressants, antibacterial and antiviral drugs, antihistamines and antiarrhythmic drugs in the last 14 days, corrected QT interval of more than 440 milliseconds in the preoperative ECG, presence of arrhythmia, myocardial infarction or pre-excitation syndrome, history of structural heart disease, history of hyperthyroidism or hypothyroidism, any non-sinus rhythm in the ECG, patients who require orotracheal intubation during surgery, and any preoperative electrolyte disturbance.

30 minutes before transferring the child to the operating room, midazolam (0.5 mg/kg) was given orally. After lying on the operating room bed, standard monitoring (Pulse oximetry, non-invasive blood pressure measurement, ECG) was established and then a lead II and V5 ECG was taken from the child as baseline at zero time (standard ECG with a paper speed of 25 mm/s and a standardization of 1 mV/cm). After venous recording, an intravenous cannula was implanted.

Children were randomly divided into two groups: Sevoflurane (S) and control (sodium thiopental, P). In the intervention group, anesthesia induction using sevoflurane (with a concentration of 8% and 100% oxygen) was continued for 10-15 minutes and the sevoflurane level was adjusted so that the end-expiratory concentration remained constant at 3%. The second ECG was taken 5 minutes after induction and the third one was taken ten minutes later and the fourth ECG was taken 15 minutes after induction of anesthesia with sevoflurane.

In group P (control group), induction of anesthesia was performed with 5 mg/kg sodium thiopental and if needed again, thiopental sodium was continued at a dose of 1-2 mg/kg and ECG was taken at the same times as group S. It is noteworthy that none of the patients underwent orotracheal intubation and anesthesia was induced using a mask in all of them. Also, no muscle relaxants were used during the operation. Finally, QT and QT_c intervals were measured, calculated, and compared in different ECGs. The QT interval is defined as the beginning of the QRS complex to the end of the T wave, and the QT_c is calculated as: QT_c=Corrected QT interval=QT/RRR sec. In each ECG, these values were measured in three consecutive complexes and in both II and V5 leads by two people separately and its average value was considered as the result.

Statistical analysis was performed using SPSS software, version 19. The variables were reported using mean and standard deviation. When comparing the means, P<0.05 was considered statistically significant. For this purpose, Kolmogorov-Smirnov test was used to check normality. Mann-Whitney, Student's t, Chi-square, and repeated measure tests were also used to compare the variables between the two groups as appropriated.

RESULTS

There was no significant difference between the two groups in terms of demographic information such as sex, age, and frequency (*Table 1*). The results of QT measurement in lead II in the four times showed that the two groups were not significantly different from each other in terms of mean QT interval and all values obtained were in the normal range and less than 0.44 seconds.

Measurement of QT in lead V5 showed that the QT interval between groups increased 10 and 15 minutes postoperatively in both groups and this increase was more in the P group than the S group (P value 10 min: 0.003, P value 15 min: 0.002). In group S, QT values in 10 and 15 minutes compared to time 0 and 5 were associated with an increase of about 0.01 seconds and the increase was not significant. In group P, the average QT values had a greater increase at 10 minutes compared to zero and 5 minutes and even compared to 15 minutes (*Table 2*).

Measurement of QT_c in lead II at the four times showed that the increase in QT_c values in groups S and P were not significant. Although the average values obtained in the two groups were reported in the normal range and less than 0.44, but in many cases these values were higher than normal.

The results of QT_c measurement in the V5 lead at the four times showed that the increase in QT_c values in each group and compared between the two groups was not significant, although the average values obtained in the two groups were in the normal range and less than 0.44. However, this value was above the normal range at 10 minutes (0.48 ± 0.16) in group P. Based on the results, it is emphasized that the normality of the numbers related to the mean does not indicate the normality of QT_c values obtained in all subjects and according to the numbers related to the standard deviation, many QT_c values in both groups were above normal (*Table 3*).

Based on the Greenhouse-Geisser statistical test, the study of QT and QT_c values in both leads II and V5 showed that no significant difference was seen in the four time points in both groups (*Table 4*).

Table 1: The patients' demographic characteristics

Group		P (Control)	S (Intervention)	P-Value
Age (± SD)		4 ± 2.41	3 ± 0.98	0.77
Gender	Boy	15	16	0.086
	Girl	11	10	

Table 2: Mean values obtained for QT intervals in lead II and V5 in two groups S and P

Indicator ECG	LED	Group	Time			
			0	5 min	10 min	15 min
QT	II	S	0.30 ± 0.037	0.29 ± 0.036	0.30 ± 0.024	0.31 ± 0.039
		P	0.31 ± 0.050	0.31 ± 0.050	0.32 ± 0.052	0.32 ± 0.046
		P-value	0.67	0.08	0.51	0.37
	V5	S	0.29 ± 0.040	0.29 ± 0.036	0.30 ± 0.035	0.31 ± 0.35
		P	0.33 ± 0.059	0.32 ± 0.054	0.35 ± 0.100	0.33 ± 0.040
		P-value	0.08	0.15	0.003	0.002

Table 3: Mean values obtained for QTc intervals in lead II and V5 in groups S and P

Indicator ECG	LED	Group	Time			
			0	5 min	10 min	15 min
QTc	II	S	0.42 ± 0.051	0.40 ± 0.055	0.43 ± 0.052	0.42 ± 0.059
		P	0.41 ± 0.071	0.42 ± 0.067	0.44 ± 0.075	0.43 ± 0.045
		P-value	0.57	0.32	0.5	0.46
	V5	S	0.41 ± 0.057	0.41 ± 0.064	0.42 ± 0.044	0.43 ± 0.049
		P	0.43 ± 0.044	0.41 ± 0.049	0.48 ± 0.16	0.43 ± 0.048
		P-value	0.09	0.65	0.18	0.83

Table 4: Mean within group values obtained for QTC and QT intervals at lead II and V5 in groups S and P

Group	QT		QTc	
	V5	II	V5	II
S	0.297 ± 0.036	0.30 ± 0.034	0.417 ±0.053	0.417 ± 0.054
P	0.332 ± 0.051	0.315 ± 0.049	0.437 ± 0.039	0.425 ± 0.064
P-value	0.14	0.67	0.09	0.57

DISCUSSION

The present study was performed on 52 children aged 2-14 years who were candidates for ophthalmic surgery. Patients were not intubated and did not receive muscle relaxants. According to previous studies, laryngoscopy and orotracheal intubation may alter arterial blood pressure, heart rate, and heart rhythm by increasing sympathoadrenal system stimulation. As a result, prolonged QT interval and QT_d can induce tachycardia, ventricular fibrillation, and even sudden cardiac death in patients with underlying heart disease (Oji M, *et al.*, 2013; Gürkan Y, *et al.*, 2003). The results of this study showed that the values related to QT intervals in all patients at all four measured times were in the normal range of about 0.3 seconds, which can be attributed to the high baseline heart rate in children.

What are very important are the values of QT_c intervals in the two groups at the desired time points and our study showed that as the anesthesia time increases, QT_c values increased in both S and P groups and in both leads, which was more in group P but was not statistically significant. The highest QT_c values were observed at 10 minutes for both groups in lead II, at 15 minutes in lead V5 for group S and at 10 minutes in lead V5 for group P. It can be argued that thiopental sodium increases QT_c interval during anesthesia more than sevoflurane.

Another finding was that statistically, only the increase in QT between the two groups in the V5 lead at 10 and 15 minutes was significant, and neither QT nor QT_c were significant relative to each other at other times, and the increase in each value was significant. Both leads in group P were more than group S. In other words, the values obtained at times 0, 5, 10 and 15 minutes, were not significant although being different from each other and it is noteworthy that malignant ventricular arrhythmia was not seen in any of the groups.

In a similar study on children in the early stage of anesthesia, the researchers found some degree of irregularity in the ECG following anesthesia with halothane, sevoflurane, and intubation. These changes in QT and QT_d were less in the sevoflurane group than in the halothane group. In our study, an increase in QT and QT_c was seen in the sevoflurane group less than the sodium thiopental group. The two studies differed with respect to laryngoscopy and orotracheal intubation, which can increase the QT interval and QT_d by stimulating the sympathoadrenal system (Gürkan Y, *et al.*, 2003). In another study, the relationship between end-tidal sevoflurane concentration and QT_c in 20-50 years old patients were examined. The results showed that QT_c change correlated with the level of anesthesia and that these changes occurred at sevoflurane concentrations, which is clinically significant. However, in our study, despite keeping the expiratory concentration of sevoflurane constant, QT_c interval increased over time, but its values were in the normal range, and QT_c was not completely normal at any of the studied times.

Acquired causes of QT prolongation include drugs, electrolyte imbalances, cardiac disease, autonomic neuropathy, and neurological injury such as subarachnoid hemorrhage. An acute increase in QT interval also occurs in people who have poor blood glycemic control or who have taken fluconazole infusion and ondansetron, especially in patients receiving sevoflurane for anesthesia, which can lead to torsade de pointes (Thiruvenkatarajan V , *et al.*, 2010; Tacken MC, *et al.*, 2011; Tanskanen PE, *et al.*, 2002; Lee JH, *et al.*, 2014). However, in our present study, all the factors that can prolong QT interval were eliminated, and the patients were exposed to sevoflurane, which ultimately lowered QT and QT_c interval to the normal range.

In contrast, in studies on adults and children who were candidates for non-cardiac surgery, there was no difference between sevoflurane and desflurane and propofol and halothane in terms of their effect on QT and QT_{cd} and p dispersion (Kazanci D, *et al.*, 2009; Michaloudis D, *et al.*, 2000). Other studies compared the effect of desflurane and sevoflurane, and found no change in QT interval between the two groups. However, QT_c increase was significantly higher in the desflurane group (Kweon TD, *et al.*, 2008).

In another study comparing the effect of desflurane and sevoflurane on maintenance of anesthesia in children, no statistically significant change was observed in QT_c in the sevoflurane group 2%, but a significant increase was observed in QT_c in the group receiving 6% sevoflurane (Aypar E, *et* *al.*, 2007). Inconsistently, Whyte and colleagues found that consumption of sevoflurane significantly increased QT_c, and although it increased the duration of myocardial repolarization, the risk of torsade de pointes did not increase because the transmural dispersion of repolarization time was not affected (Whyte SD, *et al.*, 2005). Also, in a clinical trial, sevoflurane prolonged the QT and QT_c interval in both children with congenital sensorineural hearing loss and children with chronic otitis media, but there was no difference in the heterogeneity of transmural repolarization between the two groups (Kim HS, *et al.*, 2009).

Silay E, *et al.*, 2005 compared the effect of desflurane and sevoflurane on QT_c interval and its dispersion. No change in QT dispersion was observed in the two groups, but despite the increase in QT_c interval in both groups, this effect was significantly more in the desflurane group. Considering the age differences between the mentioned study and our study, our results showed that short-term use of sevoflurane during anesthesia did not increase QT and QT_c levels.

Gürkan Y, *et al.*, 2013 concluded that halothane and sevoflurane cause some degree of irregularity in the ECG following intubation; these changes in QT and QT_c dispersion were significantly more pronounced in the halothane group than in the sevoflurane group. Similar to ours, the mentioned study was performed in the pediatric group and showed that sevoflurane increased QT_c. However, this increase was higher in the halothane group (Kleinsasser A, *et al.*, 2000), similar to our study showing that thiopental sodium increased QT and QT_c interval more than sevoflurane. The mentioned study was performed in the same way as our study in the early minutes of anesthesia, but the difference with our study is that the patients in that study underwent orotracheal intubation, while our patients did not. As previously stated, laryngoscopy and orotracheal intubation can stimulate the QT interval and its diffusion by stimulating the adrenal sympathetic system. It is noteworthy that in our study no irregular ECG and malignant arrhythmia were observed.

One of the limitations of the study is that we did not measure the time between the peak and the end of the T wave as a transmural dispersion of repolarization, which indicates the potential for torsade de pointes. Moreover, the digital electrocardiography device was not used to record the ECG of patients and was used to measure distances based on the opinion of two people experienced in cardiology.

CONCLUSION

Short-term use of sevoflurane does not increase QT and QT_c levels in children undergoing surgery without intubation and the need for muscle relaxants. Short-term use of sevoflurane is suitable for induction of anesthesia in people with high preoperative QT. However, it cannot be said that short-term use of sevoflurane is suitable for inducing anesthesia in people with prolonged QT intervals before surgery, and this issue should be proven in separate studies in patients with prolonged QT before surgery.

AUTHOR CONTRIBUTIONS

Saeed Khademi: Supervison, writing; Reza Jouybar: Methodology; Maryam Ghadimi: Writing, review and editing; Mahsa Razavi: Formal analysis and investigation; Ensiyeh Shahriyary: Writing, original draft preparation; All authors reviewed the manuscript.

ETHICAL APPROVAL

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1395.39). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments.

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DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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