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Comparison of the Effects of Propofol and Sevoflurane on QT Interval in Pediatrics Undergoing Cochlear Implantation: A Randomized Clinical Trial Study

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Abstract

Background: Children with sensorineural hearing loss are at risk of cardiac electrophysiologic abnormalities. Inhalational Sevoflurane induction in these children can cause QT prolongation.
Objectives: In order to evaluate the safety of inhalational induction of anesthesia with sevoflurane in children with sensorineural hearing loss, who are candidates for cochlear implant, its electrophysiologic effects was compared with intravenous induction of anesthesia with propofol.
Methods: In this double-blind randomized clinical trial, 61 children aged between one and eighteen years old, who were candidates for cochlear implantation, were randomly allocated to groups receiving anesthesia with sevoflurane (n = 32) or propofol (n = 29) for induction of anesthesia. Two 12-leads ECG were taken from all of patients before and after induction and QTc, Tp-e interval, and JTc were measured and compared.
Results: Two cases, who had pre-induction QTc longer than 500 ms were excluded from the study. Patients had similar age (102.58 $\pm$ 87 versus 101.46 $\pm$ 67 months, P = 0.95) and gender (males: 48.3% versus 56.3%, P = 0.53) distribution. The researchers observed significant post induction difference in QTc values between these groups (propofol 422.5 + 40, sevoflurane 445.0 + 29, P = 0.016). There was no significant difference in the percent QTc and Tp-e changes in propofol and sevoflurane groups. Greater percentage of patients with increased Tp-e interval (> 100 ms) in the sevoflurane group than the propofol group was also seen. There was no significant long QTc difference (QTc > 500 ms or more than 60 ms increase from baseline) after induction of anesthesia in the sevoflurane group compared to the propofol group (15.6% versus 13.8%, P = 0.84).
Conclusions: After electrophysiological evaluations in children with sensorineural hearing loss, in patients whose pre-induction QTc is not longer than 500 ms, propofol seems safer than inhalational sevoflurane for induction of anesthesia.

Keywords: Sevoflurane, Propofol, Cochlear Implantation, Long QT

1. Background

Cochlear implant surgery is a standard treatment for children with profound sensorineural hearing loss, which must be done under general anesthesia. Some of these patients have Jervell Lange-Nielsen syndrome (JLNS), meaning the child had sensorineural hearing loss and long QT syndrome (LQTS) (QT is the interval from the beginning of the QRS complex to the end of the T wave), possibly leading to life threatening arrhythmia during surgery (1, 2). Some JLNS cases have borderline QT interval duration; in addition, it seems that sensorineural deafness even without JLNS is associated with some degree of abnormal electrophysiology of QT interval.

Electrical depolarization and repolarization of the ventricles was shown through the QT interval (3). The QT interval varies with heart rate and by using Bazett's formula, its corrected form (QTc) is used to outline its abnormalities (4). This corrected form enables the comparison of QT prolongation effect of two drugs (i.e. propofol and sevoflurane) when they have different effects on heart rate of the patients (5). Prolongation of the QT could be associated with potentially dangerous ventricular arrhythmias, seizure-like episodes, and sudden cardiac death, which in the general population has been associated with increased

risk of all-cause and cardiovascular death (6).

Although QT prolongation is used for diagnosing LQTS, it seems that the Tp-e index (the interval from peak of T wave to end of the T wave) is an indicator of transmural dispersion of repolarization (TDR) and can be a better predictor of ventricular arrhythmia (i.e.Torsades de pointes, TdP) (3). The QT prolongation could be caused by different congenital abnormalities, electrolyte disturbances, and different drugs (7). In patients with congenital repolarization disorders, drugs which have the ability to further increase QT interval should be avoided as they can initiate cardiac arrhythmias. Dropridol, which was once used for anesthesia maintenance and for controlling post operative nausea and vomiting was abandoned (8) due to its ability of prolonging the QT interval.

Almost all anesthetics have some effects on cardiac electrical activity (9). Propofol seems to have the least effect (10-12). Sevoflurane in different studies could prolong the QTc interval yet it had no effects on Tp-e (13-21). The effects of sevoflurane on cardiac electrophysiology in healthy children and adults as well as patients prone to repolarization abnormalities in comparison with normal subjects has been evaluated in different studies (12, 13, 16, 22).

2. Objectives

In this study, the researchers studied and compared the effect of propofol and sevoflurane as the induction agents on QT (primary outcome), Tp-e interval, and JTc (JTc = QTc - QRS duration) (secondary outcome) in pediatric patients undergoing cochlear implantation. Using inhalational induction of anesthesia with sevoflurane is sometimes the only choice for pediatric anesthesia, so its safety should be evaluated in children with repolarization disorders with more scrutiny.

3. Methods

In this double-blinded randomized clinical trial, 61 patients participated and all underwent cochlear implantation surgery, aged between one and 18 years old, and were American Society of Anesthesiology (ASA) class I or II with a preoperative QTc < 500 ms. Exclusion criteria were: patients or family history of Jerrell Lange Nielsen syndrome, history of seizure, history of sudden death in the patient family, electrolyte imbalances, being treated with drugs known to prolong the QTc interval, or any evidence of cardiovascular diseases.

This study was registered in IRCT with number IRCT2017082131487N2) and received institutional Ethics' approval from Iran University of Medical Sciences. Written informed consent was obtained from all parents.

The trial was powered to detect an effect size of d $\geq$ 0.70 as statistically significant in a two-tailed test with α = 0.05 and power of 0.80 with N = 28 per condition. As there was possibility that some patients would not complete the study, the research included 33 patients in each group. Using RANDLIST 1.2 software, random numbers were produced and according to sample size, patients were enrolled in the study. Patients and physicians, who assessed the results of the treatment were unaware of the group assignment.

All patients were premedicated orally with 0.3 mg/kg midazolam (up to 5 mg) 60 minutes before the first ECG recording. At the operating room reception, if the patient was not sedated properly, an intravenous line was inserted and intravenous midazolam was titrated to allow proper ECG recording. The ECG was recorded and QTc intervals were measured by an anesthesiologist; if patients had QTc > 500 ms, they were excluded. Two patients were excluded in this phase. Patients were transported to the operating room and were monitored with standard monitoring (three lead ECG, non-invasive blood pressure and pulseoximetry) and intravenous line was also inserted. Oxygen with face mask was administered. No other drugs were used for premedication. In the propofol group, anesthesia was induced intravenously by administering 2.5 mg/kg propofol; the drug was infused 100 μg/kg/min after loss of consciousness. Inhalational induction with face mask was performed in the sevoflurane group by administering 7.0% sevoflurane; this concentration was reduced to 3.0% after loss of consciousness. FiO_2 was 40% and end-tidal concentration of carbon dioxide was monitored and maintained at 35 to 40 mmHg throughout the study by manual ventilation assistance. Neuromuscular blockade was not done in both groups. In older children, whose anesthesiologist could have better communication, face-mask induction was done easier than smaller children.

The second ECG was obtained five minutes after the induction of anesthesia. A cardiologist blinded to the study groups calculated PR (the time from the onset of the P wave to the start of the QRS complex), QT and QTc, Tp-e, JT (QT - QRS), and JTc intervals and compered them with the operating room measurements. The QT interval was measured from the beginning of the QRS to the end of the T wave with the isoelectric line. The QTc was calculated using Bazett's formula (QTc: QT/$\sqrt{}$RR sec) (7). After administering the induction agent, QTc prolongation was considered clinically significant if the QTc interval was > 500 ms, or increased to more than 60 ms from baseline. Measurement of the Tp-e was performed from the peak of the T wave to the end of the T wave. To record three consecutive beats, leads V2 and

V5 were used and then the average was calculated. By subtracting the QRS duration from the QT or QTc, the JT interval and JTc were obtained. Measurement of the QT and JT was conducted in DII, V2, and V5 leads.

3.1. Statistical Analysis

All data were analyzed using SPSS20 (version 20; SPSS Inc., Chicago, IL). Results are expressed as mean ± standard deviation or percentage. Nominal categorical data between study groups were compared using the chi-square test or Fisher's exact test as appropriate and an independent *t*-test was used to evaluate the changes in the variables during the study period. A paired samples t-test was used to compare the changes before and after induction of anesthesia in each group. P values of less than 0.05 were considered statistically significant.

4. Results

Sixty-one patients that had undergone cochlear implant had induction of anesthesia with either propofol (n = 29) or sevoflurane (n = 32). Two patients were excluded before induction due to their long QT > 500 msec. Propofol and sevoflurane groups had similar age (102.58 ± 87 versus 101.46 ± 67 months, P = 0.95) and gender distribution (males: 48.3% versus 56.3%, P = 0.53) (See CONSORT flow chart).

The ECG findings before and five minutes after induction of anesthesia in propofol and sevoflurane groups are shown in Tables 1 and 2, respectively. There were no significant differences in ECG findings of the propofol group. In the sevoflurane group, QTc had no significant difference before and after induction and there was only a significant increase in the JTc interval following induction of anesthesia in this group (P = 0.01). Pre-induction QTc intervals in the propofol and the sevoflurane group showed no significant difference (propofol 413.7 ± 39 and sevoflurane 427.6 ± 36, P = 0.16). The researchers observed significant post induction difference in QTc values between these groups (propofol 422.5 + 40 and sevoflurane 445.0 + 29, P = 0.016). Clinically significant QTc was observed in five patients (15.6%) in the sevoflurane group and four cases (13.8%) in the propofol group (P = 0.84).

Prolonged Tp-e (Tp-e > 100 ms) was seen in 17 (58.6%) of propofol and 22 (68.7%) of sevoflurane patients before induction (P = 0.032). After induction of anesthesia, Tp-e > 100 msec was seen in 20 (68.9%) of propofol and 27 (81.4%) of sevoflurane group (P = 0.001) (23, 24).

Because the researchers observed significant differences in QTc between these groups after induction, they calculated the percentage of change in ECG parameters in each group, and observed no significant differences in any of the evaluated parameters (Table 3). The anesthesiologists did not report any arrhythmia in the induction period.

5. Discussion

This study was performed on 61 children with sensorineural hearing loss, who were candidates for cochlear implant surgery and showed that in patients with QTc shorter than 500 ms, induction of anesthesia with sevoflurane could cause significant increase in QTc in comparison with propofol and there was also a significant post induction difference in the Tp-e interval (as an indicator of TDR) between these drugs.

Different studies have shown that Tp-e is a better index for demonstrating TDR and can indicate cases susceptible to TdP arrhythmia. The normal ranges of Tp-e are reported differently yet 40 to100 ms is considered normal. QTc prolongation alone does not predispose to TdP (9, 13, 25-30). However, it has been demonstrated that QTc values above 500 ms could have high correlation with cardiac arrhythmia and is considered as an independent predictor of syncope and deaths in population under 50 years old (31). Automated measurements of these indices have yielded similar results with manual measurements (10, 14).

Cochlear implantation is usually performed at younger ages and the necessity of inhalational induction of anesthesia in pediatric anesthesia should always be considered. Nowadays, inhaled induction is almost confined to sevoflurane administration, thus, the safety of this method should also be evaluated in subgroup populations. Most patients with sensorineural hearing loss do not have JLNS, yet it seems that repolarization disorders exist at some degrees in all of these patients (32, 33). In addition, JLNS patients could be clinically asymptomatic, with no positive family history and could have QTc duration less than 500 ms in electrophysiological studies (34, 35). In patients undergoing cochlear implantation, anesthetic drugs should be chosen with more caution. Amirsalari and colleagues (36) studied 203 children with sensorineural hearing loss and found very Long QTc (more than 500 ms) in 2.46% of children, which is similar to the current result (3.3% in our cases). Higher rate of long QTc in patients with congenital deafness has not been recorded in some studies. Tutar and colleagues (37) observed that when children were grouped according to their heart rate, the observed difference of QTc interval between deaf and normal children disappears and even suggested that ECG study is not necessary in deaf children. On the other hand, Tuncer and colleagues (32) observed that deaf mute children (without Jervell and Lange-Nielsen syndrome)

Table 1. ECG Findings Before and 5 Minutes After Induction in Propofol Group

Propofol Group	Before Induction	After Induction	P Value
Heart rate, min/beat	97.86 ± 20.43	102.48 ± 29.99	0.36
RR interval, msec	641.94 ± 146.00	637.51 ± 203.49	0.89
QT interval, msec	328.55 ± 39.86	331.31 ± 43.04	0.61
QTc interval, msec	413.72 ± 38.65	422.51 ± 39.89	0.36
JT interval, msec	256.82 ± 39.48	259.44 ± 40.78	0.65
JTc interval, msec	322.32 ± 32.57	329.89 ± 33.64	0.31
e interval-Tp, msec	79.17 ± 18.43	81.93 ± 18.99	0.38

Table 2. ECG Findings Before and 5 Minutes After Induction in Sevoflurane Group

Sevoflurane Group	Before Induction	After Induction	P Value
Heart rate, min/beat	122.69 ± 26.53	126.10 ± 27.93	0.50
RR interval, msec	510.79 ± 108.93	501.36 ± 123.12	0.61
QT interval, msec	304.82 ± 35.31	311.03 ± 31.88	0.40
QTc interval, msec	429.67 ± 35.07	443.98 ± 30.52	0.10
JT interval, msec	232.68 ± 35.63	243.86 ± 33.49	0.10
JTc interval, msec	327.04 ± 34.86	348.13 ± 38.39	0.01
e interval-Tp, msec	80.96 ± 17.02	85.93 ± 17.81	0.09

Table 3. Percent of Change in ECG Findings After Induction in Propofol and Sevoflurane Group

Percent of change	Propofol	Sevoflurane	P Value
Heart rate	6.20 ± 5.81	4.53 ± 3.94	0.81
RR interval	0.20 ± 4.54	0.31 ± 3.93	0.93
QT interval	1.15 ± 1.65	3.06 ± 2.58	0.53
QTc interval	2.88 ± 2.39	3.99 ± 2.04	0.72
JT interval	1.70 ± 2.31	6.32 ± 3.10	0.23
JTc interval	3.10 ± 2.38	7.19 ± 2.47	0.29
Tp-e interval	5.41 ± 3.80	7.88 ± 3.75	0.64

with similar RR interval, had longer QTc values and subtle depolarization abnormalities. Moss and colleagues (31) studied 3343 individuals from 328 families with one or more members with LQTS and followed them for 10 years, 688 of family members who were affected had QTc > 0.44 sec (mean QTc of 0.48 sec), 1% had congenital deafness, and 5% had cardiac events during the 10 year follow-up. In that study, the risk of subsequent syncope or probable LQTS-related death before 50 years of age, were meaningfully made by the three following factors, which also act independently: (1) QTc, (2) history of cardiac event, and (3) heart rate. Therefore, it seems that patients undergoing cochlear implantation are at greater risk for QTc related disorders and drugs used for anesthesia must be evaluated with more scrutiny in these patients. Different genetic features in geographic areas, where studies have been conducted, can also be a cause for different results.

Propofol seems to have less effect on ventricular repolarization and patients in whom anesthesia induced by IV propofol were considered as the control group. In the study of Hume-Smith and colleagues (10), propofol with three different plasma concentrations did not have a significant effect on QTc and Tp-e. In some studies, propofol has reduced the time of re- polarization (11, 12). There are also fewer reports that propofol could increase QTc interval (38).

Unlike propofol, it seems that sevoflurane could increase QT interval. Sevoflurane can block delayed potassium channels and prolong QT and QTc in children and adults (13-19). Although in many studies sevoflurane has

been shown to prolong QTc, it does not seem to prolong Tp-e interval (20). In the study of Whyte and colleagues (21), evaluating the effects of sevoflurane with three different concentrations, sevoflurane prolonged QTc interval yet did not affect Tp-e.

Sevoflurane is thought to be responsible for the occurrence of arrhythmia in some studies (39-44). However, the study of Nathan et al. (45) was performed on 114 patients with long QT and three cases of arrhythmia were reported, two in the isoflurane group and one in the desflurane group, while no arrhythmia was reported in the sevoflurane group. Sevoflurane and propofol have been compared in different studies. In healthy adults (12, 16, 22), pre-medicated with midazolam, sevoflurane has been shown to significantly prolong QTc after induction, and Tp-e interval changes were not investigated. In healthy children, Whyte and colleagues (13) compared the effects of these drugs, showed that propofol did not affect QTc and Tp-e and sevoflurane caused QTc prolongation yet did not prolong Tp-e, which indicate no TDR impairment. In children at risk of long QT interval, effects of sevoflurane were compared with healthy children (14). In this study, anesthesia was induced with sodium thiopental and maintained with sevoflurane, after injection of muscle relaxant patients were intubated and then ECG changes were evaluated. It showed that prolongation of QTc with sevoflurane yet no changes in the Tp-e interval. The effect of sevoflurane was similar in both healthy and deaf children. The current study demonstrated that the effects of anesthesia induction with inhalational sevoflurane and intravenous propofol in patients with sensorineural hearing loss were not similar. The authors used midazolam for sedation, which by reducing anxiety, can minimize the effects of sympathetic stimuli on the ECG indices yet have no effect on QT by itself (1). It is noteworthy to mention that the researchers needed additional intravenous midazolam administration for an artifact free ECG recording in some patients (a deaf pediatric patient difficult to communicate), so its dosage was not equal in all patients. On the other hand, as no other additional drug was prescribed and second ECG recording was before intubation, the effects of other additional drugs and excitatory stimuli were minimized (i.e., separation, laryngoscopy, and intubation) and ECG changes could be considered as almost pure effects of propofol and sevoflurane on cardiac electrophysiology. All drugs used for premedication and induction of anesthesia can affect cardiac electrophysiology at some degree. In this study, two children with QTc > 500 ms were excluded and all the cases with QTc below 500 ms (which is still out of normal range) were evaluated.

A significant increase was found in post induction QTc and also greater percentage of patients with increased Tp-e interval (> 100 ms) in the sevoflurane group than the propofol group. This finding indicates that inhalational induction with sevoflurane may carry an increased risk of TDR in patients with sensorineural hearing loss. Since QTc > 500 ms was observed in some patients, preoperative electrophysiologic study is necessary in these patients.

5.1. Conclusions

According to electrophysiologic findings of the current study, induction of anesthesia in sensorineural hearing loss pediatric patients when QTc interval is shorter than 500 ms with propofol has lower risk of torsades de pointes than sevoflurane.

In this study, the researchers used manual measurement of ECG indices, which limited evaluation of some other indices, such as QT Variability Index (QTVI).

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Footnotes

Authors' Contribution: Reza Safaeian and Valiollah Hassani conceived, designed, and revised and approved the final version of the paper; Masood Mohseni, Aslan Ahmadi, Haleh Ashraf, Gholamreza Movaseghi, Mahzad Alimian drafted the article and contributed in analyzing the data; Elham Mohebi, Zahra Sadat Koleini, and Shayesteh Pourkand contributed in the collection of the data, analysis, and interpretation of the data.

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References

1. Kies SJ, Pabelick CM, Hurley HA, White RD, Ackerman MJ. Anesthesia for patients with congenital long QT syndrome. *Anesthesiology*. 2005;**102**(1):204–10. doi: 10.1097/00000542-200501000-00029. [PubMed: 15618804].
2. Booker PD, Whyte SD, Ladusans EJ. Long QT syndrome and anaesthesia. *Br J Anaesth*. 2003;**90**(3):349–66. doi: 10.1093/bja/aeg061. [PubMed: 12594150].

3. Postema PG, Wilde AA. The measurement of the QT interval. *Curr Cardiol Rev*. 2014;**10**(3):287–94. doi: 10.2174/1573403X10666140514103612. [PubMed: 24827793]. [PubMed Central: PMC4040880].
4. Desai M, Li L, Desta Z, Malik M, Flockhart D. Variability of heart rate correction methods for the QT interval. *Br J Clin Pharmacol*. 2003;**55**(6):511–7. doi: 10.1046/j.1365-2125.2003.01791.x. [PubMed: 12814443]. [PubMed Central: PMC1884246].
5. Yap YG, Camm J. Risk of torsades de pointes with non-cardiac drugs. Doctors need to be aware that many drugs can cause qt prolongation. *BMJ*. 2000;**320**(7243):1158–9. doi: 10.1136/bmj.320.7243.1158. [PubMed: 10784527]. [PubMed Central: PMC1127571].
6. Nielsen JB, Graff C, Rasmussen PV, Pietersen A, Lind B, Olesen MS, et al. Risk prediction of cardiovascular death based on the QTc interval: Evaluating age and gender differences in a large primary care population. *Eur Heart J*. 2014;**35**(20):1335–44. doi: 10.1093/eurheartj/ehu081. [PubMed: 24603310]. [PubMed Central: PMC4028611].
7. Ornek E, Ornek D, Alkent ZP, Ekin A, Basaran M, Dikmen B. The effects of volatile induction and maintenance of anesthesia and selective spinal anesthesia on QT interval, QT dispersion, and arrhythmia incidence. *Clinics (Sao Paulo)*. 2010;**65**(8):763–7. doi: 10.1590/S1807-59322010000800004. [PubMed: 20835552]. [PubMed Central: PMC2933124].
8. Kao LW, Kirk MA, Evers SJ, Rosenfeld SH. Droperidol, QT prolongation, and sudden death: What is the evidence? *Ann Emerg Med*. 2003;**41**(4):546–58. doi: 10.1067/mem.2003.110. [PubMed: 12658255].
9. Staikou C, Stamelos M, Stavroulakis E. Impact of anaesthetic drugs and adjuvants on ECG markers of torsadogenicity. *Br J Anaesth*. 2014;**112**(2):217–30. doi: 10.1093/bja/aet412. [PubMed: 24305646].
10. Hume-Smith HV, Sanatani S, Lim J, Chau A, Whyte SD. The effect of propofol concentration on dispersion of myocardial repolarization in children. *Anesth Analg*. 2008;**107**(3):806–10. doi: 10.1213/ane.0b013e3181815ce3. [PubMed: 18713888].
11. Oji M, Terao Y, Toyoda T, Kuriyama T, Miura K, Fukusaki M, et al. Differential effects of propofol and sevoflurane on QT interval during anesthetic induction. *J Clin Monit Comput*. 2013;**27**(3):243–8. doi: 10.1007/s10877-012-9420-7. [PubMed: 23242843].
12. Scalese MJ, Herring HR, Rathbun RC, Skrepnek GH, Ripley TL. Propofol-associated QTc prolongation. *Ther Adv Drug Saf*. 2016;**7**(3):68–78. doi: 10.1177/2042098616641354. [PubMed: 27298717]. [PubMed Central: PMC4892405].
13. Whyte SD, Booker PD, Buckley DG. The effects of propofol and sevoflurane on the QT interval and transmural dispersion of repolarization in children. *Anesth Analg*. 2005;**100**(1):71–7. doi: 10.1213/01.ANE.0000140781.18391.41. [PubMed: 15616054].
14. Kim HS, Kim JT, Kim CS, Kim SD, Kim K, Yum MK. Effects of sevoflurane on QT parameters in children with congenital sensorineural hearing loss. *Anaesthesia*. 2009;**64**(1):3–8. doi: 10.1111/j.1365-2044.2008.05678.x. [PubMed: 19086998].
15. Loeckinger A, Kleinsasser A, Maier S, Furtner B, Keller C, Kuehbacher G, et al. Sustained prolongation of the QTc interval after anesthesia with sevoflurane in infants during the first 6 months of life. *Anesthesiology*. 2003;**98**(3):639–42. doi: 10.1097/00000542-200303000-00011. [PubMed: 12606907].
16. Kuenszberg E, Loeckinger A, Kleinsasser A, Lindner KH, Puehringer F, Hoermann C. Sevoflurane progressively prolongs the QT interval in unpremedicated female adults. *Eur J Anaesthesiol*. 2000;**17**(11):662–4. doi: 10.1046/j.1365-2346.2000.00739.x. [PubMed: 11029563].
17. Yildirim H, Adanir T, Atay A, Katircioglu K, Savaci S. The effects of sevoflurane, isoflurane and desflurane on QT interval of the ECG. *Eur J Anaesthesiol*. 2004;**21**(7):566–70. doi: 10.1017/S0265021504007112. [PubMed: 15318470].
18. Kleinsasser A, Loeckinger A, Lindner KH, Keller C, Boehler M, Puehringer F. Reversing sevoflurane-associated Q-Tc prolongation by changing to propofol. *Anaesthesia*. 2001;**56**(3):248–50. doi: 10.1046/j.1365-2044.2001.01717.x. [PubMed: 11251432].
19. Han DW, Park K, Jang SB, Kern SE. Modeling the effect of sevoflurane on corrected QT prolongation: A pharmacodynamic analysis. *Anesthesiology*. 2010;**113**(4):806–11. doi: 10.1097/ALN.0b013e3181f26d34. [PubMed: 20808206].
20. Lee JH, Park YH, Kim JT, Kim CS, Kim HS. The effect of sevoflurane and ondansetron on QT interval and transmural dispersion of repolarization in children. *Paediatr Anaesth*. 2014;**24**(4):421–5. doi: 10.1111/pan.12339. [PubMed: 24372925].
21. Whyte SD, Sanatani S, Lim J, Booker PD. A comparison of the effect on dispersion of repolarization of age-adjusted MAC values of sevoflurane in children. *Anesth Analg*. 2007;**104**(2):277–82. doi: 10.1213/01.ane.0000252417.23986.6e. [PubMed: 17242080].
22. Hanci V, Aydin M, Yurtlu BS, Ayoglu H, Okyay RD, Tas E, et al. Anesthesia induction with sevoflurane and propofol: Evaluation of P-wave dispersion, QT and corrected QT intervals. *Kaohsiung J Med Sci*. 2010;**26**(9):470–7. doi: 10.1016/S1607-551X(10)70074-7. [PubMed: 20837343].
23. Castro Hevia J, Antzelevitch C, Tornes Barzaga F, Dorantes Sanchez M, Dorticos Balea F, Zayas Molina R, et al. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. *J Am Coll Cardiol*. 2006;**47**(9):1828–34. doi: 10.1016/j.jacc.2005.12.049. [PubMed: 16682308]. [PubMed Central: PMC1474075].
24. Mozos I, Serban C. The relation between QT interval and T-wave variables in hypertensive patients. *J Pharm Bioallied Sci*. 2011;**3**(3):339–44. doi: 10.4103/0975-7406.84433. [PubMed: 21966153]. [PubMed Central: PMC3178939].
25. Antzelevitch C, Shimizu W, Yan GX, Sicouri S. Cellular basis for QT dispersion. *J Electrocardiol*. 1998;**30 Suppl**:168–75. doi: 10.1016/S0022-0736(98)80070-8. [PubMed: 9535495].
26. Shimizu W, Antzelevitch C. Sodium channel block with mexiletine is effective in reducing dispersion of repolarization and preventing torsade des pointes in LQT2 and LQT3 models of the long-QT syndrome. *Circulation*. 1997;**96**(6):2038–47. doi: 10.1161/01.cir.96.6.2038. [PubMed: 9323097].
27. Shimizu W, Antzelevitch C. Cellular basis for the ECG features of the LQT1 form of the long-QT syndrome: Effects of beta-adrenergic agonists and antagonists and sodium channel blockers on transmural dispersion of repolarization and torsade de pointes. *Circulation*. 1998;**98**(21):2314–22. doi: 10.1161/01.cir.98.21.2314. [PubMed: 9826320].
28. Lubinski A, Lewicka-Nowak E, Kempa M, Baczynska AM, Romanowska I, Swiatecka G. New insight into repolarization abnormalities in patients with congenital long QT syndrome: The increased transmural dispersion of repolarization. *Pacing Clin Electrophysiol*. 1998;**21**(1 Pt 2):172–5. doi: 10.1111/j.1540-8159.1998.tb01083.x. [PubMed: 9474667].
29. Sanatani S, Whyte S. Normal Tp-e values in children. *Anesth Analg*. 2012;**114**(1):240. author reply 240-1. doi: 10.1213/ANE.0b013e31823554ac. [PubMed: 22184612].
30. Haarmark C, Graff C, Andersen MP, Hardahl T, Struijk JJ, Toft E, et al. Reference values of electrocardiogram repolarization variables in a healthy population. *J Electrocardiol*. 2010;**43**(1):31–9. doi: 10.1016/j.jelectrocard.2009.08.001. [PubMed: 19740481].
31. Moss AJ, Schwartz PJ, Crampton RS, Tzivoni D, Locati EH, MacCluer J, et al. The long QT syndrome. Prospective longitudinal study of 328 families. *Circulation*. 1991;**84**(3):1136–44. doi: 10.1161/01.cir.84.3.1136. [PubMed: 1884444].
32. Tuncer C, Cokkeser Y, Komsuoglu B, Ozdemir R, Guven A, Pekdemir H, et al. Assessment of ventricular repolarization in deaf-mute children. *Pediatr Cardiol*. 2000;**21**(2):135–40. doi: 10.1007/s002469910021. [PubMed: 10754083].
33. El Habbal MH, Mahoney CO. QT interval in children with sensory neural hearing loss. *Pacing Clin Electrophysiol*. 2002;**25**(4 Pt 1):435–9. doi: 10.1046/j.1460-9592.2002.00435.x. [PubMed: 11991368].
34. Broomfield SJ, Bruce IA, Henderson L, Ramsden RT, Green KM. Cochlear implantation in children with Jervell and Lange-Nielsen syndrome - a cautionary tale. *Cochlear Implants Int*. 2012;**13**(3):168–72.

doi: 10.1179/1754762810Y.0000000006. [PubMed: 22333885].
35. Scuderi PE. Sevoflurane and QTc prolongation: An interesting observation, or a clinically significant finding? *Anesthesiology*. 2010;**113**(4):772–5. doi: 10.1097/ALN.0b013e3181f2b088. [PubMed: 20808205].
36. Amirsalari S, Honaramooz A, Khosravi A, Saburi A, Tafreshi R, Ajalloueyan M. The frequency of congenital long QT syndrome based on new formula in children with sensori-neural hearing loss. *Indian J Otol*. 2015;**21**(2):114–8. doi: 10.4103/0971-7749.155297.
37. Tutar E, Tekin M, Ucar T, Comak E, Ocal B, Atalay S. Assessment of ventricular repolarization in a large group of children with early onset deafness. *Pacing Clin Electrophysiol*. 2004;**27**(9):1217–20. doi: 10.1111/j.1540-8159.2004.00612.x. [PubMed: 15461711].
38. Saarnivaara L, Hiller A, Oikkonen M. QT interval, heart rate and arterial pressures using propofol, thiopentone or methohexitone for induction of anaesthesia in children. *Acta Anaesthesiol Scand*. 1993;**37**(4):419–23. doi: 10.1111/j.1399-6576.1993.tb03740.x. [PubMed: 8322572].
39. Saussine M, Massad I, Raczka F, Davy JM, Frapier JM. Torsade de pointes during sevoflurane anesthesia in a child with congenital long QT syndrome. *Paediatr Anaesth*. 2006;**16**(1):63–5. doi: 10.1111/j.1460-9592.2005.01593.x. [PubMed: 16409532].
40. Thiruvenkatarajan V, Osborn KD, Van Wijk RM, Euler P, Sethi R, Moodie S, et al. Torsade de pointes in a patient with acute prolonged QT syndrome and poorly controlled diabetes during sevoflurane anaesthesia. *Anaesth Intensive Care*. 2010;**38**(3):555–9. doi: 10.1177/0310057X1003800323. [PubMed: 20514968].
41. Abe K, Takada K, Yoshiya I. Intraoperative torsade de pointes ventricular tachycardia and ventricular fibrillation during sevoflurane anesthesia. *Anesth Analg*. 1998;**86**(4):701–2. doi: 10.1097/00000539-199804000-00004. [PubMed: 9539586].
42. Kumakura M, Hara K, Sata T. Sevoflurane-associated torsade de pointes in a patient with congenital long QT syndrome genotype 2. *J Clin Anesth*. 2016;**33**:81–5. doi: 10.1016/j.jclinane.2016.03.011. [PubMed: 27555138].
43. Hamaguchi E, Kawano H, Kawahito S, Kitahata H, Oshita S. [Torsade de pointes associated with severe bradycardia after induction of general anesthesia]. *Masui*. 2011;**60**(9):1097–100. Japanese. [PubMed: 21950046].
44. Tajiri O, Ito H, Yago Y, Masumori Y. [Torsade de pointes (TdP) observed during general anesthesia for cerebral aneurysm clipping in a patient with QT prolongation]. *Masui*. 2011;**60**(9):1090–3. Japanese. [PubMed: 21950044].
45. Nathan AT, Berkowitz DH, Montenegro LM, Nicolson SC, Vetter VL, Jobes DR. Implications of anesthesia in children with long QT syndrome. *Anesth Analg*. 2011;**112**(5):1163–8. doi: 10.1213/ANE.0b013e3182121d57. [PubMed: 21346158].