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Duration of the Surgery and Age are Risk Factors for QTc Interval Prolongation under General Anesthesia with Volatile Anesthetics

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Abstract

Background: Prolongation of the QT interval signals disordered cardiac repolarization which poses a significant risk to patients undergoing surgical procedures under anesthesia.

Methods: This study analyzed the demographic, clinical, and pharmacological factors in relation to QT interval prolongation under different types of anesthesia. This prospective observational study compared demographic characteristics, clinical and pharmacological factors from patients who demonstrated a prolonged QTc interval under GA (general anesthesia) and in those who had QTc interval prolongation while receiving RA (regional) or MAC (monitored anesthesia care).

Results: Duration of surgery correlated strongly with QTc interval prolongation in patients who were exposed to volatile anesthetics (r=.228, p=.010), but not in patients who received RA/MAC (r=.121, p=.444). Likewise, older patients were more likely to experience QTc interval prolongation only when they were exposed to volatile anesthetics (r=.190, p=.033), but not in patients who received RA/MAC (r=.019, p=.906). Perioperative use of insulin correlates strongly with QTc interval prolongation in patients who were exposed to volatile anesthetics (F=4.567, p=.035), but not in patients who received RA/MAC (F=1.372, p=.248). Perioperative use of antiemetic (serotonin inhibitors, steroids and metoclopramide), and beta-blockers did not have any significant effect on the QTc interval change.

Conclusions: Our results show that the duration of exposure to volatile anesthetics is the most important predictor of postoperative QTc interval prolongation. Volatile anesthetic agents cause greater QTc interval prolongation in older patients who had longer surgery.

Keywords: Anaesthetic agents; Diabetes; Heart; Age; Duration of surgery; Monitoring; Electrocardiography

Introduction

QT interval prolongation indicates disordered cardiac repolarization and is associated with an increased risk for arrhythmia and sudden cardiac death [1,2]. Various risk factors for QT interval prolongation have been noted in a general population of patients, including electrolyte imbalances, age [3], hypertension (HTN) [4,5], diabetes mellitus (DM) [6,7], and previous cardiac events, such as myocardial ischemia, recent conversion from atrial fibrillation and congestive heart failure [8,9]. Although volatile anesthetics are well known to cause QT interval prolongation in *in vitro* and *in vivo* studies [10-12], little is known about associated risk factors that predispose to QT interval prolongation and resultant potential for significant morbidity in the perioperative setting. We therefore designed this observational study to analyze the demographic characteristics, clinical and pharmacological factors in relation to QT interval prolongation during different types of anesthesia.

Material and Methods

Ethics

Ethical approval for this study (No IRB # 04-083) was provided by Institutional Review Board of the Cook County Bureau of Health Services, Chicago, IL (Chairperson Lynda Brodsky, Director, Research Affairs, Cook County Bureau of Health Services) on June 6, 2006 under the protocol title: "Characterization of QT prolongation in perioperative period."

We collected the data from 168 patients. Those individuals selected for the study met the following inclusion criteria: 1) patients undergoing non-cardiac surgery; 2) patients who had both a preoperative and postoperative 12-lead electrocardiogram (ECG); 3) age ≥18 years of either gender. Individuals with any of the following were excluded: pacemakers/defibrillators, atrial fibrillation, and a QRS interval greater than 120 msec (complete left or right branch bundle blocks and intraventricular conduction delay), acute myocardial infarction, pregnancy, incarceration, or a poor quality ECG.

Individuals who met the inclusion criteria for our study were first screened by the telemetry (MUSE Cardiology Information System, with version 5E, windows Server 2003, from GE Healthcare) in the post anesthetic care unit (PACU) for a prolonged QT interval. We obtained a postoperative 12-lead ECG to confirm either normal or abnormal QTc. Standard 12-lead ECGs were recorded in all subjects at a speed of 25 mm/s with a 10 mm/mV gain.

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We compared QT intervals from the most recent preoperative ECG and the first ECG in PACU. A cardiologist, who was blinded to patient information, type of anesthesia and timing of ECG measured all QT intervals manually. Each QT interval was measured from the onset of the QRS to the end of T wave, which was defined as the point of return to the isoelectric line. QT interval duration was assessed from lead II (or other leads if it could not be measured in lead II). The QTc interval was calculated by the method of Bazett [13]. R-R interval was determined by computer measurement if the rhythm was regular; if the rhythm was irregular, R-R was determined manually.

For this study, we defined prolongation of the QTc as an interval ≥440 msec in males and ≥450 msec in females. Based upon the results and the anesthetic procedures, participants were divided into two groups as shown in table 1. Group 1 (n=61) included patients who received general anesthesia with volatile anesthetic agent and in whom preoperative QTc was normal and postoperative prolonged QTc. Group 2 (n=65) included patients who received GA with volatile anesthetic agent and had normal preoperative QTc and normal postoperative QTc. Group 3 (n=13) included patients who had either regional anesthesia (RA) or monitored anesthesia care (MAC) in whom preoperative QTc was normal and postoperative prolonged QTc. Group 4 (n=29) included patients who had RA or MAC and who had normal QTc had normal preoperative QTc and normal postoperative QTc. Of note, individuals in groups 3 and 4 were not exposed to any volatile anesthetic agents.

Data collection

We collected the following information from each patient: type of anesthesia received, preoperative and postoperative 12-lead ECG, demographical data (Table 2: age, gender, weight and race), clinical factors (duration of surgery, initial temperature in PACU, presence or absence of hypertension, diabetes mellitus, and status as a smoker. In addition, we assessed various pharmacological factors, such as the volatile anesthetic agent used, perioperative administration or use of 5-HT3 antagonists (dolasetron, dol, or ondansetron, ondan), and the use of metoclopramide, dexamethasone (or other steroids), insulin, and beta-blockers. These anesthetists have not administrated to droperidol and haloperidol to these patients.

Data analysis

Statistical analysis of the data was performed with Statistical Product and Service Solutions (SPSS). Descriptive data for all groups and variables were expressed as mean ± SD for continuous measures or percent of a group for discrete measures. Continuous clinical factors were analyzed with Pearson correlations with change in QTc used as a dependent variable. Discrete clinical factors were analyzed with repeated measures analysis of variance analysis (RM-ANOVA). The RM-ANOVA was a 2×2 design with the within-subject factor of time (preoperative and postoperative) crossed with the diagnostic group (e.g., hypertensive versus normotensive). A significant interaction term would indicate a larger increase in QTc in one of the two groups. We then examined graphs of the means to interpret the direction of the effect. Statistical significance was assumed if the $p < 0.05$ throughout these analyses. Effect sizes analysis used a standard method of Cohen [14].

Type of Anaesthesia	Preoperative normal QTc & postoperative normal QTc	Preoperative normal QTc & postoperative prolonged QTc	Totals
General Anaesthesia	65 (Group 2)	61 (Group 1)	126
Regional Anaesthesia or MAC	29 (Group 4)	13 (Group 3)	42
Total	94	74	168

Table 1: Distribution of patients according to type of anaesthesia and perioperative QTc interval changes.

	General Anaesthesia		Regional Anaesthesia and Monitored Anaesthesia Care	
	Group 1 (Prolonged)	Group 2 (Normal)	Group 3 (Prolonged)	Group 4 (Normal)
Preoperative QTc (msec)	426 ± 15	416 ± 18	428 ± 13	408 ± 24
Postoperative QTc (msec)	472 ± 22	425 ± 18	460 ± 17	415 ± 22
Change in QTc (msec)	**46 ± 22**	**8 ± 19**	**29 ± 22**	**8 ± 19**

All data were expressed as mean ± SD

Table 2: Changes in QTc interval.

A

GENERAL ANAESTHESIA	NORMAL QTc	PROLONGED QTc	p-value
Gender (%)	Females 66.2 Males 33.8	Females 57.4 Males 42.6	.386
RACE (%)			.614
Black	46.2	44.3	
Hispanic	24.6	21.3	
White	21.5	21.3	
Other	7.7	13.1	
Age (years) ± SD	53.8 ± 13.3	57.9 ± 12.3	**.033**
Weight (kg) ± SD	81.3 ± 20.4	81.7 ± 20.6	.958

B

RA & MAC	NORMAL QTc	PROLONGED QTc	p-value
Gender (%)	Females 48.3 Males 51.7	Females 38.5 Males 61.5	.832
RACE (%)			.859
Black	31	38.5	
Hispanic	31	15.4	
White	13.8	15.4	
Other	24.1	30.8	
Age (years) ± SD	55.3 ± 12.7	56.0 ± 13.1	.906
Weight (kg) ± SD	81.5 ± 12.8	89.4 ± 24.3	.216

Table 3: Demographic characteristics of patients who received general Anaesthesia and regional Anaesthesia /monitored Anaesthesia care.

Results

In order to analyze the influence of the type of anesthesia on QTc interval prolongation in the perioperative period, we collected demographic, clinical and pharmacological factors from the patients who demonstrated a prolonged QTc interval under GA (Group 1) and in those who had QTc interval prolongation while receiving RA or MAC (Group 3). Controls for each of these groups (Groups 2 and 4) consisted of patients who did not experience prolongation of the QTc interval. Distribution of patients was shown in table 1, and the preoperative and postoperative QTc intervals for each group were summarized in table 2.

Demographic characteristics of the patients who received either GA or RA/MAC are shown in table 3. There were no differences in gender distribution among groups. Similarly, race distribution was not different among groups and was consistent with the patient population in our hospital (Table 3). There were no differences in age and weight between the group receiving GA and the group receiving RA/MAC ($p=0.763$ and 0.523, respectively). However, the patients who had prolonged QTc after GA were older as compared to the group who had normal QTc after receiving GA (Table 3).

Various clinical and pharmacological factors have been associated

A

General Anaesthesia		
Risk factors	**Pearson correlation (r)**	**p value**
Age	0.190	0.033
Duration of Surgery	0.228	0.010
Weight	0.005	0.958
Temperature	0.000	0.453
Glucose	0.190	0.154

B

Regional Anaesthesia/Monitored Anaesthesia Care		
Risk factors	**Pearson correlation (r)**	**p value**
Age	0.019	0.906
Duration of Surgery	0.121	0.444
Weight	0.195	0.216
Temperature	0	0.437
Glucose	0	0.432

Table 4: Clinical risk factors for perioperative QTc interval prolongation in different types of Anesthesia.

A

General Anaesthesia		
Risk Factor	**p-value**	**95% CI for mean (total)**
Smoking	0.858	0.39-0.64
Insulin	**0.035**	**0.19-0.35**
Steroids (IV)	0.308	0.24-0.40
Beta blockers	0.752	0.69-0.84
Metoclopramide	0.736	0.46-0.64
Serotonin inhibitors	0.81	0.57-0.74

B

Regional Anaesthesia/Monitored Anaesthesia Care		
Risk Factor	**p-value**	**95% CI for mean (total)**
Smoking	0.666	0.44-0.75
Insulin	0.248	0.16-0.46
Steroids (IV)	0.064	0 .03-0.25
Beta blockers	0.671	0.32-0.63
Metoclopramide	0.395	0.37-0.68
Serotonin inhibitors	0.787	0.07-0.31

All data were analyzed by ANOVA

Table 5: Pharmacologic risk factors for QTc prolongation.

with the QTc interval prolongation in general population. We examined the association between these factors and the perioperative QTc interval prolongation in patients receiving different types of anesthesia (Tables 4 and 5). Our data show that the QTc interval prolongation was more likely in patients who had longer surgery under GA and in older patients (Table 4). Interestingly, these factors were not significantly different in patients who demonstrated prolonged QTc interval under RA/MAC, compared to the control (Table 4).

A number of different classes of antiemetic have been associated with significant QTc interval prolongation in the general population. When we compared QTc interval change in relation to the most commonly used antiemetic intraoperatively (serotonin inhibitors, steroids and metoclopramide) we did not observe significant differences between the groups when these medications were administered during perioperative period (Table 5). In addition, perioperative use of beta-blockers did not have any significant effect on the QTc change regardless of the type of anesthesia (Table 5). Likewise, history of smoking was not associated with QTc interval prolongation perioperatively (Table 5). However; insulin administration to control intraoperative glucose level in diabetic patients was associated with QTc interval prolongation under GA (Table 5)

Because there were fewer patients who were not exposed to volatile agents (RA/MAC group) than those who had GA, we considered that a lack of effect might be attributable to the small sample size, rather than the lack of a relationship. Accordingly, we constructed a table of effect sizes for both anesthesia groups. It can be argued that effect sizes are better estimates of clinical effectiveness than probability values. Effect sizes do not change with different sample sizes, while probability values do [15]. If the risk factor was continuous, the effect size is expressed in terms of the Pearson correlation coefficient 'r' (Table 6). Age demonstrated a strong positive correlation with QTc interval prolongation in patients who received GA, whereas it correlated negatively in patients who received RA/MAC (Table 6). Duration of surgery correlated strongly with QTc interval prolongation in patients who were exposed to volatile anesthetics, but not in patients who received RA/MAC (Table 6). These results confirm our earlier observations presented in table 4 that duration of surgery and age are important risk factors in perioperative QTc interval prolongation only in patients exposed to volatile anesthetics.

For discrete clinical risk factors (HTN and DM), we used the standardized mean difference (Cohen's d). Our analysis revealed a small to medium effect size in age-matched diabetic patients in both GA and RA/MAC groups (Table 7). This implies that DM may be an important clinical risk factor for perioperative QTc interval prolongation regardless of the type of anesthesia. These data also suggest that a larger sample size is needed to obtain adequate statistical power to draw a definite conclusion. The sample size of 168 produced a power of .82 with a one-tailed alpha of .05, and a Cohen's d of .40. Cohen would classify this effect size as just below a 'medium' effect (d=.50), but it also indicates that we would be unable to detect what he calls a 'small' effect (d=.20). In order to detect a small effect, we would need a sample of 600 participants to achieve a power of .79, keeping our other assumptions unchanged.

In age-matched hypertensive patients Cohen's d showed less pronounced effect (Table 7). Thus, the effect of HTN on perioperative QTc interval prolongation cannot be excluded. Our analysis showed that HTN strongly correlated with age of the patients (older patients

	GENERAL ANESTHESIA		**REGIONAL ANESTHESIA AND MONITORED ANESTHESIA CARE**	
Risk factors	**Pearson correlation (r)**	**p value**	**Pearson correlation (r)**	**p value**
Age	**0.262**	**0.001**	**-0.400**	**0.004**
Weight	-0.062	0.444	0.088	0.547
Temperature	-0.090	0.311	-0.261	0.070
Duration of Surgery	**0.278**	**<0.001**	0.115	0.430
Glucose	0.118	0.322	0.149	0.459

Table 6: Correlation of QTc interval change and clinical risk factors in different types of Anesthesia.

	GENERAL ANAESTHESIA		**REGIONAL ANAESTHESIA AND MONITORED ANAESTHESIA CARE**	
Variable	**QTc Interval Change (msec) (mean ± SD)**	**Cohen's d**	**QTc Interval Change (msec) (mean ± SD)**	**Cohen's d**
HTN*	6.68 ± 40.18	0.17	8.93 ± 26.11	0.34
DM**	12.10 ± 32.51	0.37	11.69 ± 29.88	0.39

*regardless of the presence of DM, matched age
**regardless of the presence of HTN, matched age

Table 7: Effect sizes for QTc interval change in the presence of Hypertension and Diabetes mellitus in different types of Anaesthesia.

were more likely to have HTN), so QTc interval prolongation in older patients could be partially due to the presence of HTN.

Discussion

In this prospective observational study we compared demographic, pharmacological and clinical risk factors for QTc interval prolongation in patients receiving general anesthesia, monitoring anesthesia care, and regional anesthesia for noncardiac surgery.

In an overall study population of 168 individuals, 94 patients exhibited QTc prolongation during the perioperative period. In patients who received general anesthesia, duration of surgery, age, and perioperative insulin administration emerged to be important risk factors associated with QTc prolongation. This effect was not observed in RA/MAC group. Since, volatile anesthetic are well known to cause QTc interval prolongation in both in vitro and in vivo studies [10-12,16], we concluded that the duration of exposure to volatile anesthetic poses a significant risk for QTc interval prolongation in susceptible patients.

Antiemetic medications that we included for analysis in our study, as well as beta-blockers and tobacco use, did not have significant effect on QTc prolongation during perioperative period. These results confirm our clinical observation that the antiemetic are safe to use for postoperative nausea and vomiting prophylaxis in the perioperative period.

Certain underlying clinical conditions are well known to have significant risk for cardiac complications during surgery. DM is now recognized as an important risk factor for the development of postoperative cardiac events due to the presence of subclinical cardiac disease, autonomic neuropathy affecting cardiac conduction system and cardiac electrical instability [17,18]. In general population, DM is associated with QTc interval prolongation [19,20]. Moreover, in diabetic patients the presence of QTc interval prolongation has been shown to predict sudden cardiac death [20,21]. Both genetic factors and acquired subclinical cardiac disease influence the QTc interval in this patient population [7,18,20,22,23]. Our study showed that DM could be an important clinical predictor for QTc interval prolongation during perioperative period, regardless of type of anesthesia. Larger prospective clinical studies are needed to define the association between the presence of DM and the perioperative QTc interval changes, since these changes could signify underlying cardiac electrical instability and may predispose these patients to the development of malignant arrhythmia and even sudden cardiac death in the postoperative period.

Hypertension has also been identified as a risk factor for QTc interval prolongation [24]. In our study, HTN correlated strongly with age, and together they had significant influence on the QTc interval prolongation. It seems that age related changes in cardiac muscle, with underlying diastolic dysfunction due to increased stiffness [25,26] are more important that the presence of HTN itself.

Conclusion

In this study, we examined demographic, pharmacological and clinical factors for QTc interval prolongation in patients receiving different types of anesthesia. Our results show that duration of exposure to volatile anesthetic agents poses a significant risk for the QTc interval prolongation, which is especially pronounced in older patients. Diabetes mellitus seems to be an important clinical predictor for perioperative QTc interval prolongation regardless of the type of anesthesia, especially in patients who needed insulin for perioperative glucose control. Further, larger outcome clinical studies are needed to confirm whether these perioperative changes translate to increased risk for postoperative cardiac complications.

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References

1. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM (2003) What clinicians should know about the QT interval. JAMA 289: 2120-2127.
2. Wisely NA, Shipton EA (2002) Long QT syndrome and anaesthesia. Eur J Anaesthesiol 19: 853-859.
3. Nakao S, Hatano K, Sumi C, Masuzawa M, Sakamoto S, et al. (2010) Sevoflurane causes greater QTc interval prolongation in elderly patients than in younger patients. Anesth Analg 110: 775-779.
4. Pshenichnikov I, Shipilova T, Kaik J, Volozh O, Abina J, et al. (2003) QT dispersion in relation to left ventricular geometry and hypertension in a population study. Scand Cardiovasc J 37: 87-90.
5. Oikarinen L, Nieminen MS, Viitasalo M, Toivonen L, Jern S, et al. (2004) QRS duration and QT interval predict mortality in hypertensive patients with left ventricular hypertrophy: The Losartan intervention for endpoint reduction in hypertension study. Hypertension 43: 1029-1034.
6. Lee SP, Yeoh L, Harris ND, Davies CM, Robinson RT, et al. (2004) Influence of autonomic neuropathy on QTc interval lengthening during hypoglycemia in type 1 diabetes. Diabetes 53: 1535-1542.
7. Stettler C, Bearth A, Allemann S, Zwahlen M, Zanchin L, et al. (2007) QTc interval and resting heart rate as long-term predictors of mortality in type 1 and type 2 diabetes mellitus: a 23-year follow-up. Diabetologia 50: 186-194.
8. Roden DM (2004) Drug-induced prolongation of the QT interval. N Engl J Med 350: 1013-1022.
9. Moss AJ (2003) Long QT Syndrome. JAMA 289: 2041-2044.
10. Riley DC, Schmeling WT, al-Wathiqui MH, Kampine JP, Warltier DC (1988) Prolongation of the QT interval by volatile anesthetics in chronically instrumented dogs. Anesth Analg 67: 741-749.
11. Kuenszberg E, Loeckinger A, Kleinsasser A, Lindner KH, Puehringer F, et al. (2000) Sevoflurane progressively prolongs the QT interval in unpremedicated female adults. Eur J Anaesthesiol 17: 662-664.
12. Owczuk R, Wujtewicz MA, Sawicka W, Lasek J, Wujtewicz M (2005) The Influence of desflurane on QTc interval. Anesth Analg 101: 419-422.
13. Bazett HC (1920) An analysis of the time-relations of the electrocardiogram. Heart 7: 353-370.
14. Cohen J (1988) Statistical Power Analysis for the Behavioral Sciences. (2ndedn), Edition, Lawrence Erlbaum and Associates.
15. Wilkinson L (1999) Statistical methods in psychology journals: Guidelines and explanations. American Psychologist 54: 594-604.
16. Kleinsasser A, Kuenszberg E, Loeckinger A, Keller C, Hoermann C, Lindner KH, Puehringer F (2000) Sevoflurane, but not propofol, significantly prolongs the Q-T interval. Anesth Analg 90: 25-27.
17. Milaskiewicz RM, Hall GM (1992) Diabetes and anaesthesia: the past decade. Br J Anaesth 68: 198-206.
18. Whitsel EA, Boyko EJ, Rautaharju PM, Raghunathan TE, Lin D, et al. (2005) Electrocardiographic QT interval prolongation and risk of primary cardiac arrest in diabetic patients. Diabetes Care 28: 2045-2047.
19. Whitsel EA, Boyko EJ, Siscovick DS (2000) Reassessing the role of QTc in the

diagnosis of autonomic failure among patients with diabetes: a meta-analysis. Diabetes Care 23: 241-247.

20. Rana BS, Lim PO, Naas AA, Ogston SA, Newton RW, et al.(2005) QT interval abnormalities are often present at diagnosis in diabetes and are better predictors of cardiac death than ankle brachial pressure index and autonomic function tests. Heart 91: 44-50.

21. Linnemann B, Janka HU (2003) Prolonged QTc interval and elevated heart rate identify the type 2 diabetic patient at high risk for cardiovascular death: The Bremen Diabetes Study. Exp Clin Endocrinol Diabetes 111: 215-222.

22. Lehtinen AB, Newton-Cheh C, Ziegler JT, Langefeld CD, Freedman BI, et al. (2008) Association of NOS1AP genetic variants with QT interval duration in families from the Diabetes Heart Study. Diabetes 57: 1108-1114.

23. Veglio M, Bruno G, Borra M, Macchia G, Bargero G, et al. (2002) Prevalence of increased QT interval duration and dispersion in type 2 diabetic patients and its relationship with coronary heart disease: a population-based cohort. J Intern Med 251: 317-324.

24. Salles GF, Cardoso CR, Muxfeldt ES (2009) Prognostic value of ventricular repolarization prolongation in resistant hypertension: a prospective cohort study. J Hypertens 27: 1094-1101.

25. Frohlich ED (1999) State of the Art lecture: Risk mechanisms in hypertensive heart disease. Hypertension 34: 782-789.

26. Krishnan P, Ventura HO, Uber PA, Arcement LM, Mehra MR (2003) Treatment of hypertension for patients with diastolic dysfunction. Curr Opin Cardiol 18: 272-277.