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IS THERE ANY DIFFERENCE BETWEEN THE EFFECT OF REMIFENTANIL AND ALFENTANIL ON QT INTERVAL IN ELECTIVE SURGERY UNDER GENERAL ANAESTHESIA?

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ABSTRACT

Either acquired or congenital, Long QT syndrome (LQTS) is an arrhythmogenic disorder as a result of a defect in the cardiac ion channels. Anesthetic drugs, supposed to increase QT interval, leading to life-threatening arrtythmia in patients with LQTS. Data regarding two widely used narcotics in anesthesia, Remifentanil and Alfentanil , according to their effects on QT interval are scarce in patients undergoing elective surgery under general anesthesia.

Sixty female patients, aged 18- 35, scheduled for elective otolaryngologic operations under general anesthesia with American Society of Anesthesiologists physical status I (ASA I), were randomly allocated to two groups. In each group bolus dose of remifentanil or alfentanil was followed by infusion of the same drug. Anesthesia was induced with propofol and muscle relaxation facilitated by cisatracurium .ECG (Three-lead electrocardiogram), heart rate and non-invasive blood pressures were recorded at the following times: before and 90 seconds after the induction of anesthesia, 1 min. and 5 min. after endotracheal intubation.

At all time-points of study , QTc interval was not significantly prolonged in comparison to their baseline values in each group (P>0.05). Besides, trend of changes in heart rate and mean arterial pressure showed to be similar in both groups (P>0.05).

Administration of Alfentanil or Remifentanil can prevent the rise of HR and BP after laryngoscopy and intubation without prolonging QTc interval in adult females undergoing general anesthesia.

Keywords: QT interval, remifentanil, alfentanil , anesthesia, Statistics

INTRODUCTION

Some anesthetic drugs have been shown to increase QT interval.

Bolus dose of remifentanil & alfentanil was administered during induction of anesthesia followed by infusion. After baseline EKG, it was repeated at 3 consequent time-points.

During the study period , QTc interval was not significantly prolonged in each group.

Remifentanil and Alfentanil had no statistically significant effect on QT interval .

QT interval is a the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. In general, the QT interval represents electrical depolarization and repolarization of the left and right ventricles. A lengthened QT interval is a biomarker for ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.(1,2)

Many drugs used in anesthesia may interfere with the duration of the QT interval. However, it is difficult to determine the effects of individual anesthetic agents because of multiplicity of drugs, which are used during the course of an anesthesia(2).For example, propofol has reduced QT interval in some investigations(3) but increases this interval in patients with coronary artery disease during intubation(4). The combination of two or more agents prolonging the QT interval is believed to increase the risk of arrhythmia development (5).

Overall, it is optimal to avoid drugs that could prolong the QT interval preoperatively. This is especially important during laryngoscopy, intubation, and extubation of the trachea. So, administration of a potent short acting opioid (alfentanil, remifentanil) or administration of a β - adrenergic blocker (esmolol) and the use of topical anesthesia on the vocal cords to prevent QT prolongation is prudent(3). Alfentanil and remifentanil have rapid onset and short-acting opioid effects. Remifentanil has a very quick onset of action while its duration of action is shorter than that of alfentanil(8).

In the present study we compared the effect of remifentanil and alfentanil on the QT interval, heart rate and blood pressure in healthy, female patients (as drug-induced symptomatic long QT

syndrome have a female predominance (9)) undergoing elective surgery under general anesthesia.

This study was a step forward to enhance the clinical awareness of selection of preferred synthetic opioids (remifentanil or alfentanil) with lesser effect in prolonging QT interval.

METHODS

This study was a prospective double blind research that aimed to determine the effects of remifentanil and alfentanil on QT interval in elective surgery under general anesthesia among healthy female patients.

Sixty patients, residents of Fars province who had been referred to ENT clinics of Shiraz University of medical sciences were included in our study if aged 18-35years, ASA grade I and schedule for admitted for elective surgery under general anesthesia with tracheal intubation. University ethics committee approval was taken for the study (registered no. CT-87-4291) and informed consent obtained for each subject. Patients with abnormal serum electrolytes, cardiovascular or psychiatric problems, idiopathic or acquired prolonged QT interval, anticipated difficulty in tracheal intubation, patients taking any medication affecting QTc interval e.g. (tricylic antidepressant ,antidysrhythmics, β-adrenergic antagonists, calcium channel blockers), existence of cardio valvular disease, any cardiac rhythm abnormality, diabetes mellitus, pregnancy or obesity (body mass index > 30) or hypersensitivity reaction to egg, fish or soya bean were excluded from the study. Furthermore, any patient who developed significant decrease in heart rate or change in blood pressure requiring drug therapy were excluded from our study. No premedication was administered.

Upon arrival to operating theatre standard monitorings were established for patients (including non-invasive blood pressure, ECG, pulse oxymeter, capnometer and temperature). The standard lead II would be monitored and selected for subsequent recordings (ECG monitor: code master XL; AD Instruments, Colorado Springs, CO, USA).

All patients received Ringer's solution 5 ml /kg over 5-10 min before any recording. The first ECG recording and the control measurements of heart rate, noninvasive systolic, diastolic and mean arterial pressure were obtained just before induction of anesthesia. Patients were allocated into each group by a computer-conducted randomization. For induction of anesthesia, group A (n= 30) received a bolus of remifentanil 2 μ g/ kg over 60 seconds followed by an infusion of remifentanil at 0.15 μ g/kg/min. group b

(n=30) received a bolus of alfentanil 20 μ g/ kg over 60 seconds followed by an infusion rate of 0.25 μ g/ kg / min. Both drugs were diluted by normal saline to equal volumes (10cc).

Anesthesiologist and the technician who gathered data were both blind to the type of administered drug. Drug Infusion in both groups were continued through the study period. Immediately after the bolus of the study drug, propofol 2 mg / kg was administered followed by an infusion of 100 μ g / kg / min. Cisatracurium 0.1 mg / kg was given to produce neuromuscular blockade. A third party prepared all study drugs and infusions so that the investigators were unaware of their identity. Five minutes later all patients were intubated and ventilated mechanically with 100% 02, regarding maintenance of normoxia and normocapnia. The second, third and fourth ECG recordings and measurements of heart rate and blood pressure (systolic, diastolic and mean) were obtained before intubation , one and five minutes after intubation.

The study was terminated at this point and anesthesia and surgery were allowed to proceed without constraint. All of the four ECG recordings were coded and analyzed blindly by a cardiologist.

The QT interval was measured in lead II from the onset of the QRS complex to the end of the T wave, defined as a return to the T-P baseline.

QTc was calculated from Bazett's formula QTc = QT / $\sqrt{RR}$ and compared between two groups.

Statistical analysis was performed by one-way analysis of variance followed by independent t-tests as indicated, with spss 16.0 (SPSS Inc., Chicago, IL, USA). All values were expressed as mean (SD). We consume that in our study the effect of Remifentanil (A) and Alfentanil (B) on QTC is 30 units with standard deviation of 35(θ =35), (α=0.5), (β = 0.1), based on the formula ($N = \frac{4(Z_{\alpha/2} + Z_{1-\beta})^2 \delta^2}{d^2}$) the desired calculated in each group is 30. A p value of < 0.05 was considered significant.

RESULTS

A total of 60 patients (30 in each group) were studied. Demographic characteristics were similar in both groups (Table 1).

All patients had normal QTc intervals at rest, and no significant differences among the baseline QTc values of the two groups (P>0.05) were noticed. Although 90 Sec after the induction of anesthesia with remifentanil or alfentanil, no statistically significant QTc prolongation was demonstrated in both groups (P>0.05).

At 1 min. & 5 min. after intubation, the values did not change in any of the groups compared with the preceding values (P>0.05) and no prolongation of QTc statistically was observed, but difference between two groups were attenuated (Mean difference 0.0067 and 0.0063 respectively compared with 0.13).

The mean baseline values of SBP (systolic blood pressure) in two groups were comparable. The SBP decreased significantly in two groups 1 min after intubation compared with the corresponding baseline values(P<0.05),but in remifentanil group SBP decreased more as compared with alfentanil group (Mean difference 10.53).

There were no significant differences in DAP (diastolic arterial pressure) between the two groups at any time.

The mean baseline values of HR (heart rate) and MAP (mean arterial pressure) in two groups were comparable. At all time points trend of changes in heart rate and mean arterial pressure showed to be similar in both groups (P>0.05) , although MAP and HR 1 min after intubation decreased more in remifentanil than alfentanil group (table 2 and figure 1).

DISCUSSION

Our results showed that the QTc interval were not significantly prolonged after the administration of neither remifentanil 2.0 μg/kg nor alfentanil 20 μg/kg before or after laryngoscopy and tracheal intubation in healthy female patients. We also showed that SBP was significantly decreased after intubation in both groups. The values of HR and MAP and DBP did not change in any of the groups compared with the preceding values (P>0.05).

The results of previous studies showed that laryngoscopy and intubation caused increases in heart rate and blood pressure (16), but in our study administration of alfentanil or remifentanil before laryngoscopy and intubation prevented significant changes in HR and BP.

However, there is disagreement about the efficacy of alfentanil in preventing the QT prolongation during tracheal intubation, and the effects of other opioids such as fentanyl and sufentanil on QTc interval have not been elucidated completely. It has been shown that alfentanil 25 μg/kg prevented the prolongation of the QT interval following laryngoscopy and intubation (17), but in another study alfentanil 30 μg/kg did not attenuate QT prolongation after intubation (18), and in our study alfentanil 20 μ g/ kg over 60 seconds did not produce

prolongation of the QT interval following laryngoscopy and intubation.

The results of previous studies may complicate the interpretation of the effect of alfentanil on attenuation of the QTc prolongation induced by intubation because many anaesthetic drugs, including thiopental and suxamethonium, cause significant prolongation of the QTc interval(18). Therefore, in our study, induction with alfentanil, was performed without premedication or intravenous induction agents to avoid the complex effect of other anesthetic drugs on the QTc interval.

Alfentanil and esmolol attenuate the hemodynamic responses to laryngoscopy and tracheal intubation, and although higher doses have sometimes been used, comparable doses have also been effective. Higher doses of alfentanil or esmolol, or a combination, might attenuate the cardiovascular responses more effectively, although hypotension is more likely. In a study conducted by Maguire et al, after intubation, arterial pressure decreased sooner in the alfentanil than esmolol group but values were well within the physiological range, and the incidence of hypertension, hypotension and bradycardia requiring escape medication in both groups was low (12), which is compatible with the findings of our study that showed both alfentanil and remifentanil produced similar effects on arterial pressure, heart rate and QTc after endotracheal intubation.

The effect of various opioids on the interval of QT has not been thoroughly clarified yet. Fentanyl decreased the QTc interval in patients with long QT syndrome, but in other studies, the QTc increased significantly following injection of fentanyl or sufentanil in patients with coronary artery disease. The QTc interval 90 s after injection of remifentanil 0.5 μg/kg and 1.0 μg/kg did not change compared with that before injection. It is considered that 0.5–1.0 μg/kg remifentanil itself might have little or no effect on the interval of QTc, although the effect of 3% sevoflurane on QTc could not be excluded completely(18).Our study showed that remifentanil 2.0 μg/kg had no effect on QTc interval.

In a previous study, after induction of anesthesia with sevoflurane, the QTc interval increased in all patients . Enflurane, isoflurane and sevoflurane, when administered as the sole agent for induction and maintenance, all prolong the QT interval in unpremedicated healthy humans, and they can also extend the QTc to beyond the upper limit of the normal range (19). It is not known whether the QTc prolongation by sevoflurane can be

attenuated if a certain agent or drug is administered prior to sevoflurane induction. The exact mechanism of QT prolongation by sevoflurane is still unclear, but is probably related to blockade of the rapidly activating potassium repolarising current, independent of the autonomic nervous system tone (20).

Our results suggest that a dose of remifentanil was sufficient to block adrenergic stimulation for preventing the QTc prolongation during intubation. It is also possible that the QTc interval may be prolonged at any time when the adrenergic response to surgical stimulation is not properly attenuated, although the QTc interval was not monitored during surgery in our study.

The induction of anesthesia with sevoflurane significantly prolongs the QT and the QTc interval, whereas induction with total IV anesthesia with propofol significantly shortens the QT but not the QTc interval. Heart rate was reduced by sevoflurane, but not by propofol (11), because propofol assumed to have no QTc prolongation effect, therefore, we used this drug for induction of anesthesia, which is compatible with our results that no QTc prolongations have been seen following administration of propofol plus alfentanil or remifentanil.

Congenitally long QT syndrome may be related to mutations in genes for encoding cardiac potassium and sodium channels, and acquired forms of long QT syndrome result from many causes including drugs and cardiac, neurologic, endocrine, and metabolic and electrolyte disturbances. Although the etiology of congenital and acquired prolongations of the QT interval might be different, the activation of the sympatho-adrenal system threatens extremely prolonged QT and torsades de pointes, a hallmark of both syndromes. Therefore it can be inferred that remifentanil can reduce the risk of arrhythmia in patients with long QT syndrome, but further investigations are needed to substantiate this finding.

Although synthetic opioids are routinely used in daily anesthesia practice, there is lack of evidence in the literature about the exact and comparative effects of different opioids on the QT interval in humans(2), so this study was designed and showed that remifentanil or alfentanil had no effect on QTc interval during three time points, 90 secinds after induction of anesthesia , one and five minutes after laryngoscopy and tracheal intubation.

In conclusion, the present study suggests that both remifentanil and alfentanil have no effect on QTc interval after induction of anesthesia and up to 5 minutes after

tracheal intubation . Administeration of both drugs during induction of anesthesia followed by infusion can prevent the rise of HR and BP after laryngoscopy and intubation without prolonging QTc interval. Future , larger samples, multicenter studies in different subsets of patients is needed to perfectly prove this finding.

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Table 1- Demographic data of female patients in remifentanil and alfentanil groups. Values are mean (SD).

Group	Number	Age; years	Weight;kg
Remifentanil	30	26(5.57)	51(7.3)
Alfentanil	30	23(4)	51(4)

Table 2 -Descriptive statistics of variables; Changes in heart rate (HR, beat/min), QTc interval (ms), systolic (SBP) and diastolic (DBP) blood pressure and mean (MAP) arterial blood pressure (mmHg). Mean (SD) in female patients under general anesthesia either received remifentanil or alfentanil .

	Baseline	90 Sec after induction before intubation	1 min after intubation	5 min after intubation
Remifentanil				
HR	**88(18)**	**82(15)**	**78(19)**	**72(13)**
QTc	**420(30)**	**430(41)**	**432(38)**	**424(37)**
SBP	**120(11)**	**95(19)**	**96(21)**	**103(17)**
DBP	**77(8)**	**56(15)**	**60(14)**	**66(15)**
MAP	**91(11)**	**69(16)**	**72(15)**	**78(15)**
Alfentanil				
HR	**92(14)**	**79(11)**	**84(15)**	**74(10)**
QTc	**405(25)**	**417(50)**	**432(28)**	**418(27)**
SBP	**118(13)**	**93(16)**	**107(18)**	**105(13)**
DBP	**76(11)**	**52(14)**	**65(17)**	**66(14)**
MAP	**90(11)**	**65(14)**	**79(17)**	**79(13)**

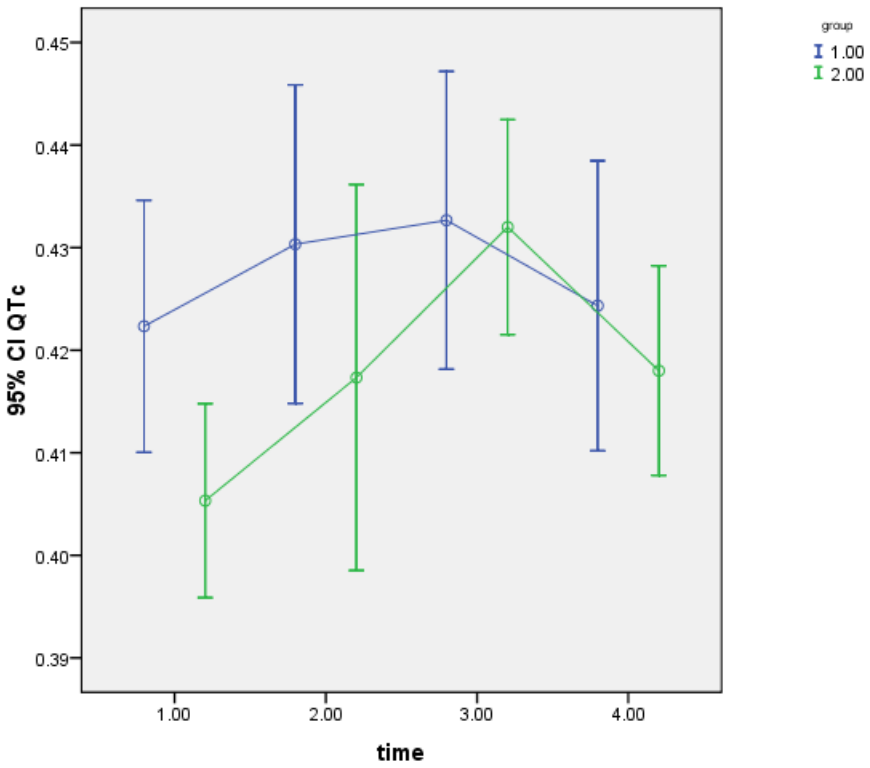

Fig.1. Duration of QTc interval; mean (SD). Time point 1:Baseline ECG on arrival to operating theater , Time point 2: 90 seconds after induction anesthesia with propofol plus remifentanil or alfentanil, Time point3: one minute after laryngoscopy and intubation, Time point 4: five minutes after intubation, group 1:Remifentanil, group 2:Alfentanil