Comparison of the Effects of Alfentanil and Remifentanil on QT Interval Following Local Epinephrine Infiltration in Septoplasty Under General Anesthesia

Mansoor Masjedi (1)
Golnar Sabetian (2)
Fatemeh Tubaei (2)
Mahnaz Rakhshan (3)
Hossein Haddad Bakhodaei (4)

(1) Anesthesiology and Critical Care Research Center, Trauma Research center, Shiraz University of Medical Sciences, Shiraz, Iran
(2) Department of Anesthesiology and Critical Care, Shiraz University of Medical Sciences, Shiraz, Iran
(3) School of Nursing and Midwifery, Shiraz University of Medical Sciences, Shiraz, Iran
(4) Department of Neurosurgery, Shiraz University of Medical Sciences, Shiraz, Iran

Corresponding author:
Golnar Sabetian
Anesthesiology Department, Nemazi Hospital, Nemazi Square,
Shiraz, Iran
Tel: +98 71 36474270; Fax: +98 71 36474270
Email: gsabetian@yahoo.com

Abstract

Background and Objectives: Corrected QT interval (QTc) prolongation can lead to life threatening arrhythmias. Previous studies denote that many anesthetic drugs and catecholamine release due to endotracheal intubation and surgery could induce QTc prolongation .Short acting opioids such as alfentanil and remifentanil are supposed to reduce the catecholamine release and to prevent QTc prolongation. The objective of this study was to compare the effect of alfentanil and remifentanil on QTc interval in patients under general anesthesia following local nasal submucosal epinephrine infiltration during septoplasty.

Materials and Methods: As a double blind study, 84 patients aged 18-50 years old with American Society of Anesthesiologist physical status I and II (ASA PS I&II) scheduled for septoplasty and planned to receive local epinephrine injection under general anesthesia were randomly allocated in to two groups; Alfentanil (A) and Remifentanil (R). Patients in group A, received alfentanil 25-50 g/kg before induction followed by 0.5-2 g/kg/min infusion during maintenance of anesthesia. Group R, received remifentanil 1-2 g/kg before induction followed by 0.2-0.25 g/kg/min infusion through maintenance of anesthesia. Other anesthetics were similar in both groups. Hemodynamic parameters and corrected QT interval were recorded at baseline (T1), 3 minutes after induction (T2), following endotracheal intubation (T3), post epinephrine infiltration (T4),3-5 and also 20 minutes later (T5 &T6).

Results: Our study showed that there was no significant difference in blood pressure changes between group A and R. Heart rate was significantly lower in group R. Development of QTc interval prolongation (QTc>450 milliseconds) occurred in both groups, but shorter QTc interval was prominent in group R at two time-points; post-intubation and 3-5 minutes after epinephrine infiltration .

Conclusion: Neither alfentanil nor remifentanil could completely prevent QTc prolongation, following catecholamine surge in anesthetized patients, although remifentanil is more potent in this regard.

Key words: general anesthesia, alfentanil, remifentanil, QT prolongation

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Background and Objectives

Prolongation of QTc interval is associated with life-threatening dysrrhythmia as such as polymorphic ventricular tachycardia (torsade de points), ventricular fibrillation, asystole and sudden cardiac death (1-4) .

It is known that most of volatile and intravenous anesthetics can influence the QTc interval. Many studies have investigated their effects. However it is difficult to determine the exact effect of a single anesthetic agent due to multiplicity of drugs used during anesthesia. For example, in spite of much research , there is controversy about the effect of propofol on QTc interval (2, 5-7).

Short acting potent opioids such as alfentanil and remifentanil which are strong receptor agonists can attenuate the stress induced by intubation and surgery and correlated sympathetic over-activity which is able to induce QTc prolongation (1, 8-13). On the other hand, it is shown that local injection of epinephrine which is a sympathomimetic drug (catecholamine) is able to induce 'torsade de points' in patients with long QT syndrome during surgery (14-16). Although, in a single study ,it was reported to shorten QTc interval (17).

Since there has been no previous study comparing the effect of alfentanil with remifentanil on QTc interval under general anesthesia following local infiltration of epinephrine, we decided to elucidate this issue.

Methods

This clinical trial was approved by research and ethics committee of Shiraz University of Medical Science (No. CT-P-92-6118) and registered in national clinical trial system (registration No.: IRCT2014020816524N1).

Informed consent was taken from participants. This prospective double blind randomized study enlisted 82 patients with American Society of Anesthesiology, physical Status I and II (ASA-PS: I&II), 18 to 50 years old who were scheduled for septoplasty in Shahid Dastghib Hospital (a university affiliated referral hospital of Shiraz, south-west of Iran). All surgery was performed between 08:00 - 12:00 AM to minimize the influence of circadian variation in cardiac autonomic nervous system activity.

Patients were excluded from the study if any of the following criteria were met:

1) Use of any drug affecting QT interval in last 14 days including: tricyclic antidepressants (TCAs), anti-arrhythmic drugs, blockers and calcium channel blockers
2) Idiopathic or acquired QTc prolongation >450 msin preoperative electrocardiogram(ECG)
3) Any electrical conduction abnormality (e.g. bundle branch block, pr-eexcitation syndrome or AV nodal arrhythmia)
4) Any baseline arrhythmia
5) Structural heart disease
6) Electrolyte disturbance
7) Hypo or hyperthyroidism
8) Obesity with BMI >30
9) Diabetic neuropathy
10) Allergy to propofol, egg or soya bean
11) Intra operative administration of blockers or volatile anesthetics to reduce surgical site bleeding

Patients were randomly allocated into two groups, alfentanil (A) and remifentanil (R) based on a computer-generated sequence of numbers.

Standard monitoring including heart rate (HR), non-invasive systolic, diastolic and mean arterial pressure monitoring and pulse oxymetry were established.

Upon arrival to the operating theater, a preoperative 12-lead standard ECG and a baseline recording of study parameters were recorded (T1). All patients received 5-7 cc/kg saline, before midazolam (0.03 mg/kg) and morphine (0.1 mg/kg) as premedication. This was followed by alfentanil 25-50 g/kg or remifentanil 1-2 g/kg in group A or R. Induction was induced by sodium thiopental 4 mg/kg and muscle relaxation by atracurium, 0.6 mg/kg. Three minutes later (T2) and just after endotracheal intubation (T3), data collection was done.

Then, propofol was administered at 100 g/kg/min associated with infusion of alfentanil (0.5-2 g/kg/min) in group A and remifentanil (0.2-0.25 g/kg/min) in group R. A and R solutions were prepared in equal volumes by a nurse and were given to resident of anesthesia who was unaware of the type of opioid. Anesthesia nurse who recorded the parameters was also not aware of the type of opioid infusion.

After prep and drape 20 cc of epinephrine (1/100000 dilution) plus lidocaine (1.5%) was infiltrated at the site of surgery by surgeon.

The 4th,5th and 6th data collection were just after epinephrine infiltration, 3-5 and also 20 minutes later. (T4,T5,T6).QT interval in lead II of ECG were calculated manually and corrected according to Bazett's formula (QTc=) by resident of anesthesia who was not aware of study group.

Data were analyzed by SPSS 19 software and expressed as mean ± standard deviation (SD). Demographic data were also analyzed by the chi-square or ANOVA tests. Inter-group comparison was done by repeated–measures ANOVA and a p-value of <0.05 was considered to be statistically significant. A sample size of 36 patients per group needed with 80% power (α=0.05).

Results

84 patients were assigned to this study, from which 12 were excluded according to exclusion criteria. (Figure 1) Patients in both groups had similar demographic characteristics (that is age and sex). (Table 1)

Figure 1: patients' flow diagram

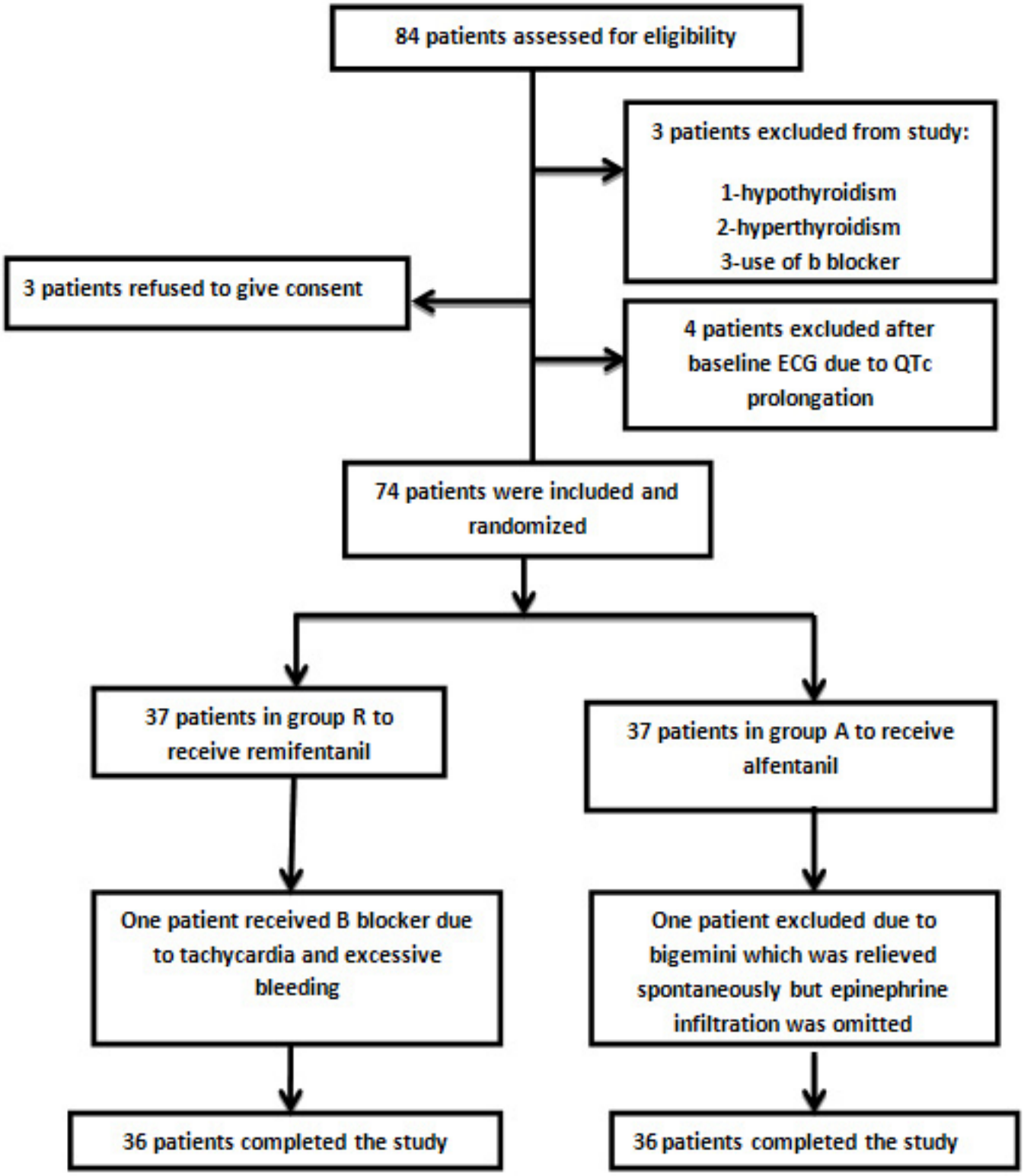


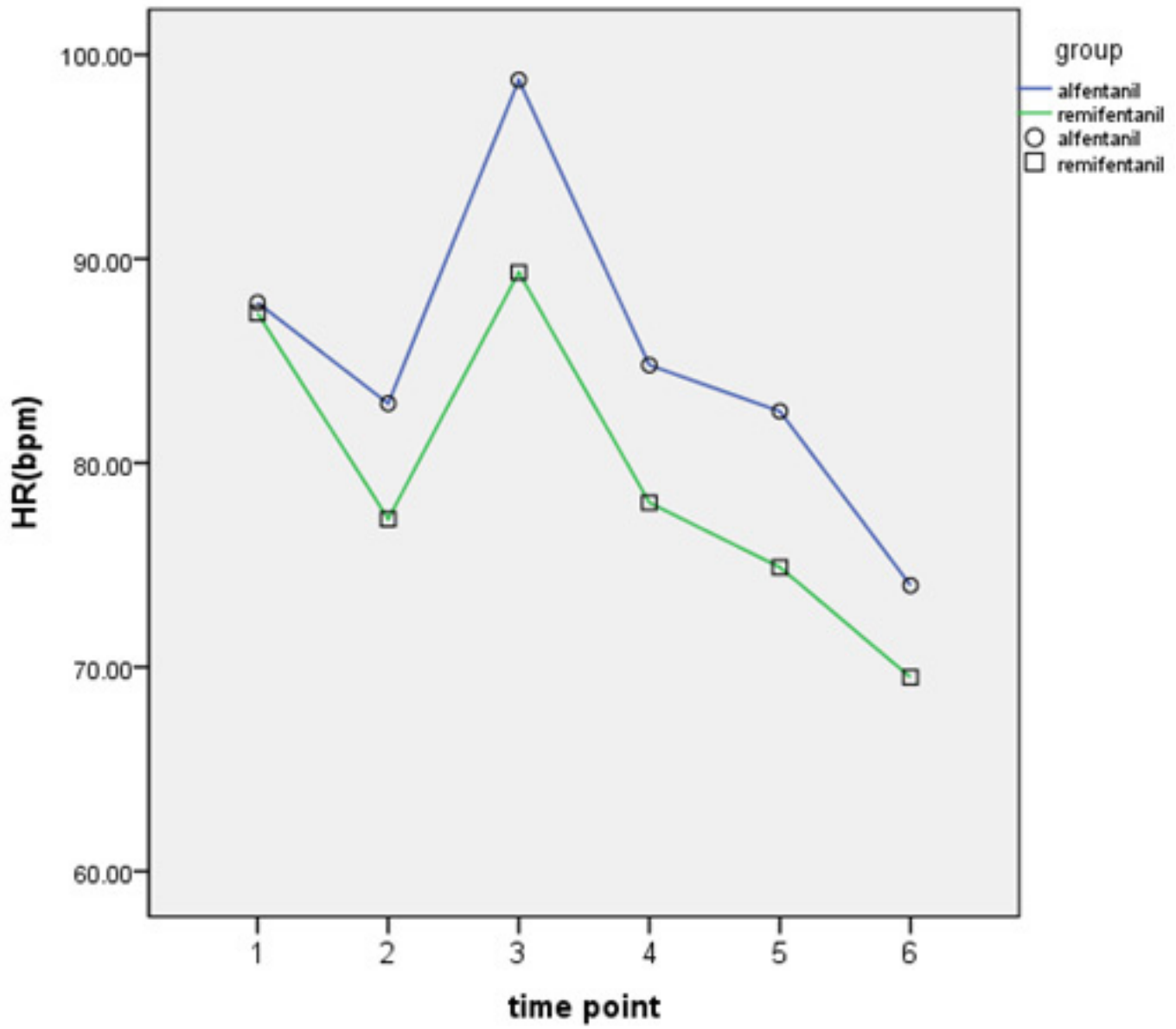
Table 1: Demographic data of the patients in group A (alfentanil) and R (remifentanil)

	Group A	Group R	P Value
Sex (M/F)	18/18	19/17	
Age	27(6.7)	25(7.4)	0.577

Values for age are mean (SD)

There was no statistically significant difference in baseline hemodynamic variables. During the course of study, although trend of changes in systolic, diastolic and mean arterial pressure (MAP) were alike in both groups (p>0.05), heart rates were much lower in group R (p=0.017). (Figure 2)

Figure 2: HR changes during the study
(1:baseline ECG , 2:three minutes after induction of anesthesia, 3:post laryngoscopy and intubation, 4:after epinephrine infiltration , 5&6:three to five and twenty minutes after epinephrine infiltration)



Regarding QTc interval, it was similarly prolonged in both groups (p>0.05). If we consider QTc to be prolonged when it is more than 450 milliseconds, many patients had QTc lengthening from 2nd to 6th time points in both groups.

Meanwhile, more patients with QTc prolongation were in group A at 3rd (immediately after intubation) and 5th (3-5 minutes after epinephrine injection) time points. (P values respectively 0.001 and 0.002) Table 2 and Figure 3.

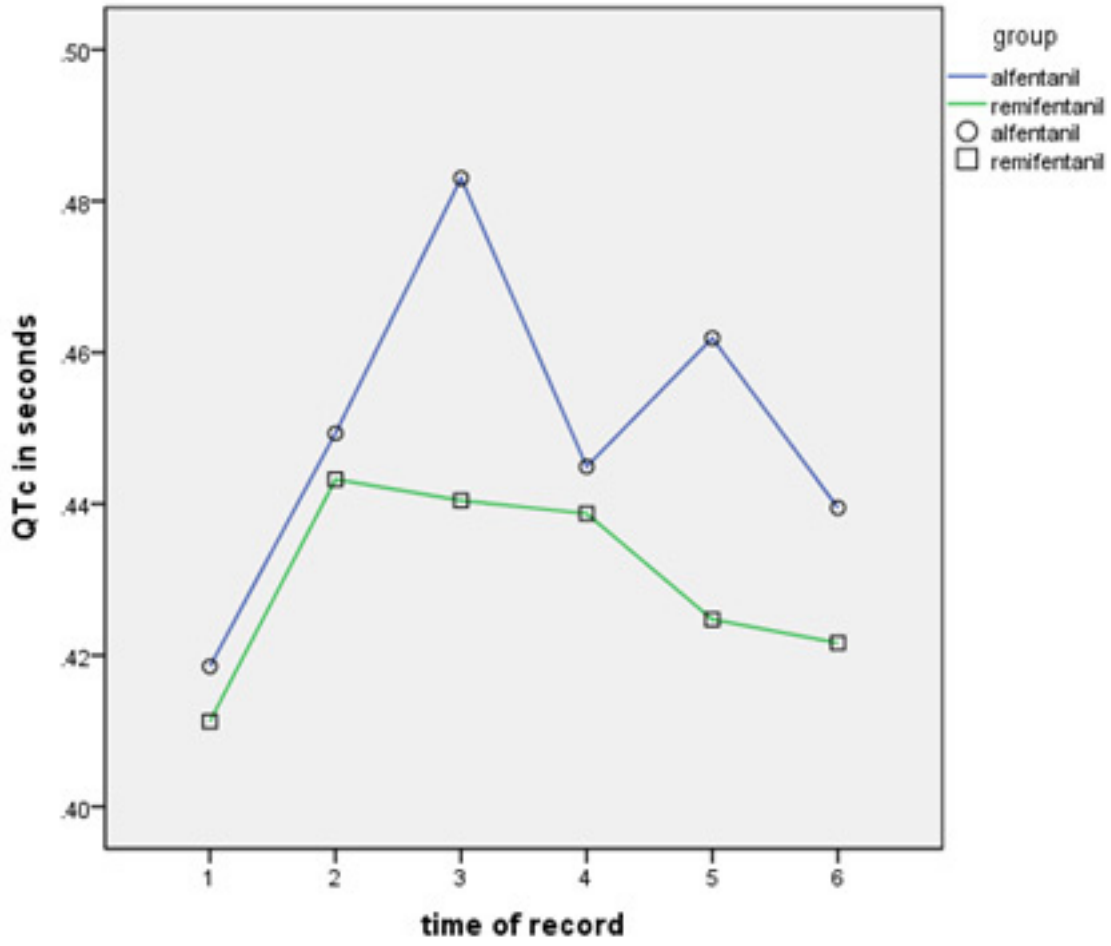
Table 2: mean QTc interval at six time points (SD).(data in milliseconds)

Time of record	QTc in Alfentanil group	QTc in Remifentanil group	P value
T1	418(24)	411(29)	>0.05
T2	449(37)	443(39)	>0.05
T3	483(50)	440(39)	0.004
T4	444(33)	438(38)	>0.05
T5	461(30)	424(34)	0.004
T6	439(30)	421(35)	>0.05

Table 3: percent of patients with QTc>450 milliseconds (ms) at six time points

	A group>450 ms	R group>450 ms	P value
T1	0%	0%	>0.05
T2	30.6%	47.2%	>0.05
T3	69.4%	27.8%	<0.05
T4	36.1%	36.1%	>0.05
T5	61.1%	25%	<0.05
T6	32.4%	19.4%	>0.05

Figure 3: QTc interval at six different time points in alfentanil and remifentanil groups
(1:baseline ECG, 2:three minutes after induction of anesthesia, 3:post laryngoscopy and intubation, 4:after epinephrine infiltration, 5&6:three to five and twenty minutes after epinephrine infiltration)



Discussion

The purpose of this study was to compare the effect of A and R on attenuation of prolongation of QTc interval following catecholamine surge (both endogenous and exogenous sources) in patients under general anesthesia.

Previous studies showed that R is capable of depressing sinus node function and so attenuating QTc prolongation during anesthetic induction when used in bolus doses (5) (6) (15). Korpinen et al. and Lindgren et al. showed A could prevent prolongation of QTc interval during induction of anesthesia but there is still some controversy. (8) (9)

Our study showed that, neither A nor R (at prescribed doses) is potent enough to prevent QTc prolongation following endogenous catecholamine release or administration of epinephrine, although no life threatening arrhythmia occurred in each group. It differs considerably from that of Dogan et al. who found that R shortened QTc interval, and those of Kim et al. and Kweon et al. who found that R prevented QTc prolongation. It also differs from findings of Lindgren et al. and Korpinen et al. that A prevented QTc>450 ms after endotracheal intubation (1) (18) (19).

These controversies may arise from different baseline QTc intervals of patients in these studies .Other disturbing factors may include administration of sodium thiopental or propofol infusion during anesthesia; Denoted in both Harvey and Lindgren et al. studies that sodium thiopental can prolong the QTc interval through inhibition of turnover of dopamine and noradrenaline in central nervous system

(8) (20). And in Saarvina et al. and Kim et al. that propofol increases QTc interval (21) (22). The effect of sodium thiopental and propofol could not disturb the result of our study, because both groups (A& R) received the same doses.

Statistically, there was no significant difference between R and A on QTc interval, but some noticeable points need consideration. After laryngoscopy and intubation (T3), QTc interval is shorter in R than in A group (p=0.004). The same happened again 3-5 minutes after local infiltration of epinephrine (T5) (p=0.004). This may be the result of epinephrine surge in blood. In other words, prolongation of QTc interval is more prominent in group A than R at two time points, T3 and T5.

Laryngoscopy and intubation can induce a surge in plasma catecholamine concentration (23). This raise may be associated with QTc prolongation and cardiac arrhythmias. Besides, exogenous catecholamine causes QTc prolongation and U wave amplification even in normal subject (15).

Although various opioids have been used to abolish catecholamine related hemodynamic response to tracheal intubation, ambiguity exists about the efficacy of remifentanil in preventing QTc prolongation and even more about alfentanil (8) (9).

Moreover multiple studies have shown that, the proposed effect of remifentanil on QTc interval is dose dependent (18, 19, 24).

We didn't find any study regarding the effect of injection of epinephrine on QTc interval in subjects receiving remifentanil or alfentanil.

Trend of changes in systolic, diastolic and mean arterial pressure were similar in both A and R groups. Alfentanil was less effective than remifentanil in attenuation of heart rate responses following endotracheal intubation. Previous studies denote controversy about the effect of A or R on suppressing hemodynamic responses following endotracheal intubation (8) (9).

This study has some limitations. First, although the most popular formula to correct QTc interval regarding HR is Bazett's formula, this method is known to overcorrect the QTc interval for fast HRs and under-correct it for slow HRs. Therefore, estimation of the QTc interval with this formula could lead to a false diagnosis of prolonged QTc interval in patients with increased HR (25). This may have disturbed calculation of exact QTc interval in our study.

Secondly, it was performed on a specified subgroup; Healthy young and middle aged patients without any cardiac disorder, and it limits the external validity of our study.

Thirdly, exogenous epinephrine was mixed with lidocaine before local infiltration which may have influenced changes in QTc interval.

Fourthly, the probable effect of other anesthetic drugs, alone or in combination should be considered. We didn't measure the serum concentration of alfentanil, remifentanil and catecholamine.

Conclusion

Neither remifentanil nor alfentanil (at prescribed doses) could completely prevent QTc prolongation following catecholamine surge in patients under general anesthesia. Remifentanil is more potent in this regard.

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