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Effects of Neostigmine and Sugammadex on QT Interval and QT Dispersion

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ABSTRACT

Dispersion of QT dispersion (QTD) in 12-lead electrocardiogram is a useful index for assessment of ventricular arrhythmia risk and cardiovascular event. To determine the effects of reversal of nondepolarizing neuromuscular blockade on cardiovascular event, we evaluated the QT interval QTD after reversal of the neuromuscular blockade by neostigmine or sugammadex.

After obtaining the approval of the ethics committee of Dokkyo Medical University Hospital, 40 patients with ASA physical status I or II were allocated to following two groups. Patients in the groups N (n=16) and S (n=15) received combination of neostigmine (40 μg/kg) and atropine (20 μg/kg) or sugammadex (2 mg/kg) as a reversal of neuromuscular blockade after the operation under 1% sevoflurane anesthesia, respectively. The RR interval, QT interval (QT), corrected QT interval (QTc), QT dispersion and corrected QT dispersion (QTcD) were consecutively recorded using computerized measurement before and after administration of reversal agents in both groups.

RR interval in the group N significantly decreased 1-4 min after reversal of the neuromuscular blockade, but not in the group S. However, in the groups N and S, QT interval, QTc interval, QTD and QTcD were not changed after reversal of the neuromuscular blockade. Moreover, there was no significant difference between both groups in QT interval, QTc interval, QTD and QTcD during the study.

Our results suggest that neither neostigmine nor sugammadex may increase the risk of ventricular arrhythmia and cardiovascular events in reversal of the neuromuscular blockade under sevoflurane anesthesia.

Key words : neostigmine, sugammadex, QT interval, QT dispersion

INTRODUCTION

Several anesthesia-related drugs are associated with life-threatening cardiovascular events. Particularly, anticholinesterase, one of reversal of neuromuscular blockades may cause bradycardia and bradyarrthythmias such as junctional rhythm or asystole[1]. Neostigmine is an anticholinesterase and usually used for reversal of the residual neuromuscular blockade. It is well known that neostigmine induces bradycardia by inhibiting hydrolysis of acetylcholine released by parasympathetic neurons regulating the heart[2]. It has been suggested that reversal of the neuromuscular blockade by neostigmine produces serious complication such as cardiac arrest due to its cholinergic effect[3,4]. To avoid such serious adverse effects, atropine should be routinely administrated together with neostigmine for reversal of the neuromuscular blockade.

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QT interval prolongation caused by anesthetics and opioids is also another problem during anesthesia because of a risk of *torsades de pointes*[5,6]. The previous study revealed that neostigmine may produce prolongation of rate- corrected QT (QTc) interval on electrocardiogram[1]. In contrast, it has been reported that neostigmine with anticholinergic agent has no effect on QTc interval during anesthesia[7].

Sugammadex, a selective relaxant binding agent which is a modified γ-cyclodextrin compound, reverses the effect of steroidal nondepolarising neuromuscular blocking agents, rocuronium bromide and vecuronium bromide by immediate encapsulation[7~9]. Sugammadex is used for complete and rapid reversal for moderate or deep muscle relaxant[6,10]. Since sugammadex does not block acetylcholinesterase unlike neostigmine, co-administration of anticholinergic agent is not required[6]. Moreover, it has been demonstrated that 4 mg/kg sugammadex did not prolong QTc interval under the propofol or sevoflurane anesthesia[7]. Sugammadex is thought to have fewer adverse cardiovascular effects, compared to neostigmine.

Dispersion of QT interval (QTD) is defined as maximal QT interval minus minimal QT interval on 12-lead of the surface electrocardiogram (ECG) reflects regional heterogeneity of ventricular repolarization[11], and is significantly greater in patient with ventricular arrhythmia than in those without[12~14]. QTD is also considered as an important predictor of a serious cardiac event such as ventricular arrhythmia. Our previous study suggested that tracheal intubation is associated with a risk for increase of QTD[15]. In our study, the increase in QTD during tracheal intubation was prevented by landiolol, which is an ultra- short acting β1-adrenoceptor antagonist.

Although adverse effects of neostigimine on the cardiovascular system including QT interval prolongation are well known, the effect of reversal of the neuromuscular blockade on QTD has not been assessed. The purpose of this study is to determine the effects of neostigmine and sugammadex on RR interval, QT interval, rate-corrected QT (QTc) interval, QTD and rate-corrected QTD (QTcD) using computerized measurement.

METHODS

After obtaining the approval of the ethic committee of Dokkyo Medical University and written informed consent for each patient, 40 patients with ASA physical status I or II aged 20-60 years who were scheduled to undergo elective otorhinolaryngological surgery were studied. They were 15% of ideal body weight. All patients with cardiovascular respiratory, metabolic or cerebrovascular disease were excluded from this study. Patients with predicted difficulty in tracheal intubation were also excluded. No patient received any medication. No premedication was given to any patients. Patients were randomly allocated following two groups : patients in the groups N (n=16) and S (n=15) received combination of neostigmine (40 μg/kg) and atropine (20 μg/kg) or sugammadex (2 mg/kg) as reversal of neuromuscular blockade after the operation under 1% sevoflurane anesthesia, respectively.

After patient arrival at the operation room, standard 12- lead ECGs (FDX-4521L ; Fukuda Denshi Co. Ltd., Tokyo, Japan), noninvasive arterial blood pressure, pulse oximetry were monitored. After preoxygenation with 100% oxygen, anesthesia was induced with IV propofol 1.5 mg/kg, rocuronium 0.6 mg/kg and remifentanil 0.2 μg/kg/min. During mask ventilation, 2% sevoflurane with 100% oxygen was added. Tracheal intubation was performed by an experienced anesthesiologist who was accomplished within 20 seconds. Anesthesia was maintained with remifentanil (0.2-0.3 μg/kg/min), air- oxygen mixture and sevoflurane (1-1.5%). The ventilator was adjusted to end-tidal carbon dioxide tension ($P_{ET}CO_2$) was 35-40 mmHg during the study. All patents received a continuous infusion of acetate Ringer's solution at a rate of 5 mg/kg/h during the study. No additional rocuronium was given during the maintenance of anesthesia.

At the end of surgery, remifentanil was stopped, and then 12-lead ECG was measured under 1% sevoflurane. Six minutes after the end of operation, neostigmine or sugammadex was administrated as reversal of the neuromuscular blockade. Measurement of RR interval, QT interval, QTc interval, QTD and QTcD were performed at every minute from the end

Table Demographic data

	Group S (n=15)	Group N (n=16)
Gender (male/female)	9/6	10/6
Age (yrs)	54±15	51±15
Height (cm)	163±8	166±8
Weight (kg)	66±18	68±15

There is no significant difference between both groups.
The group S : Sugammadex was administered after the surgery.
The group N : Neostigmine was administered together with atropine after the surgery.

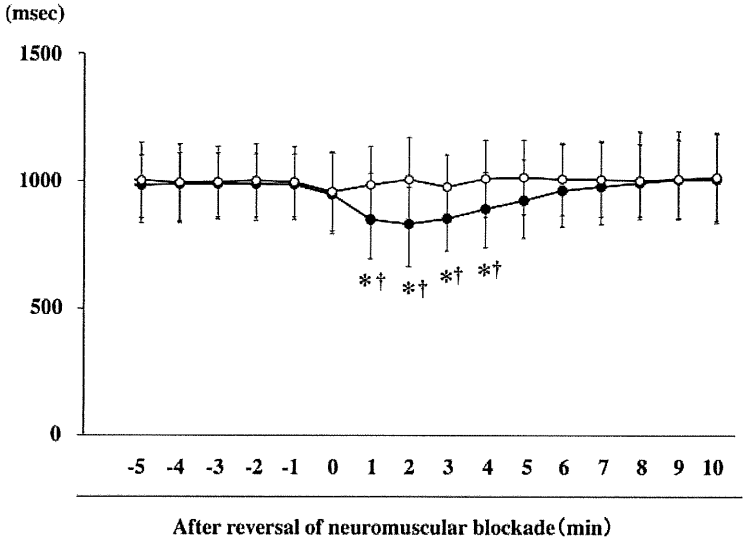

Figure 1

Changes in RR interval. ● : the group N, ○ : the group S. All values are expressed as means±SD. *$p<0.05$ vs 5 minutes before reversal of the neuromuscular blockade. †$p<0.05$ vs the group S.
RR interval significantly decreased after reversal of the neuromuscular blockade in the group N, but not in the group S.

of surgery to 10 minutes after reversal of the neuromuscular blockade.

From the ECG consecutive beat- to- beat data were digitally recorded at a sample rate of two- milliseconds. QT intervals were determined by QTD-1 (Fukuda Denshi Co. Ltd.), which detected the onset of the Q wave and the end of the T wave. This technique determines the onset of the Q wave as the intersection of a threshold level with the differential of the Q wave, and the end of the T wave as the intersection of a threshold level with the differential of the T wave, respectively. The software used the differential threshold technique has been previously described in detail[16,17]. QT intervals were measured in all 12 leads and corrected for heart rate by Bazett's formula. QTD was defined as the difference between the maximum and minimum average QT interval in 12 lead ECG. Similarly, QTcD was defined as the difference between the maximum and minimum average QTc interval. The average value of data- derived from three successive beats for each lead was used for analysis. Leads in which the end of the T wave could not be clearly detected were excluded from this study.

Data are presented as mean±SD. Intergroup differences were analyzed by two-way analysis of variance (ANOVA) for the repeated-measures design. When a significant overall effect was detected, Tukey's *post*

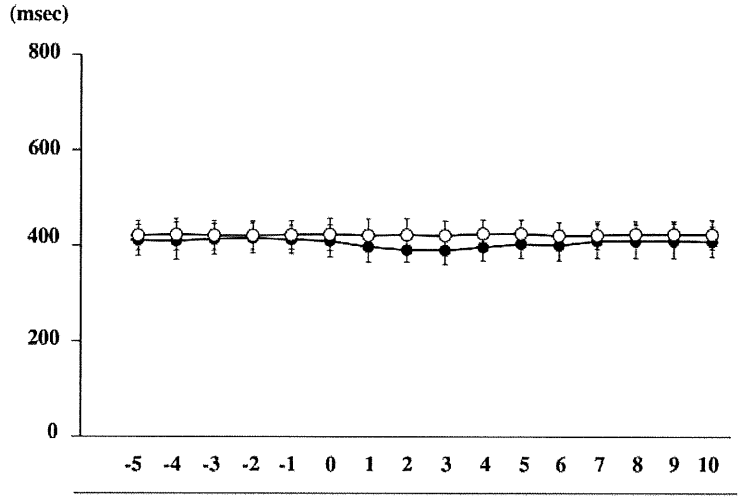

Figure 2

Changes in QT interval. ● : the group N, ○ : the group S. All values are expressed as means ± SD.
There is no significant change in QT interval during the study in both groups.

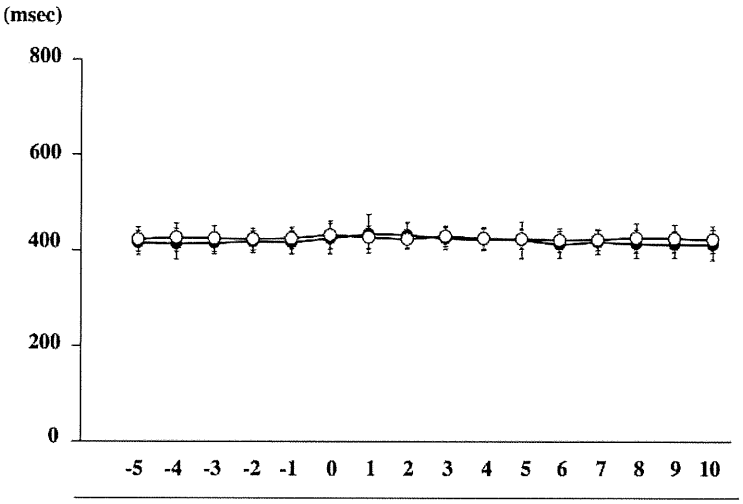

Figure 3

Changes in rate-corrected QT (QTc) interval. ● : the group N, ○ : the group S. All values are expressed as means ± SD.
There is no significant change in QTc interval during the study in both groups.

hoc test was conducted for comparison of the mean values for the two variables. In all analyses, probability to detect the difference was set at the 5% level ($P < 0.05$).

RESULTS

There were no significant differences in age, gender, height, or body weight between two groups (Table). No complication was observed throughout this study. There is no patient who has abnormalities of RR interval, QT interval, QTc interval, QT dispersion and QTc dispersion in both groups.

Figure 1 shows the changes in the RR interval before and after reversal of the neuromuscular block-

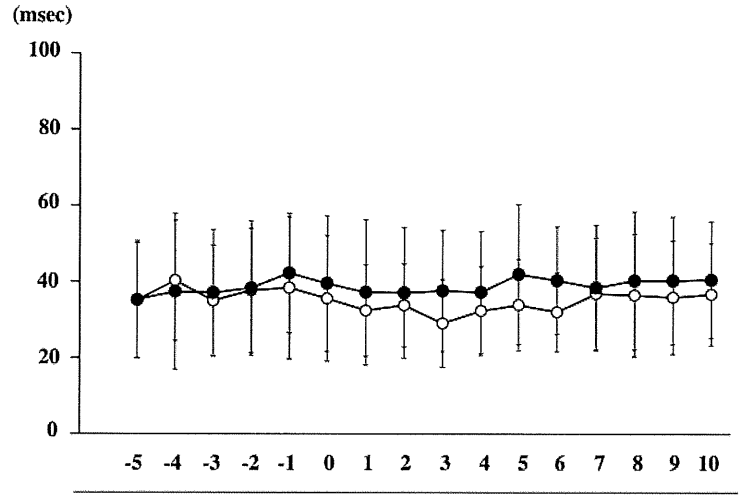

Figure 4

Changes in QT dispersion. ● : the group N, ○ : the group S. All values are expressed as means ± SD.
There is no significant change in QT dispersion interval during the study in both groups.

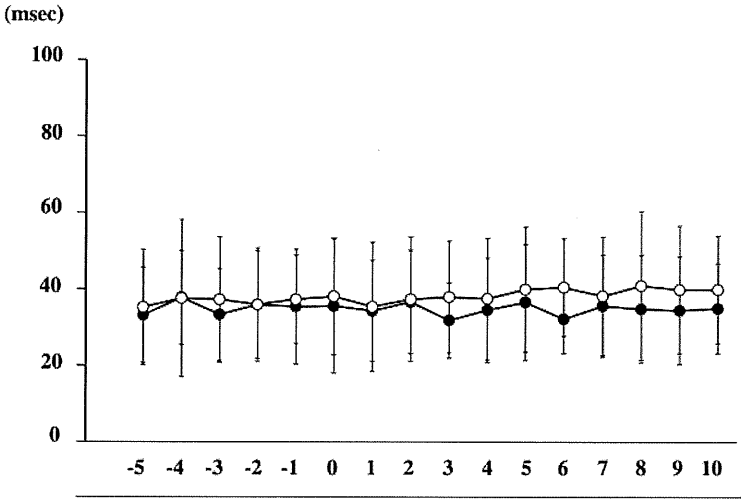

Figure 5

Changes in rate-corrected QTc dispersion (QTcD). ● : the group N, ○ : the group S. All values are expressed as means ± SD.
There is no significant change in QTcD during the study in both groups.

ade in both groups. The RR interval in the group N was significantly decreased from 1 to 4 min after administration of neostigmine and atropine compared with baseline (baseline : 978 ± 133 msec, 2 min after administration of neostigmine : 830 ± 134 msec, $P < 0.05$). Furthermore, the RR interval in the group N was significantly lower than that in the group S during 1 to 4 min after reversal of the neuromuscular blockade (the group N : 830 ± 134 msec, the group S : 1005 ± 166 msec, 2 min after reversal of the neuromuscular blockade, respectively, $p < 0.05$)

Both QT and QTc intervals did not have any changes after reversal of the neuromuscular blockade in the groups N and S (Figure 2 and 3). Furthermore,

there was no significant difference in both QT and QTc intervals between the groups N and S during the study.

QTD and QTcD also did not have any changes after reversal of the neuromuscular blockade in the group N and S (Figure 4 and 5). Furthermore, there was no significant difference in both QTD and QTcD between the groups N and S during the study.

DISCUSSION

Sugammadex is the first selective relaxant binding agent to reverse the neuromuscular blockade in a different manner from other agents such as neostigmine or edrophonium. Sugammadex encapsulates and inactivates nondepolarizing neuromuscular blockade by preventing them to bind to acetylcholine receptor at the neuromuscular junction[18,19]. This agent is recommended for reversal of moderate or deep muscle relaxation induced by rocuronium and vecuronium. Although the efficacy and safety of sugammadex has been established, it has several problems for clinical use, such as anaphylactic shock, cost, and others.

It has been reported that supra-therapeutic or therapeutic doses of sugammadex is not associated with QTc prolongation during anesthesia[7,20~22]. In contrast, sugamadex under 1.5 minimum alveolar concentration (MAC) sevoflurane affected to QTc interval, but not under propofol anesthesia[23]. In the present study, QT and QTc intervals were not prolonged by therapeutic use of sugammadex (4 mg/kg) under 1% sevoflurane anesthesia. We hypothesized that these differences arose from the depth of sevoflurane anesthesia. Generally, inhaled anesthetics such as sevoflurane or isoflurane may dose-dependently produce QTc interval prolongation[22]. Thus, lower level of inhaled anesthetic is likely to have less adverse effect on QT interval.

Neostigmine may produce cardiovascular effects such as bradyarrythmia. To prevent the effect of anticholinesterase, anticholinergic, such as atropine is commonly added for reversal of the neuromuscular blockade. It is well known that QT interval prolongation is induced by an imbalance in the cardiac sympathetic tone[24]. Such an imbalance is also observed by using of anticholinesterase- anticholinergic combination[1]. This combination may affect the sympathetic tone, resulted in QT interval prolongation. Previous study suggested that neostigmine produces transient QTc interval prolongation during a few minutes after the administration[1]. Our hypothesis was that the combination of neostigmine and atropine might have effect on QTc or QTcD. As it is, the combination of neostigmine and atropine decreased RR interval from 1 min to 4 min after administration, whereas QT and QTc interval were unaffected in the present study. These results may be supported by the findings which QTc interval was not prolonged by neostigmine with glycopyrrolate under propofol anesthesia[21]. However, neostigmine is likely to prolong QTc interval under higher concentration of sevoflurane anesthesia.

Similar to neostigmine, sugammadex did not affect QT and QTc intervals in the present study. It is easy to explain these results, because there are not any cholinergic effects and it is not necessary to do co-administration with any anticholinergics in case of sugammadex

The variability of the QT interval in ECG which is defined as dispersion of QT reflects regional differences in ventricular repolarization[11]. Therefore, increased QTD has been shown to predispose to ventricular arrhythmias. It has been suggested that QTD increase in patients with myocardial infarction[14,25,26], subarachnoid hemorrhage[27] or diabetes mellitus[28]. de Bruyne et al. emphasized that QTD is considered as a predictor of cardiac mortality in elderly men and women[12]. Although the effects of neostigmine and sugammadex on QTc have been established, the effect on QTD and QTcD has not been assessed and cleared. This is the first study for the assessment of the effects of sugammadex and neostigmine on QTD and QTcD. Our results indicated that both sugammadex and neostigmine have no effect on QTD and QTcD under 1% sevoflurane anesthesia. Hence, the effect of reversal of the neuromuscular blockade on QTD can be excluded in this case.

In the present study, there is a limitation to evaluate the cardiovascular risk of reversal of the neuromuscular blockade. These results were observed under 1% sevoflurane anesthesia. In a clinical situation, reversal of the neuromuscular blockade is usually performed under many different conditions, such as light sevoflurane anesthesia, propofol anesthesia, awake condition and others. Therefore, assessments

the effects of sugammadex and neostigmine on QTD under other conditions are essential. Further studies under other conditions are required to conclude the effect of these agents on QTD.

We conclude that sugammadex and neostigmine at therapeutic doses have no effect on QT interval and QTD under 1% sevoflurane anesthesia. Our findings may reflect that the possibility of increased risk of ventricular arrhythmias is equivalent between sugammadex and neostigmine.

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