

Remifentanyl can Prevent the Increase in Qt Dispersion During Modified Electroconvulsive Therapy: A Randomized Controlled Clinical Trial

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Abstract

Objective: To clarify the hemodynamic-stabilizing effect of remifentanyl in the context of modified electroconvulsive therapy (mECT), we measured electrocardiographic alterations in the corrected QT interval (QTc) and corrected QT dispersion (QTcD), considered predictive of ventricular arrhythmia, during mECT.

Methods: Sixty patients scheduled for mECT were divided randomly into 3 groups. Patients in the low-dose remifentanyl administration group (group L, N=20) were administered 0.5 µg/kg of remifentanyl before mECT. Patients in the high-dose group (group H, N=20) were administered 1.0 µg/kg of remifentanyl, and those in the control (group C, N=20) were administered a similar volume of normal saline solution. Modified ECT was performed in the same manner in all groups with propofol and suxamethonium. Changes in QTc and QTcD values were analyzed using a repeated measures analysis of variance, and between-group comparisons were conducted using the Bonferroni method.

Results: During mECT, an increase in the mean arterial pressure, decrease in the R wave-to-R wave interval, elongation of QTc, and increase in QTcD were observed in group C, whereas these alterations were attenuated in group L and were not observed in group H. The differences observed in group C relative to the other groups were statistically significant ($P < 0.05$).

Conclusion: Compared with the control treatment and a 0.5 µg/kg dose, a 1.0 µg/kg dose of remifentanyl had a preventive effect on ventricular arrhythmia after mECT, as well as on hemodynamic changes, according to the observed alterations in QTc and QTcD. Therefore, our results indicate that a 1.0 µg/kg dose of remifentanyl could suppress hemodynamic changes, prevent myocardial ischemia or cerebral hemorrhage, and minimize the development of fatal arrhythmias such as ventricular tachycardia and/or ventricular fibrillation.

Keywords: Remifentanyl; QT interval; QT dispersion; Modified electroconvulsive therapy; Ventricular arrhythmia; Hemodynamic changes; Major depression

Background

Modified electroconvulsive therapy (mECT) is used to treat patients with schizophrenia and severe depression who cannot adequately receive pharmaceutical treatment [1]. Recently, a combination of propofol and suxamethonium has been administered to induce sleep and muscle relaxation during mECT and avoid the harmful joint hyperextension and dislocation and fractures in the extremities caused by unexpected body motion. However, the extreme sympathetic instability induced by mECT can cause various arrhythmias during an electro-stimulation course. For example, bradycardia, tachycardia, and premature constriction may be observed via electrocardiograph (ECG) during mECT. In particular, ventricular premature contraction (VPC) may cause fatal arrhythmias such as ventricular tachycardia (VT) and/or ventricular fibrillation (VF). Therefore, ventricular arrhythmias must be prevented during mECT to ensure safe anesthetic management [2,3].

The QT interval (QT) is a well-known potential cause of ventricular arrhythmia. However, QT dispersion (QTD), a value obtained by

subtracting the minimum QT interval from the maximum QT interval as determined using a recorded 12-lead ECG, is considered an indicator of instability during ventricle repolarization. In addition, QT and QTD appear to correlate with autonomic regulation instability [4-6] and are potential causes of ventricular arrhythmias [7] or severe cardiac adverse events [8], such as myocardial infarction or cardiac sudden death [9-13]. In addition, several reports have indicated that both values increase as a result of various perioperative surgical procedures [14,15].

Previously, we reported increased QT and QTD values during mECT in propofol and suxamethonium-treated patients with psychiatric disorders [16]. In that report, we described elongation of the QT interval and an increase in QTD, which might reflect non-uniform localized ventricle repolarization during perioperative ECG in patients taking antidepressants to treat psychiatric disorders. Our study indicated that propofol and suxamethonium could not reduce these harmful sympathetic fluctuations associated with mECT. Accordingly, we believed that a different anesthetic would better stabilize this sympathetic nerve activation. Remifentanyl is a short-acting pure mu-opioid agonist with the potential to ameliorate increases in heart rate and blood pressure during the course of sympathetic nerve stimulation inhibition. However, no previous reports have discussed the effectiveness of remifentanyl anesthesia for

avoiding the harmful adverse events associated with mECT. Therefore, in the present study, we evaluated the QT and QTD values to determine whether remifentanil could reduce the occurrence of fatal arrhythmias caused by mECT.

Methods

Ethical considerations

This study was conducted after receiving approval from the Dokkyo Medical University Hospital Ethics Committee (registration number: 90566605, date: August 21, 2009).

Patient classification

For this randomized controlled clinical trial, we recruited 60 patients with physical status classifications of I or II from the American Society of Anesthesiologists, who were scheduled to undergo mECT for the treatment of major depression. The patients ranged in age from 20 to 65 years, and patients with a history of any heart disease or present arrhythmia were excluded. The sample size in the present study was calculated based on our previous research [16]. Accordingly, we allocated 20 patients per group to account for dropout cases.

After obtaining written, informed consent from each patient and/or their family, patients were divided into 3 groups according to a previous study by Zaballos et al. [17]: 1) control group (group C, N=20), in which all patients received a single 20-ml injection of saline solution prior to mECT; 2) low-dose remifentanil group (group L, N=20), in which all patients received a single 20-ml injection of saline solution containing 0.5 µg/kg of remifentanil prior to mECT; and 3) high-dose remifentanil group (group H, N=20), in which all patients received a single 20-ml injection of saline solution containing 1.0 µg/kg of remifentanil prior to mECT.

Monitoring and data sampling

The procedures used in this study were conducted in our operating room under various monitors. After admission to the operating room, non-invasive blood pressure (NIBP), ECG, and O₂ saturation monitors were attached to the patients. We recorded the mean arterial pressure (MAP), heart rate (HR), and 12-lead ECG, and used a multi-function electrocardiograph (FDX-4520TM, Fukuda Denshi, Tokyo, Japan) to measure QT and the corrected QT interval (QTc). These values were used to calculate the QTD and corrected QTD (QTcD) during anesthesia and mECT, as described below.

Anesthetic management

None of the patients received premedication. In all patients, we maintained an intravenous line to administer various drugs and delivered oxygen via masked inhalation at a rate of 6 L/min. Before administering 1 mg/kg of propofol to induce sleep and 1 mg/kg of suxamethonium intravenously to obtain adequate muscle relaxation, we administered 20 ml of saline solution alone (group C) or containing 0.5 µg/kg (group L) or 1.0 µg/kg of remifentanil (group H). Each solution was injected intravenously over 1 minute. After administration of the muscle relaxant, we employed manual ventilation to maintain normocapnia and normoxia.

Modified ECT

Modified ECT was performed through an electrode on the skin above both frontal lobes via a pulse-wave therapy device (ThymatronTM, Somatics LLC, Lake Bluff, IL, USA). The output current was set according to the patient's age. EEG was recorded using pulse-wave therapy equipment. Modified ECT was considered successful when the spike and wave complex wave on the EEG were observed at an interval of more than 15 seconds. All treatments were administered by psychiatrists not otherwise involved in this study.

Assessment of QTD

We measured 12-lead ECG using the previously described multi-function electrocardiograph (FDX-4520TM, Fukuda Denshi). After mECT, we calculated QTD as the difference between the minimum and maximum QT on each 12-lead ECG with QT analysis software (QTD-1TM, Fukuda Denshi) and determined the corrected QT dispersion (QTcD) for each case. A QTD that exceeded 50 msec indicated a significant increase.

Statistical analysis

Results were expressed as mean (± standard deviation) for quantitative variables. A repeated measures analysis of variance (ANOVA) was used to analyze the QT, QTC, QTD, and QTcD within groups. Between-group comparisons of data were conducted using the t post hoc test according to the Bonferroni method. All statistical analyses were conducted using SPSS (SPSS Inc., Chicago, IL, USA). A result was considered significant at a critical level of 5% (P<0.05).

Results

Background

No enrolled patient discontinued the study protocol. There were no significant differences in patient characteristics (e.g., age, height, weight, gender, duration of antidepressant treatment for depression) among the groups (Table 1). Additionally, no patients developed hemodynamic or neurological complications, respiratory difficulties, or other severe adverse effects.

	Group C (N=20)	Group L (N=20)	Group H (N=20)
Age (yrs)	51 ± 13	48 ± 15	47 ± 15
Height (cm)	157 ± 7	155 ± 4	159 ± 9
Weight (kg)	57 ± 18	53 ± 11	56 ± 19
Gender (male/female)	9/11	7/13	10/10
Number of treatment with psychiatric drugs			
Treatment with antidepressant	20	20	20
Treatment with major tranquilizer	6	9	8
treatment with benzodiazepine	7	8	7

Table 1: Patient characteristics. Data are shown as means ± standard deviations, with the exceptions of gender and the number of subjects

treated with various drugs. There were no significant differences in age, height, or weight between the groups.

Mean arterial pressure (MAP)

Alterations in MAP during mECT are shown in Figure 1. None of the groups exhibited a significant decrease in MAP after anesthesia induction. However, a significant increase in MAP was observed within 7 min after mECT in group C. In contrast, a significant increase in MAP was observed within 3 min in group L, whereas no significant increase in MAP was observed in group H. Groups C and L exhibited significant increases in MAP after mECT, compared with the values before mECT. Compared with group C, group L exhibited a significant decrease in MAP 2–6 min after mECT. Notably, group H exhibited a significantly lower MAP relative to group C after 10 min of mECT, and also exhibited a significantly lower MAP value after 1 min of mECT, compared with group L.

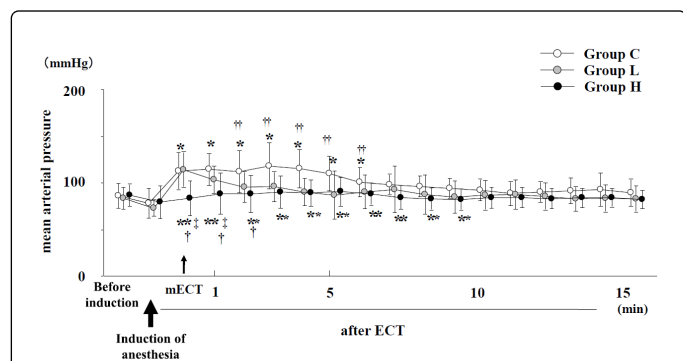


Figure 1: Changes in mean blood pressure (MBP). Values are shown as means \pm standard deviations. * $p < 0.01$ value of mean arterial pressure (MAP) before vs. after modified electroconvulsive therapy (mECT) in group C, † $p < 0.01$ value of MAP before vs. after mECT in group L. †† $p < 0.05$ value of MAP in group L vs. group C after mECT, ** $p < 0.01$ value of MAP in group H vs. group C after mECT, ‡ $p < 0.05$ value of MAP in group H vs. group L after mECT.

Heart rate (HR)

Variations in HR during mECT are shown in Figure 2. No significant changes in HR were observed in any group during anesthetic induction. Significant increases in the HR above the baseline were observed within 7 min in group C and 6 min in group L ($P < 0.05$). In contrast, a significant increase in HR was observed within 3 min in group L ($P < 0.05$). However, group H did not develop a similar significant increase in HR ($P > 0.05$). Compared with groups C and L, group H had a significantly lower HR at 10 min after mECT ($P < 0.05$).

QT and QTc

Previous studies have defined a normal QTc value as < 450 milliseconds [16]. In the present study, no significant changes in QTc were recognized in any group, and no significant differences were observed among the groups. The variations in QTc during mECT in all groups are shown in Figure 3.

QTD and QTcD

Previous studies have defined the normal range of QTD and QTcD as 10-70 milliseconds [16]. For the present study, the variations in QTD during mECT in each group are shown in Figure 4, and the variations in QTcD during mECT are shown in Figure 5. QTD did not change significantly in any group before anesthetic induction. Significant increases in QTD were observed immediately after performing mECT in group L and within 2 min in group C ($P < 0.05$). However, group H exhibited a significantly lower QTD compared with group C from 0 to 6 min after mECT ($P < 0.05$).

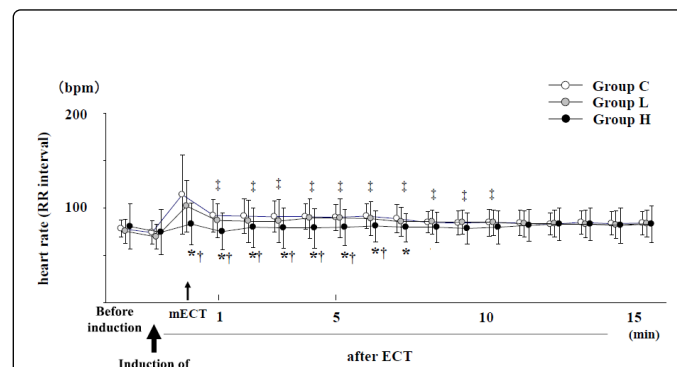


Figure 2: Changes in heart rate (HR, RR interval). Values are shown as means \pm standard deviations, * $p < 0.01$, HR value before vs. after modified electroconvulsive therapy (mECT) in group C, † $p < 0.01$, HR value before vs. after mECT in group L, ‡ $p < 0.05$, HR value in group H vs. groups C and L after mECT.

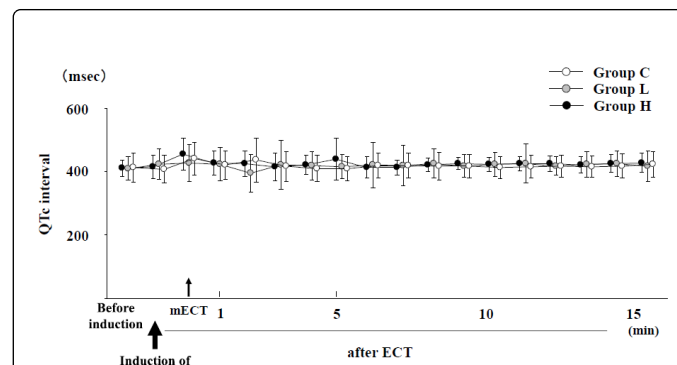
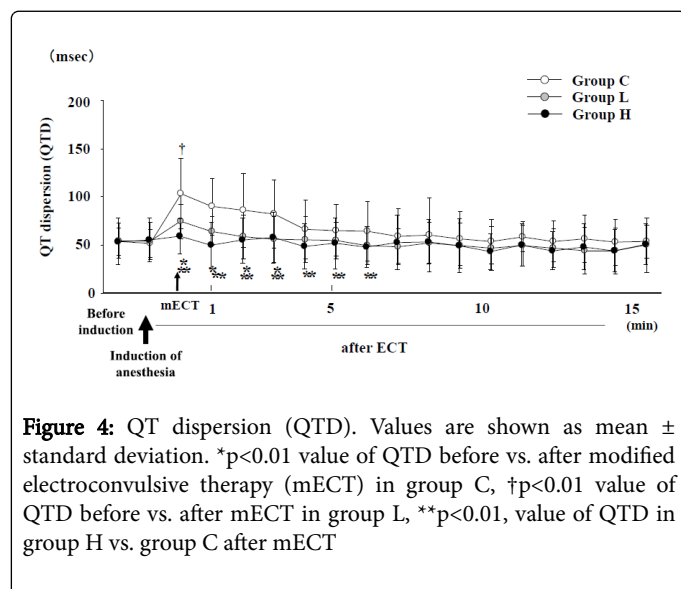


Figure 3: QTc interval. Values are shown as mean \pm standard deviation. There are no significant differences from before to after modified electroconvulsive therapy (mECT) or between the groups.

The QTcD did not change significantly in any group before anesthetic induction. However, significant increases in QTcD were observed immediately after performing mECT in group L and within 3 min in group C. Notably, the QTcD of group L was significantly lower than that of group C within 2 min after mECT. However, no increases in QTD and QTcD were observed in group H over a 70 msec period (maximum mean QTcD was 69.2 msec immediately after mECT). Groups L and H exhibited significantly lower QTcD values than did group C within 2 min after mECT. Moreover, group H exhibited a significantly lower QTcD value than group L at 1 min after mECT.

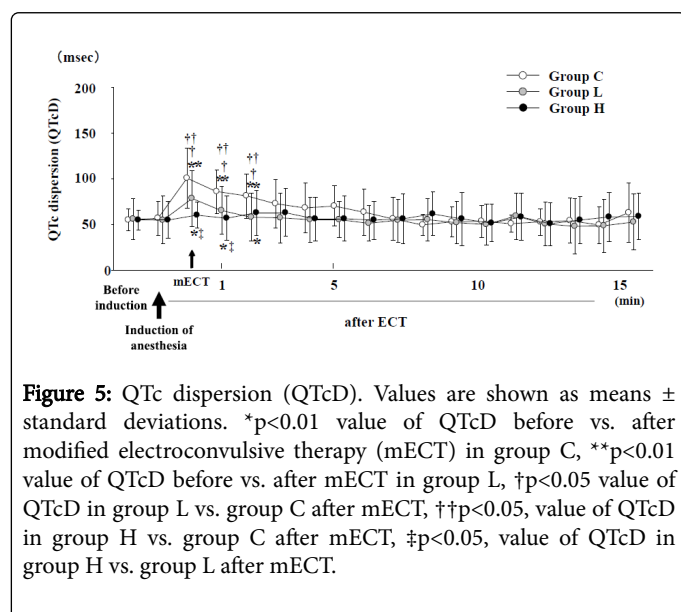
Complications

No adverse events associated with remifentanyl administration were observed in groups L and H. However, 3 cases of paroxysmal supraventricular tachycardia were observed in group C.



Discussion

Remifentanyl, a short-acting opioid analgesic, is widely used for general anesthesia because it has a strong anti-nociceptive action [18]. Compared with other well-known opioid analgesics, remifentanyl can rapidly achieve effect-site concentrations after a single injected dose. In addition, the effect-site concentration of remifentanyl can decrease rapidly after the discontinuation of administration [19].



Several studies have reported the beneficial effects of remifentanyl during mECT [20-22]. Anderson et al. reported the potential usefulness of remifentanyl for avoiding noxious stimuli during mECT caused by a reduced anesthetic dose and for extending the significant

convulsive time without delaying the resumption of spontaneous breathing [23]. However, the authors also demonstrated that remifentanyl did not significantly suppress increases in MAP and HR during mECT and speculated that a too low remifentanyl dose or reduction in the methohexital dose could affect hemodynamic changes. Recart et al. reported that remifentanyl, when administered with methohexital, suppressed increases in the MAP [24]. Locala et al. reported that increases in HR and MAP could be suppressed by a combined single injection of methohexital and 500 μg of remifentanyl [25]. A review by Chen recommended the use of remifentanyl in patients with a short convulsion time, high convulsive threshold, or unstable hemodynamic condition after mECT [26].

As mentioned above, although several studies demonstrated the usefulness of remifentanyl for stabilizing HR and MAP during mECT, no reports had discussed the effects of remifentanyl on the prevention of fatal arrhythmias during mECT. Therefore, we used QTD and QTcD values to confirm whether administering remifentanyl before mECT could prevent various arrhythmias. In previous reports, a 1.0 $\mu\text{g}/\text{kg}$ dose of remifentanyl stabilized the HR and MAP after mECT without serious adverse cardiac events [27]. Therefore, we selected this dose to confirm the influences of QTD and QTcD in the present study. Additionally, to confirm the beneficial effect of a low remifentanyl dose, we also evaluated the preventive effect of a 0.5 $\mu\text{g}/\text{kg}$ remifentanyl dose against arrhythmias, using QTD and QTcD measurements.

The results of our study revealed that 1.0 $\mu\text{g}/\text{kg}$ and 0.5 $\mu\text{g}/\text{kg}$ doses of remifentanyl could suppress increases in QTD and QTcD after mECT, when compared with the control treatment. Moreover, stronger suppression of the increases in QTD and QTcD was observed with a 1.0 $\mu\text{g}/\text{kg}$ dose of remifentanyl (group H) than with a 0.5 $\mu\text{g}/\text{kg}$ dose (group L). In particular, increases in both QTD and QTcD during mECT were substantially suppressed by a 1.0 $\mu\text{g}/\text{kg}$ dose of remifentanyl. We emphasize that a 1.0 $\mu\text{g}/\text{kg}$ dose of remifentanyl might not only stabilize HR and MAP, but could also stabilize QTD and QTcD during mECT. Our results indicate that a 1.0 $\mu\text{g}/\text{kg}$ dose of remifentanyl could suppress hemodynamic changes, prevent myocardial ischemia or cerebral hemorrhage, and minimize the development of fatal arrhythmias.

Our study had some limitations. First, we stipulated a constant propofol dose, regardless of the remifentanyl dose. However, several reports have indicated that a low propofol dose can help to maintain convulsion time prolongation [28]. Therefore, in future studies we must consider the appropriate dose of propofol to use with remifentanyl. Such a study would be clinically essential with respect to the safety and effectiveness of mECT. Second, we did not study the usefulness of remifentanyl during mECT in elderly patients. Many elderly patients may have cardiovascular complications and potential QT interval abnormalities caused by antidepressants. Moreover, increases in QTD and QTcD during elective surgery [29] and pharmacological sensitivities to remifentanyl are more frequent in the elderly than in younger patients [30]. Therefore, the association between age and the effects of remifentanyl should be studied in the future. Third, we have not examined the detailed mechanism by which remifentanyl suppresses increase in QTD. Therefore, it is necessary to consider the effects of autonomic nervous system activity or catecholamine secretion from the adrenal medulla in response to remifentanyl and mECT. Fourth, various antidepressants and antipsychotics may prolong the QT and increase the QTd prior to mECT, as shown in our previous report [15]. In fact, the prolongation in QT and QTd in patients taking these drugs prior mECT was

enhanced by electrical stimulation under anesthesia in our previous report. Therefore, we should investigate the effect of these drugs in our results in future. Lastly, suxamethonium can increase QTc prolongation. However, suxamethonium was administered to all patients, including patients in our previous series study. Therefore, we reasoned that suxamethonium did not affect our results.

In conclusion, QT, QTD, and QTcD, which are potential causes of ventricular arrhythmias, increase markedly in response to mECT. Our study indicated that the administration of 1.0 µg/kg of remifentanil prior to mECT ameliorated these increases in QTc and QTcD. Therefore, we emphasize that remifentanil can prevent complications such as ventricular arrhythmias and VT or VF, which should be avoided during mECT.

Declaration of Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

Megumi Kageyama carried out general anesthesia, collected the data and wrote this manuscript. Shinsuke Hamaguchi supported this study and helped to writing this manuscript. Shigeki Yamaguchi planned this study and helped with the writing. All authors read and approved the final manuscript.

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