Dokkyo Medical Journal
2(2): 158-163, 2023

DKMJ

Original

Effect of Remifentanil on Cardiac Autonomic Activity Changes during Electroconvulsive Therapy: A Randomized Controlled Trial

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Summary

Electroconvulsive therapy (ECT) leads to remarkable hemodynamic changes. Heart rate variability (HRV), which comprises high frequency (HF) or low frequency (LF), is an index of cardiac autonomic regulation. In the present study, we examined the effects of remifentanil on HRV changes during ECT. After obtaining approval from the ethics committee of Dokkyo Medical University Hospital, we randomly allocated 42 patients who were scheduled to undergo ECT with American Society of Anesthesiologists physical status I or II to group R (n = 21), which received remifentanil (1 μg/kg) as pretreatment, or group C (n = 21), which did not receive pretreatment. After the induction of general anesthesia, we recorded the LF/HF ratio and HF ratio every minute during ECT. Statistical analysis was performed using two-way analysis of variance. Immediately (T0) and 1 min (T1) after convulsion, heart rate, systolic and diastolic blood pressures were significantly lower in group R than in group C. The LF/HF ratio in group R was significantly lower than that in group C (group C: T0; 28.6 ± 24.3, T1; 20.1 ± 18.6, group R: T0; 16.1 ± 9.7, T1; 11.2 ± 9.9, $p < 0.05$). No significant difference was noted in the HF ratio between both groups. Pretreatment with remifentanil suppresses hemodynamic and cardiac autonomic activity changes during electroconvulsive therapy.

Key Words: Autonomic nervous system, Electroconvulsive therapy, Heart Rate Variability, Remifentanil

Introduction

Electroconvulsive therapy (ECT) is a common procedure used to treat various psychiatric disorders in cases where other treatments are unsuccessful. In many cases, ECT is performed under general anesthesia. Adverse effects such as hypertension or tachycardia are observed after electrical stimulation, and are in-

Received December 7, 2022; accepted December 13, 2022; advance publication by J-STAGE September 15, 2023
https://doi.org/10.51040/dkmj.2022-068
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duced by activation of the sympathetic nervous system. Prominent cardiac autonomic activity changes have been reported to occur during ECT[1]. This study reported the triphasic cardiac autonomic change, which consists of the first phase (parasympathetic dominance: just after electrical stimulation), second phase (sympathetic dominance: 30 to 80 seconds), and third phase (sympathetic dominance: 80 to 130 seconds) after ECT.

Power spectral analysis of heart rate variability (HRV) is a phenomenon of variation in time in consecutive heartbeats, and is known as index of cardiac autonomic activity[2]. This analysis partitions the total variance of a continuous series of beats into their frequency components. Two or three main peaks have been identified: very low frequency (VLF: < 0.04 Hz), low frequency (LF: 0.04-0.15 Hz), and high frequency (HF: 0.15-0.4 Hz)[3]. HF is believed to have a dominant parasympathetic component, whereas LF reflects both sympathetic and parasympathetic activities. Therefore, the LF/HF ratio indicates a sympathetic component[2]. Spectral analysis of HRV is available for the assessment of sympathetic or parasympathetic activities during general anesthesia[1].

Four deaths per 100,000 patients associated with ECT have been reported. In addition, most of these deaths were due to cardiovascular events, such as tachycardia or hypertension after electrical stimulation in previous studies[4,5]. To avoid acute hemodynamic changes associated with ECT, various antihypertensive agents have been examined (e.g., nicardipine, propranolol, and diltiazem)[6]. In particular, short-acting calcium antagonists can immediately lower blood pressure. However, such a short-acting calcium antagonist has been shown to increase heart rate, stimulate sympathetic activity, and consequently increase mortality[7]. It has been reported that 100 μg IV of remifentanil, a potent short-acting synthetic opioid, attenuates acute hemodynamic changes during ECT[6]. Furthermore, remifentanil can reduce the consumption of general anesthetics and prolong seizure duration in ECT[8,9].

Sometimes, blood pressure and autonomic nerve system are not paralleled[10]. Therefore, we considered to need a novel index of hemodynamic variability throughout ECT. We hypothesized that pretreatment with IV remifentanil might attenuate remarkable hemodynamic changes (heart rate, systolic and diastolic blood pressure) without stimulating sympathetic activity during ECT. This study aimed to determine the effect of remifentanil on the hemodynamic change by evaluation of HRV throughout ECT.

Materials and Methods

We included 44 patients with American Society of Anesthesiologists (ASA) physical status I or II, aged 20-65 years, who were scheduled to undergo modified electroconvulsive therapy (mECT) (Fig. 1). The study was approved by the ethics committee of Dokkyo Medical University (R-32-1), and registered with the University Hospital Medical Information Network (UMIN, registration number: UMIN000039217). We received written informed consent from all patients. All procedures were performed in accordance with the ethical standards of the institutional and national research committee and the principles of the 1964 declaration of Helsinki and its later amendments or comparable ethical standards. We excluded patients with cardiovascular, respiratory, metabolic, or cerebrovascular diseases, and those with preoperative ECG abnormalities. None of the patients had received premedication. Participants were randomly assigned to two groups: patients in group R (n = 22) received IV remifentanil (1 μg/kg) before the induction of general anesthesia, while those in group C (n = 22) received IV saline. In the operating room, standard monitoring of three-lead ECG signals, noninvasive measurement of arterial blood pressure, and pulse oximetry were performed (DS-7780W; FUKUDA DENSHI Co., Ltd., Tokyo, Japan). After adequate preoxygenation, pretreatment with 1 μg/kg remifentanil or placebo (saline) was intravenously injected, and anesthesia was induced with 1 mg/kg IV propofol. After confirming loss of consciousness, 1 mg/kg succinylcholine was intravenously administered. Subsequently, we performed assisted mask ventilation with 100% oxygen. After vanishing the fasciculation caused by succinylcholine, an electrical stimulus was delivered via bitemporal electrodes using an ECT stimulator (Thymatron System; Somatics LLC, Lake Bluff, IL, USA). The magnitude of the energy setting for the ECT stimulus was predetermined according to age. We determined the efficacy of ECT using the tourniquet technique, which is based on the obser-

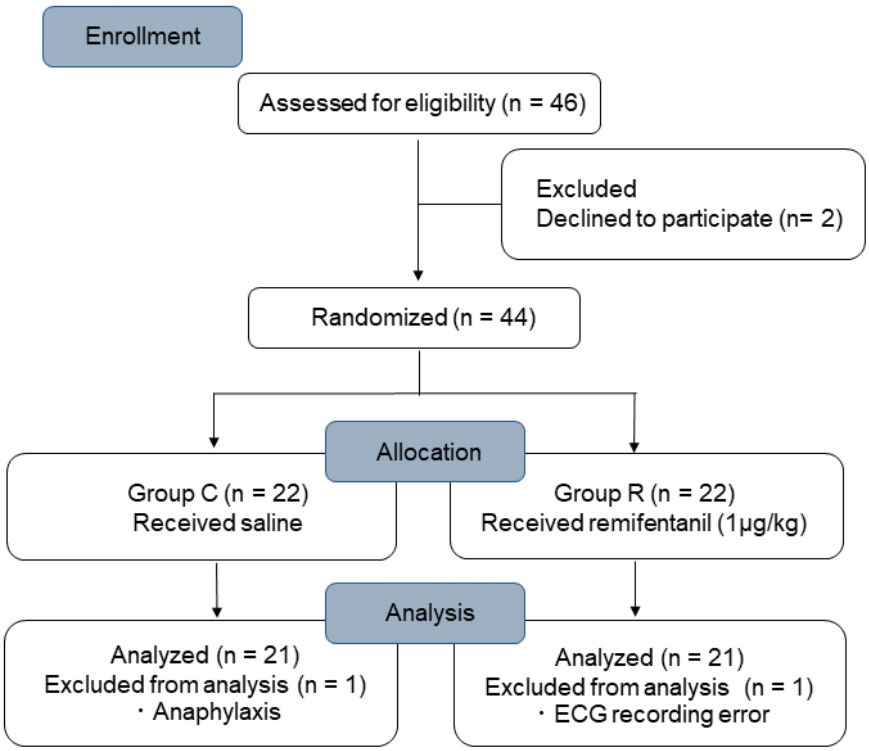

Figure 1 Flow chart of the study

vation of convulsive movements of the distal leg. Seizures were detected using an Electroencephalogram (EEG) monitor set in the electrical stimulator.

HRV analysis

We performed HRV analysis before the induction of general anesthesia, after loss of consciousness (baseline), immediately after electrical stimulus (T0), and every 1 min to 7 mins after electrical stimulus (T1-T7). Three-lead ECG signals were recorded using LRR-03 (GMS, Tokyo, Japan) for HRV analysis. Power spectral analysis of HRV was performed using the MemCalc power spectral density method with a commercial software package (Suwa Trust Co., Tokyo, Japan). We evaluated the high-frequency power between 0.15-0.4 Hz defined as HF (an index of parasympathetic component), the low frequency power between 0.04-0.15 Hz defined as LF (an index of both sympathetic and parasympathetic components) and LF/HF ratio (an index of sympathetic components). For the analysis of HF, the ratio of the measured value of HF to the baseline value was calculated.

Statistical analysis

Statistical analyses were performed using Prism 6 software (GraphPad, La Jolla, CA, USA). Data were expressed as mean ± standard deviation. Patient characteristics were analyzed using Student's *t*-test and Fisher's exact test. Changes in RR interval, systolic blood pressure (sBP), diastolic blood pressure (dBP), and LF/HF ratio were analyzed using two-way analysis of variance. When a significant overall effect was detected, Bonferroni's post hoc test was conducted. In all analyses, the probability of detecting a significant difference was set at 5% ($p < 0.05$). A sample size of 21 subjects in each group was considered adequate, based on a previous study[11], to detect a difference of 1.5 in the LF/HF ratio between the two groups at a power of 80%, with $\alpha = 0.05$.

Results

Table 1 shows the patient characteristics for this study. Two patients were excluded from this study. In group R, a patient was excluded due to anaphylaxis. In group C, a patient was excluded due to ECG recording error. We enrolled 42 patients, and there were no significant differences in age, sex, ASA physical status, or

Table 1 Patient characteristics

	Group C (n = 21)	Group R (n = 21)
Age (years)	48 ± 11	49 ± 12
Gender (male/female)	9/12	11/10
BMI (kg/m^2)	24 ± 6	23 ± 6
ASA physical status (I/II)	13/8	10/11
Diagnosis (depression/schizophrenia)	4/17	6/15
Medications		
Hypertension	4	5
Diabetes mellitus	3	2
Gastritis	1	0
Asthma	0	1

Notes: Data are presented as the means ± standard deviation.

Table 2 Hemodynamic parameters

	Group	Baseline	T0	T1	T2	T3	T4	T5	T6	T7
RR	Group C	866 ± 224	654 ± 145*	657 ± 115*	700 ± 126	728 ± 151	717 ± 136	727 ± 157	755 ± 134	752 ± 130
(ms)	Group R	948 ± 225	849 ± 249	885 ± 214	827 ± 195	805 ± 178	816 ± 141	852 ± 183	853 ± 175	855 ± 150
sBP	Group C	127 ± 16	176 ± 36*	167 ± 33	158 ± 36	148 ± 31	142 ± 29	136 ± 26	145 ± 31	136 ± 26
(mmHg)	Group R	117 ± 14	129 ± 27	140 ± 29	140 ± 30	134 ± 23	133 ± 23	130 ± 23	129 ± 21	130 ± 23
dBP	Group C	78 ± 12	107 ± 22*	101 ± 23*	95 ± 21	88 ± 18	84 ± 20	82 ± 16	88 ± 18	84 ± 20
(mmHg)	Group R	74 ± 11	75 ± 19	81 ± 20	82 ± 20	77 ± 14	75 ± 14	74 ± 15	77 ± 14	74 ± 15

Data are presented as mean ± standard deviation. *Group C*: patients received IV saline, *Group R*: patients received IV remifentanil (1 μg/kg), *T0*: immediately after electrical convulsion, *T1–T7*: 1–7 min after electrical stimulus, *RR*: RR interval, *sBP*: systolic arterial pressure, *dBP*: diastolic arterial pressure. *$p < 0.05$ versus remifentanil group.

Table 3 Measurement of LF/HF

	Group	Baseline	T0	T1	T2	T3	T4	T5	T6	T7
LF/HF	Group C	3.8 ± 3.5	28.6 ± 24.3*	20.1 ± 18.6*	6.3 ± 3.6	3.8 ± 2.7	3.2 ± 2.3	3.1 ± 2.4	2.9 ± 2.7	3.3 ± 3.1
ratio	Group R	4.6 ± 3.1	16.1 ± 9.7	11.2 ± 9.9	6.5 ± 4.9	6.9 ± 5.5	7.2 ± 6.7	5.7 ± 4.1	5.6 ± 4.1	6.1 ± 5.4
HF	Group C	1	4.2 ± 9.2	10.1 ± 26.7	8.7 ± 29.1	8.4 ± 23.6	4.5 ± 11.1	3.1 ± 7.1	5.7 ± 15.1	6.6 ± 18.8
ratio	Group R	1	10.8 ± 27.8	21.8 ± 84.4	6.0 ± 15.9	5.2 ± 10.8	10.1 ± 22.7	7.4 ± 16.9	3.3 ± 6.4	3.0 ± 5.0

Data are presented as mean ± standard deviation. *HF ratio*: ratio of the measured value to the baseline. *Group C*: patients received IV saline, *Group R*: patients received IV remifentanil (1 μg/kg), *T0*: immediately after electrical convulsion, *T1–T7*: 1–7 min after electrical stimulus. *$p < 0.05$ versus control group.

body mass index (BMI) between the two groups. No complication was observed in this study.

Table 2 shows the measured values of the RR interval and systolic and diastolic arterial pressures during the observation. The RR interval was significantly longer at T0 and T1 in group R than that in group C (group C: T0; 654 ± 145 ms, T1; 657 ± 115 ms, group R: T0; 849 ± 249 ms, T1; 885 ± 214 ms, $p < 0.05$). The sBP at T0 in group C was significantly higher than that in group R (group C: 176 ± 36 mmHg, group R: 129 ± 27 mmHg, $p < 0.05$). Similarly, dBP significantly higher at T0 and T1 in group C compared to that in group R (group C: T0; 107 ± 22 mmHg, T1; 101 ± 23 mmHg, group R: T0; 75 ± 19 mmHg, T1; 81 ± 20 mmHg, $p < 0.05$).

Table 3 shows the changes in the LF/HF ratio during the ECT. The LF/HF ratio in group C significantly increased at T0 and T1 compared to that at baseline (baseline: 3.8 ± 3.5, T0 28.6 ± 24.3, T1 20.1 ± 18.6, $p < 0.05$). Moreover, the LF/HF ratio in group R significantly lower compared to that in group C at T0 and T 1 (group C: T0; 28.6 ± 24.3, T1; 20.1 ± 18.6, group R: T

0; 16.1 ± 9.7, T1; 11.2 ± 9.9, $p < 0.05$). There was no significant difference in the HF ratio between the groups C and R.

Discussion

The present study clarified the efficacy of IV pretreatment with remifentanil for hemodynamic and cardiac autonomic changes throughout the period of ECT. A remarkable hemodynamic change, such as hypertension or tachycardia caused by electrical convulsions might induce serious consequences, which are exaggerated by sympathetic neural activation[12]. Several studies have attempted to demonstrate the efficacy of antihypertensive and hypnotic agents in preventing acute hemodynamic changes after convulsions[6,10,13]. Nicardipine, a calcium antagonist, is preferred for the treatment of acute hypertension during anesthesia; however, it might increase heart rate (which might be problematic for the cardiovascular system) after ECT[13]. Moreover, continuous infusion of nicardipine is likely to increase the sympathetic nerve system and the plasma concentration of norepinephrine[10]. The use of nicardipine for hypertension might induce tachycardia or increase sympathetic activity after convulsions. Wajima et al. reported that bolus administration of diltiazem attenuated the heart rate and mean blood pressure after an electrical stimulus[15]. Diltiazem is a calcium antagonist and reduces heart rate. However, diltiazem significantly decreased seizure duration. They suggested that diltiazem might not be recommended for ECT. Landiolol, an ultra-short-acting beta-blocker, at dose of 0.1 mg/kg and 0.2 mg/kg attenuated the increase of heart rate and rate-pressure product (RPP) after ECT whereas seizure duration was reduced at 0.2 mg/kg[16]. Low dose landiolol was recommended for ECT in this study. Labetalol and esmolol were also effective in reducing cardiovascular response[17], however, seizure time was affected at higher doses. Several studies have suggested the efficacy of remifentanil for remarkable hemodynamic changes during ECT. The benefits of remifentanil in ECT are as follows. 1) Remifentanil reduces the requirement of propofol or other anesthetic agents for induction, consequently producing adequate seizure duration for convulsion therapy[8,9]. 2) Bolus administration of remifentanil attenuates acute hemodynamic changes by suppressing the sympathetic nervous system without adverse effects. Recart et al. demonstrated that IV 100 μg, but not 25 or 50 μg of remifentanil significantly attenuated the mean blood pressure after convulsion[6]. A meta-analysis of randomized controlled trials reported that the addition of remifentanil prolonged seizure duration and decreased sBP compared with an anesthetic agent alone[8]. The present study clarified that IV pretreatment with 1 μg/kg remifentanil suppressed significant changes in sBP, dBP, and RR interval immediately and 1 min after convulsion. We emphasized the efficacy and safety of remifentanil in minimizing the hemodynamic changes induced by electrical stimuli.

The balance of the autonomic nervous system plays an important role in the regulation of cardiovascular homeostasis. Some studies have demonstrated the importance of HRV evaluation as an index of autonomic nerve regulation[1,13]. A previous study demonstrated that remifentanil suppresses LF/HF, a marker of sympathetic nerve activity, under general anesthesia[11]. Notably, nicardipine, but not remifentanil, decreased HF and increased the LF/HF ratio, even though this analysis was performed under controlled hypotension. As mentioned above, nicardipine might increase heart rate and plasma concentration of catecholamines; therefore, acute administration of short-acting calcium antagonists is thought to increase morbidity and mortality[7]. Thus, evaluating sympathetic and parasympathetic activities in ECT is essential. Our study applied this analysis to evaluate hemodynamic changes during ECT. In the control group, the LF/HF ratio significantly increased immediately and 1 min after convulsion compared to baseline. In contrast, remifentanil suppressed the increase in LF/HF ratio after convulsions. From the perspective of autonomic activity, pretreatment with remifentanil is beneficial during general anesthesia, especially in patients with hypertension or geriatric patients.

Limitations

In HF, no significant difference was found between the two groups in our study. The HF value varied widely, thus, making statistical analysis difficult. Generally, a rapid increase in parasympathetic activity may increase HF value. A previous study found that remifentanil did not affect HF, which was also true for

the present study[13]. Further precise observation for autonomic changes using HF value will be essential.

Conclusion

The current results show that 1 μg/kg of IV remifentanil attenuated acute hemodynamic response such as sBP, dBP, and heart rate immediately and 1 min after convulsion without any adverse effect. Moreover, remifentanil suppressed the LF/HF ratio, an index of sympathetic nerve activity after an electrical stimulus. We emphasize that pretreatment with remifentanil may be beneficial for safe and efficient ECT from the perspective of cardiac autonomic regulation.

References

1) Suzuki Y, Miyajima M, Ohta K, et al.: A Triphasic Change of Cardiac Autonomic Nervous System During Electroconvulsive Therapy. J ECT **31**: 186-191, 2015.
2) Billman GE: Heart rate variability - a historical perspective. Front Physiol **2**: 86, 2011.
3) Berntson GG, Bigger JT Jr, Eckberg DL, et al.: Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology **34**: 623-648, 1997.
4) Sackeim HA, Dillingham EM, Prudic J, et al.: Effect of concomitant pharmacotherapy on electroconvulsive therapy outcomes: short-term efficacy and adverse effects. Arch Gen Psychiatry **66**: 729-737, 2009.
5) Takagi S, Iwata K, Nakagawa A: Relationship between body mass index and blood pressure elevation during electroconvulsive therapy. J Clin Anesth **24**: 33-37, 2012.
6) Recart A, Rawal S, White PF, et al.: The effect of remifentanil on seizure duration and acute hemodynamic responses to electroconvulsive therapy. Anesth Analg **96**: 1047-1050, 2003.
7) Grossman E, Messerli FH: Effect of calcium antagonists on sympathetic activity. Eur Heart J **19**(Suppl F): F27-31, 1998.
8) Takekita Y, Suwa T, Sunada N, et al.: Remifentanil in electroconvulsive therapy: a systematic review and meta-analysis of randomized controlled trials. Eur Arch Psychiatry Clin Neurosci **266**: 703-717, 2016.
9) Kadoi Y, Saito S: Effects of adding remifentanil to propofol anesthesia on systemic hemodynamics, cardiac output, and middle cerebral artery flow velocity during electroconvulsive therapy: a pilot study. J ECT **31**: 98-100, 2015.
10) Koh J, Hidaka I, Miyata M: Effects of nicardipine and diltiazem on fractal features of short-term heart rate variability--application of coarse graining spectral analysis. J Anesth **16**: 108-113, 2002.
11) El Beheiry H, Mak P: Effects of aging and propofol on the cardiovascular component of the autonomic nervous system. J Clin Anesth **25**: 637-643, 2013.
12) Saito S: Anesthesia management for electroconvulsive therapy: hemodynamic and respiratory management. J Anesth **19**: 142-149, 2005.
13) Shin S, Lee J W, Kim S H, et al.: Heart rate variability dynamics during controlled hypotension with nicardipine, remifentanil and dexmedetomidine. Acta Anaesthesiol Scand **58**: 168-176, 2014.
14) Erdil F, Ozgul U, Şanli M, et al.: The Effects of Remifentanil on Hemodynamic Response Attenuation After Electroconvulsive Therapy Under Sevoflurane Anesthesia. J ECT **33**: 264-267, 2017.
15) Wajima Z, Yoshikawa T, Ogura A, et al.: The effects of diltiazem on hemodynamics and seizure duration during electroconvulsive therapy. Anesth Analg **92**: 1327-1330, 2001.
16) Nomoto K, Suzuki T, Serada K, et al.: Effects of landiolol on hemodynamic response and seizure duration during electroconvulsive therapy. J Anesth **20**: 183-187, 2006.
17) Boere E, Birkenhäger TK, Groenland TH, et al.: Beta-blocking agents during electroconvulsive therapy: a review. Br J Anaesth **113**: 43-51, 2014.