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ORIGINAL ARTICLE

Effect of divided supplementation of remifentanil on seizure duration and hemodynamic responses during electroconvulsive therapy under propofol anesthesia

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Abstract
Purpose Although a reduced dose of propofol combined with remifentanil is often used in anesthesia for electroconvulsive therapy (ECT), there have been few studies in which the optimal technique for injection of remifentanil was examined in detail. The aim of this study was to evaluate the effects of single and divided injection of remifentanil combined with propofol on seizure duration and hemodynamic responses during ECT.
Methods Twenty-six ASA I–II patients were enrolled in this study and received a total of 78 ECTs. Each patient received propofol 1.2 mg/kg (group P), remifentanil 1 μg/kg followed by propofol 0.5 mg/kg (group R1), and remifentanil 1 μg/kg followed by propofol 0.5 mg/kg and thereafter remifentanil 2 μg/kg (group R2). Succinylcholine 1 mg/kg was used for muscle paralysis after loss of consciousness.
Results Although mean motor seizure durations were significantly longer in groups R1 and R2 than in group P ($P < 0.05$), they were similar in groups R1 and R2. Although the percentage increases in mean arterial pressure after ECT were significantly smaller in groups P ($P < 0.01$) and R2 ($P < 0.05$) than in group R1, they did not significantly differ between groups P and R2.
Conclusions Divided use of remifentanil at 1 and 2 μg/kg combined with propofol 0.5 mg/kg produces an acceptable outcome in both seizure duration and hemodynamic stability during ECT compared with the standard hypnotic doses of propofol alone or remifentanil 1 μg/kg followed by propofol 0.5 mg/kg.

Keywords Propofol · Remifentanil · Electroconvulsive therapy · Seizure duration · Hemodynamic response

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Introduction

Propofol is widely used in anesthesia for electroconvulsive therapy (ECT) because of the rapid emergence from anesthesia and lower incidence of hypertension or tachycardia [1]. However, one of its limitations is a dose-dependent decrease in seizure duration [2, 3]. The induction and maintenance of a seizure is a core event in successful ECT, and duration of motor seizure of at least 20–30 s has been reported to be necessary for a favorable clinical outcome [4, 5]. Reducing the dose of propofol might increase the seizure duration but might not provide adequate hypnosis and stabilizing effect on the cardiovascular system after ECT. Recently, several trials have shown that the use of remifentanil, a potent short-acting opioid, enables the dose of propofol required for unconsciousness to be reduced to almost half the regular dose [6, 7]. However, there have been few detailed studies on optimal dose and/or timing of injection of remifentanil for achieving optimal efficacy, including increase in duration of seizure activity and attenuation of acute hemodynamic response to ECT.

The purpose of this study was to determine the optimal dose and the optimal technique for injection of remifentanil to increase seizure duration and minimize acute hemodynamic response with remifentanil supplementation to the

anesthetic regimen and with low-dose propofol during ECT.

Patients and methods

After obtaining approval from the Institutional Ethics Committee and written informed consent from each patient, 20 patients, scored as American Society of Anesthesiologists (ASA) I–II, who were scheduled for ECT treatments for depression and schizophrenia with depression were enrolled in this prospective study. Patients with myocardial infarction in the previous 6 months, atrial fibrillation or flutter, heart block, or a history of adverse responses to any of the study medications were excluded from the study. All chronic antidepressant medication was continued. All medication with remifentanil was made up to 10 ml diluted with 0.9% normal saline. Each patient received the following three intravenous regimens: (a) propofol 1 mg/kg over 20 s (group P; $n = 26$), (b) remifentanil 1 μg/kg over 60 s followed by propofol 0.5 mg/kg over 10 s for loss of consciousness (group R1; $n = 26$), and (c) remifentanil 1 μg/kg over 60 s followed by propofol 0.5 mg/kg over 10 s for unconsciousness and then received remifentanil 2 μg/kg over 60 s (group R2; $n = 26$). The sequence of these regimens was (a), (b), and (c), and the interval between ECTs was 1 week. Noninvasive systolic blood pressure (SBP) and mean arterial blood pressure (MAP), heart rate (HR), and oxygen saturation values were recorded before and after administration of medication and at 0, 1, 2, 3, 4, and 5 min after the end of the ECT-induced seizure. The baseline MAP and HR were determined from the average of three consecutive readings taken after admission in the operating room. Thereafter, rate–pressure product (RPP) was calculated from SBP and HR in each ECT session.

No patient received premedication. Additional propofol was given in 10-mg increments if the responsiveness to verbal command had not been lost within 60 s after propofol administration in each group. After loss of consciousness, a blood pressure cuff was inflated on the right or left leg to isolate the circulation to assess the duration of motor seizure activity. Succinylcholine 1.0 mg/kg was then given for muscle relaxation, and ventilation was assisted via a face mask with 100% oxygen.

Before the study, ECT-induced seizure threshold was determined by using a standardized threshold titration methodology [8]. Thereafter, a suprathreshold electrical stimulus (50% above the threshold value) was delivered via bitemporal electrodes using a Thymatron DGX device (Somatics, Palo Alto, CA, USA) immediately after resolution of muscle fasciculation.

The durations of motor and electroencephalographic (EEG) seizure activity were recorded by a blinded investigator as the times from the electrical stimulus to cessation of tonic-clonic motor activity in the isolated foot and to postictal EEG suppression, respectively. Time from the ECT stimulus to spontaneous breathing and awakening time [time from the ECT stimulus to the patient's ability to open eyes and respond to simple verbal commands (squeezing the investigator's hand on command)] were assessed. Hypotension and bradycardia during anesthesia were defined as a decrease of more than 30% from the baseline MAP and a HR less than 45 beats per minute (bpm), respectively. Side effects and adverse events were noted before discharge back to the ward.

Power analysis was performed on the basis of the previously reported 39% prolongation in the seizure duration with remifentanil [9, 10], suggesting a minimal sample size of 26 ECT sessions in each group. This sample size would also be adequate to detect a 30% reduction in the ECT-induced MAP and HR increase with a power of 90% at an error of 0.05. Data are expressed as mean ± SD and numbers (n). Intergroup comparisons of motor and EEG seizure durations, recovery time, and hemodynamic variables were performed by using two-way analysis of variance followed by Bonferroni's correction for multiple testing. P values less than 0.05 were considered statistically significant.

Results

All 78 ECT treatments in the 26 patients (11 men and 15 women) were evaluated. Fifteen patients had major depression and 11 had schizophrenia. Seventeen patients had hypertension (ASA II), and 9 had no complications (ASA I). The mean age (±SD) of the patients was 60 ± 13 years (range, 33–72 years) and mean body weight was 60 ± 12 kg (range, 45–84 kg). Patients in group P required additional use of propofol for loss of responsiveness to verbal commands, and propofol requirement was 1.2 ± 0.1 mg/kg. On the other hand, in all the patients in groups R1 and R2, loss of consciousness was obtained without any additional propofol administration.

Both mean durations of motor and EEG seizure activity were significantly longer in patients in groups R1 and R2 than in patients in group P ($P < 0.05$ and $P < 0.01$, respectively) (Table 1). All motor seizures induced by ECT lasted longer than 20 s, except for 3 patients in groups R1 and R2 and 9 patients in group P. The percentages of patients with motor seizure duration of more than 20 s was significantly larger in groups R1 and R2 than in group P ($P < 0.05$).

Table 1 Comparative data of the three regimens on seizure duration and recovery time

	Group P	Group R1	Group R2
Motor seizure durations (s)	19.7 ± 9.9	29.2 ± 8.7**	29.1 ± 9.6*
EEG seizure durations (s)	22.9 ± 8.1	33.4 ± 9.5**	33.8 ± 10.2**
No. of ECT sessions with motor seizure duration >20 s (*n*)	17 (65%)	23 (88%)*	23 (88%)*
Time to spontaneous breathing (min)	2.9 ± 1.1	4.2 ± 2.0	5.9 ± 3.2†, **
Awakening time (min)	4.7 ± 1.2	5.3 ± 1.9	6.3 ± 2.7*

Values are mean ± SD or *n* (%)

EEG electroencephalography, *ECT* electroconvulsive therapy

* $P < 0.05$ compared with group P; ** $P < 0.01$ compared with group P

† $P < 0.05$ compared with group R1

Table 2 Hemodynamic data during ECT in the three regimens

	Group P	Group R1	Group R2
Increase for MAP baseline (%)	43 ± 23	91 ± 45**	62 ± 33†
Increase for HR baseline (%)	44 ± 27	64 ± 26	53 ± 31
Maximal value of RPP	16,204 ± 4,420	17,780 ± 5,108	16,004 ± 5,152
No. of ECT sessions with RPP value >20,000 (*n*)	5 (19.2%)	13 (50.0%)*	6 (23.1%)†

Values are mean ± SD or *n* (%)

MAP mean arterial blood pressure, *HR* heart rate, *RPP* rate–pressure product

* $P < 0.05$ compared with group P; ** $P < 0.01$ compared with group P

† $P < 0.05$ compared with group R1

The baseline MAP and HR were 85.0 ± 10.3 mmHg and 68.0 ± 12.8 bpm, respectively. In all patients in three groups, MAP and HR was decreased from the baseline value by induction of anesthesia, and "Pre-ECT values" in MAP and HR in groups P, R1, and R2 were 85.2 ± 16.6, 67.4 ± 14.0, and 63.4 ± 15.0 mmHg and 64.9 ± 11.6, 59.5 ± 13.1, and 60.6 ± 12.1 bpm, respectively. Although 1, 2, and 3 patients in groups P, R1, and R2 developed hypotension during each procedure, respectively, there were no statistically significant differences. None of the patients in the three groups experienced bradycardia. By ECT stimulus, MAP was increased from the baseline value, and particularly, the percentage increases from "Pre-ECT values" to "Peak post-ECT values" in MAP for baselines were significantly larger in group R1 than in group P ($P < 0.01$) and group R2 ($P < 0.05$). However, the percentage changes in MAP during ECT did not significantly differ between groups P and R2. Although the percentage increases from "Pre-ECT values" to "Peak post-ECT values" in HR for baselines also tended to be larger in group R1 than in the other groups, these differences were not statistically significant. Maximal values of RPP were not different among the three anesthetic regimens. However, the number of ECT sessions with peak RPP of more than 20,000 was significantly larger in group R1 than in groups P and R2 ($P < 0.05$) (Table 2).

Remifentanil increased the time from the ECT stimulus to spontaneous breathing in a dose-dependent fashion. Awakening time was also significantly prolonged in group R2 compared with that in group P ($P < 0.05$) (Table 1). None of the patients had anesthetic-related side effects or adverse events.

Discussion

The results of our study indicated that divided administration of remifentanil 1 and 2 μg/kg combined with a reduced dose of propofol (0.5 mg/kg) provided longer duration of seizure activity than that in the use of hypnotic doses of propofol and less hemodynamic responses during ECT than that in the use of remifentanil 1 μg/kg followed by propofol 0.5 mg/kg but showed more prolonged recovery time than that in the other two induction regimens.

Fredman et al. [11] previously demonstrated that 0.75 mg/kg propofol was the lowest dose that reliably induced hypnosis, but even this dose of propofol may significantly decrease seizure duration in comparison with methohexital. Recently published studies [12, 13] showed that addition of 1 μg/kg remifentanil to reduced doses of propofol (0.5 mg/kg) provided loss of consciousness and increased seizure durations in patients undergoing ECT. However, there is no description in those reports of the

effect of remifentanil on acute hemodynamic responses to the ECT stimulus, and there is no detailed description of protocols, i.e., injection technique, timing of the ECT stimulus, and physical status of the subjects. Another study [14] showed that attenuation of the acute hypertensive response following ECT during methohexital anesthesia required at least 100 μg remifentanil (2 μg/kg). In addition, a sympathetic response caused by the ECT stimulus results in severe tachycardia and hypertension peaking 3–5 min [15] and lasting 5–7 min [10] after the electrical stimulus. On the other hand, half-time after bolus injection of remifentanil has been shown to be only 3–4 min [16]. In consideration of the results of these previous investigations and the pharmacokinetics of remifentanil, remifentanil 1 μg/kg combined with propofol 0.5 mg/kg required for unconsciousness might fail to blunt the hemodynamic responses to ECT, but remifentanil 2 μg/kg followed by propofol 0.5 mg/kg would cause significant hypotension before ECT and marked hypertension after ECT because of the short duration of action of remifentanil. We therefore hypothesized that injection of remifentanil (1 μg/kg) followed by a subhypnotic dose of propofol would provide unconsciousness and prolongation of seizure duration and that a second injection of remifentanil (2 μg/kg) immediately before the ECT stimulus would produce adequate attenuation of the acute hemodynamic responses to ECT.

In the current study, both groups R1 and R2 had increased duration of both motor and EEG seizure activities compared with those in group P, as found in previous studies. However, no significant difference in seizure duration was observed between groups R1 and R2. The effect of remifentanil on duration of ECT-induced seizure activity has been controversial, i.e., ranging from no effect [14] to an increase [17] in seizure duration. The use of different doses of remifentanil in groups R1 and R2 produced no significant changes in seizure duration in the present study.

The increase in MAP during ECT was significantly larger in group R1 than in the other groups. After a bolus injection of remifentanil, peak drug effect has been shown to be within 1.5 min [18]. In group R1, the time from administration of remifentanil to the electrical stimulus required more than 2.5 min, whereas the timing of the application of the ECT stimulus in group R2 was immediately after the second injection of remifentanil. Therefore, remifentanil used in group R1 would not have played an adequate role in compensating for weak cardiovascular depressant effects of low-dose propofol because of its rapid elimination. Although group P showed less elevation in MAP than that in group R2, this difference was not statistically significant. Values of RPP of greater than 20,000 have been shown to cause myocardial ischemia [19, 20]. In this study, although the number of ECT sessions associated with peak RPP value >20,000 was also fewer in groups P and R2 than in group R1, the incidences of high RPP in groups P and R2 were greater than 19%. One possible explanation for this result is the large percentage (70%) of patients with hypertension. Hypertensive patients produce an exaggerated hemodynamic response to many forms of stress, i.e., three to four times more hypertensive episodes than normotensive patients, because of long-term persistent hyperreactivity [21]. An acceptable hemodynamic changes during the ECT for hypertensive patients may, therefore, require an additional antihypertensive agents and/or techniques to these regimens in the current study.

As for emergence from anesthesia, remifentanil showed a dose-dependent prolongation in the time to spontaneous breathing. Awakening time also tended to be prolonged by the use of remifentanil in the present study. This finding was probably a result of increase in seizure duration associated with the use of a reduced dose of propofol obtained by anesthetic-sparing effects of remifentanil, because the duration of seizure activity has been reported to be the primary determinant of early recovery rather than the dose of the hypnotic drug [3].

In conclusion, divided supplementation of remifentanil at 1 and 2 μg/kg combined with a reduced dose of propofol (0.5 mg/kg) is preferable with respect to both seizure duration and hemodynamic stability during ECT to the use of standard hypnotic doses of propofol alone or remifentanil 1 μg/kg followed by propofol at 0.5 mg/kg.

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