Original contribution

Effects of the concurrent use of a reduced dose of propofol with divided supplemental remifentanil and moderate hyperventilation on duration and morphology of electroconvulsive therapy-induced electroencephalographic seizure activity: A randomized controlled trial

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ABSTRACT

Study objective: The clinical adequacy of electroconvulsive therapy (ECT) depends on not only seizure duration but also seizure amplitude and postictal suppression. The objective of this study was to evaluate the effects of combination of a reduced dose of propofol and moderate hyperventilation on seizure duration and electrical stimulus requirement for adequate ictal amplitude and postictal suppression.
Design: Prospective, randomized, controlled trial.
Setting: Operating room at a municipal hospital.
Patients: Sixty ASA physical status I or II patients scheduled to receive a total of >300 ECT treatments.
Interventions: Patients were randomly assigned to have the three interventions: the use of a standard dose (1 mg/kg) of propofol and normoventilation ($ETCO_2$ of 40–45 mm Hg) (group P/N), the use of a reduced dose (0.5 mg/kg) of propofol with divided remifentanil injections and normoventilation (group RP/N), and the use of a reduced dose of propofol with divided remifentanil injections and moderate hyperventilation ($ETCO_2$ of 30–35 mm Hg) (group RP/H). Patients in groups RP/N and RP/H received remifentanil 1 μg/kg followed by propofol 0.5 mg/kg for unconsciousness and thereafter remifentanil 1 μg/kg immediately before the electrical stimulus.
Measurements and main results: Patients in group RP/H had significantly longer durations of electroencephalographic (EEG) seizures in the early phase of the ECT course ($P < 0.05$) and lower intensities of electrical stimulus in the late phase of the ECT course ($P < 0.05$) than those in groups P/N and RP/N.
Conclusion: A reduced dose of propofol combined with divided supplemental remifentanil under moderate hyperventilation during ECT may contribute to reduced electrical dosage due to the ability of its augmentation of seizure amplitude and postictal suppression in the late phase of the ECT course.

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1. Introduction

Electroconvulsive therapy (ECT) is widely used to treat depression and schizophrenia which respond poorly to conventional pharmacotherapies, and it ensures clinical adequacy by eliciting a therapeutic seizure. Advanced age [1], increment of ECT treatments [2], and use of hypnotic agents with anticonvulsant properties [2,3] have been reported to result in high seizure thresholds and shorter seizure durations. Although seizure duration during ECT generally does not correlate with clinical efficacy [4], it is common in ECT practice for clinicians to take

seizure-prolonging measures if the durations are short because no seizure or a brief seizure duration is considered to be less effective ECT [5]. However, essential elements to induce optimally therapeutic seizures have been shown not only to produce minimum seizure duration but also to optimize electroencephalographic (EEG) morphology [6].

Propofol is widely used in anesthesia for ECT because of its rapid onset, brief duration of action and minimal impact on cognition. However, because of its dose-dependent decreasing action in seizure duration, reducing the dose of propofol with remifentanil has been reported to be effective for prolongation of seizure duration in several previous trials [7–10]. On the other hand, the use of hyperventilation prior to ECT stimulus has been shown to result in significant improvements in seizure morphology [11,12]. To our knowledge, however,

there have been no reports on effects of this combined technique on seizure morphology. In the present study, therefore, for augmentation strategies to improve the seizure quality in patients refractory to standard ECT settings, concomitant application of a reduced dose of propofol combined with divided remifentanil supplementation and moderate hyperventilation was conducted for ECT anesthesia. The purpose of this study was to evaluate the influence of this seizure-augmenting intervention on both seizure adequacy and adverse effects during ECT procedures.

2. Materials and methods

After obtaining approval from the Institutional Ethics Committee at Muroran City General Hospital and written informed consent from each patient, 60 ASA physical status I or II patients refractory to numerous psychotropic medications were enrolled in a prospective, randomized, controlled trial. Exclusion criteria were age younger than 20 years or older than 80 years, myocardial infarction in the previous 6 months, coronary artery disease, atrial fibrillation or flutter, heart block, uncontrollable hypertension, chronic respiratory disease, cerebrovascular diseases, and drug allergy. ECT treatments were given to all patients 3 times per week with 2-day intervals. One sequential ECT treatment consisted of 5 to 10 ECT treatment sessions. None of the patients were premedicated. The patients were assigned to the following three groups ($n = 20$ each) in a stratified, randomized order: (a) a group in which patients had a standard dose of propofol alone for anesthetic induction and received normoventilation before ECT (group P/N), (b) a group in which patients had a reduced dose of propofol with divided injections of remifentanil and received normoventilation before ECT (group RP/N), and (c) a group in which patients had a reduced dose of propofol with divided injections of remifentanil and received moderate hyperventilation before ECT (group RP/H). Patients in group P/N received propofol at 1 mg/kg over 20 s, and patients in groups RP/N and RP/H received remifentanil at 1 μg/kg over 60 s followed by propofol at 0.5 mg/kg over 10 s to induce unconsciousness. On loss of consciousness, a blood pressure cuff was inflated on the right or left leg, and 1 mg/kg succinylcholine was administered intravenously in each group. Patients in groups RP/N and RP/H were thereafter given remifentanil at 1 μg/kg over 60 s again immediately before the ECT stimulus. All medication with remifentanil was prepared in a 10-mL syringe with 0.001% solution diluted with 0.9% normal saline. From after succinylcholine injection to immediately before the ECT stimulus, patients in groups P/N and RP/N were manually ventilated using a facemask with 100% oxygen with normoventilation [end-tidal carbon dioxide partial pressure ($ETCO_2$) of 40–45 mm Hg] being performed, and patients in group RP/H were ventilated with hyperventilation ($ETCO_2$ of 30–35 mm Hg) being performed. The values of $ETCO_2$ were obtained by the capnography (5250 RGM; Datex Co, Ltd, Helsinki, Finland) attached to facemask. After resolution of muscle fasciculation and manual ventilation over 120 s an electrical stimulus was delivered via bifrontotemporal electrodes using a pulse wave ECT device (Thymatron DGX, Somatics, Palo Alto, CA, USA) with constant pulse width (0.5 ms) and amplitude (0.9 A).

In the present study, manual and computer ratings were adopted for ictal EEG features and therapeutically adequate EEG seizure activity was defined by the following three criteria: (1) EEG seizure duration >15 s or motor seizure duration >10 s, (2) EEG seizure activity of type 3 or 4 as classified according to the following five types (Fig. 1): type 0 = a curve without paroxysmal activity, type 1 = a curve of very low paroxysmal intensity, type 2 = a curve of low paroxysmal intensity, type 3 = a curve of appropriate paroxysmal intensity, and type 4 = a curve of very high to exaggerated paroxysmal intensity, described by Christensen et al. [13] and Hrdlicka et al. [14], and (3) postictal suppression index (PSI) ≧74% [15] or postictal suppression of type 2 or 3 as rated on a 4-point scale (Fig. 2): type 0 = cannot tell where the seizure ends, type 1 = seizure termination is clear, but suppression is poor (not

flat), type 2 = good seizure suppression (very flat), but transition to flat is gradual, type 3 = good seizure suppression (very flat), and transition to flat is abrupt [16].

In the first session in the ECT series, the magnitude of stimulus intensity was determined by the "half-age" stimulation strategy [17]. In subsequent sessions, on the basis of the above definition of adequate seizure activity, if ictal EEG data met all three conditions, the same stimulus dosage as the used in the first session was delivered in the next session, but if more than one of the three conditions were not met, an electrical dose 1.5 times larger than that in the first session was applied in the next session (stepwise increase method [18]). These evaluations were done by an experienced psychiatrist blinded to group and drug information.

The durations of motor and EEG seizure activities were recorded using electromyographic (EMG) and EEG monitors attached to the ECT device as the times from the electrical stimulus to cessation of tonic-clonic motor activity in the isolated foot and to postictal EEG suppression, respectively.

A power analysis was performed on the basis of the previously reported 30–50% prolongation in the duration of EEG seizure activity with remifentanil [7]–[10], and results of the analysis suggested that a sample size of 18–20 patients in each group would have a 90% power to detect a 30–50% difference in EEG seizure duration with Type I error probability of 0.05. Data are presented as means ± SD and numbers (n). Patients' characteristics and recovery profiles were compared using single-factor analysis of variance (ANOVA) with post hoc tests. Statistical intergroup comparisons of electrical stimulus intensity, EEG and motor seizure durations in the series of five sessions were performed using repeated-measures ANOVA followed by Student's t-test. A probability value <0.05 was considered significant.

3. Results

A total of 68 patients were assessed for eligibility. Of these, 60 patients were randomized for the study, and two patients were withdrawn after randomization. The efficacy analysis population was therefore conducted on 20 patients in group P/N, 19 patients in group RP/N, and 19 patients in group RP/H (Fig. 1). The demographic and clinical characteristics of the three treatment groups were similar (Table 1). None of the patients in three groups had experienced previous ECT.

The intensities of the electrical stimulus by session number in the three groups are presented in Fig. 2. Although the required stimulus intensities gradually increased with session number in the three groups, the electrical dosage required in group P/N was significantly higher than that required in group RP/N in the fourth ($P = 0.026$) and fifth ($P = 0.007$) sessions and than that required in group RP/H in the second ($P = 0.042$), third ($P = 0.018$), fourth ($P < 0.001$), and fifth ($P < 0.001$) ECT sessions. Additionally, the electrical dosage required in group RP/H was significantly lower than that required in group RP/N in the fifth ECT session ($P = 0.010$).

Examples of ECT-induced seizure ratings and postictal suppression are presented in Figs. 3 and 4, respectively. Sixty-four (80%), forty-two (53%), and thirty-two (40%) of the second to the fifth sessions (total 80 sessions) in groups P/N, RP/N and RP/H required increased stimulus dosage due to inadequate seizure activities, and the causes in 79%, 81% and 83% of the sessions in groups P/N, RP/N and RP/H, respectively, were low slow-wave amplitude and/or poor postictal suppression but not short seizure durations. Low slow-wave amplitude, poor postictal suppression and both of these variables accounted for 10%, 40% and 50%, 5%, 50% and 45%, and 10%, 55% and 35% of the causes of increased energy dosage in groups P/N, RP/N, and RP/H, respectively.

The durations of EEG seizure activities were significantly longer in group RP/H than in group P/N in the first ($P < 0.001$), second ($P < 0.001$), and third ($P = 0.010$) sessions and were significantly longer in group RP/N than in group P/N in the first session ($P < 0.001$). A significant prolongation of EEG seizure duration was also found in group RP/H