Ketamine as an Alternative Anesthetic for Augmenting Seizure Durations During Electroconvulsive Therapy: A Retrospective Observational Study

Sarara Mutoh, MD*; Michiko Kinoshita, MD, PhD*; Yuki Maeda, MD*; Katsuya Tanaka, MD, PhD*

* Department of Anesthesiology, Tokushima University Hospital, 2-50-1 Kuramoto-cho, Tokushima-shi, Tokushima 770-8503, Japan.

Address for Correspondence and Reprints: Michiko Kinoshita
2-50-1 Kuramoto-cho, Tokushima-shi, Tokushima 770-8503, Japan.
Telephone number: +81 (0)88-633-7181, Fax number: +81 (0)88-633-7182
Email: michiko-kinoshita@tokushima-u.ac.jp

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Abstract

Objective:

Electroconvulsive therapy (ECT) is highly effective for severe psychiatric disorders; however, short seizure durations may lead to ineffective therapy. This retrospective study aimed to examine the risks and benefits of switching to ketamine anesthesia to augment seizure durations during an acute course of ECT.

Methods:

We included 33 patients who underwent ketamine anesthesia due to suboptimal seizures during an acute course of ECT. We assessed seizure duration, stimulus dose, hemodynamic variability, and post-seizure complications before and after switching to ketamine.

Results:

Age was significantly associated with suboptimal seizures during ECT ($p = 0.040$). After switching to ketamine, 32 patients (97%) experienced prolonged seizure duration. Ketamine significantly prolonged both electroencephalogram and motor seizure durations with a mean difference of 34.6 s (95% CI, 26.4 to 42.7; $p < 0.001$) and 26.6 s (95% CI, 19.6 to 33.6; $p < 0.001$), respectively. It also significantly reduced stimulus dose (mean difference: −209.5 mC [95% CI, −244.9 to −174.1], $p < 0.001$). Additionally, maximum changes in systolic blood pressure and heart rate during ECT sessions significantly increased with ketamine (mean difference: 27.2 mmHg [95% CI, 12.0 to 42.4; $p = 0.001$]; 25.7 bpm [95% CI, 14.5 to 36.8; $p < 0.001$], respectively). Patients reported more headaches with ketamine ($p = 0.041$).

Conclusions:

Our results provide evidence that ketamine as an alternative anesthetic can augment

seizure durations in specific patients experiencing suboptimal seizures during an acute course of ECT. However, its use requires greater attention to circulatory management and post-seizure complications.

Key Words:
augmentation, alternative anesthetic, electroconvulsive therapy, ketamine, seizure duration

Introduction

Electroconvulsive therapy (ECT), which is generally performed under anesthesia, is considered safe and highly effective for severe major depression, bipolar disorder, and schizophrenia. [1-4] Therapeutic seizures induced by stimulus doses higher than the seizure threshold are essential for the efficacy of ECT, and according to the American Psychiatric Association guidelines, at least 15 seconds of seizure duration is required. [5] Seizure duration has been negatively correlated with the number of ECT sessions, suggesting that the seizure threshold increases with an increasing number of sessions. [6,7] Given the clinical ineffectiveness of short seizure duration, augmentation strategies are needed for patients with elevated seizure thresholds exceeding the maximum stimulus dose. [8]

Ketamine, an N-methyl D-aspartic acid receptor antagonist, may provide additional benefits for ECT in patients with major depression owing to its independent antidepressant effect. [9-11] Although the efficacy of ketamine as a first-line anesthetic for ECT has been inconsistent and controversial in randomized controlled trials (RCTs), [12-15] a meta-analysis has shown that ketamine induces a longer seizure duration than other anesthetics, including propofol, thiopental, and methohexital. [16] Therefore, ketamine may improve the quality of seizures that maybe short or difficult to induce using other anesthetics. [17] However, to the best of our knowledge, few studies have examined the efficacy of switching to ketamine during acute course ECT, [18,19] and clinical evidence on the effects of ketamine during acute course ECT remains limited.

This retrospective study aimed to examine the risks and benefits of ketamine as a second-line anesthetic to augment seizure durations during the acute course This study was also designed to address the following clinical questions:

1. What factors are involved in patients experiencing suboptimal seizures during acute ECTs?
2. Does ketamine, as a second-line anesthetic, augment seizure durations in patients with elevated seizure thresholds?
3. Does ketamine increase hemodynamic variability during ECT sessions and post-seizure complications?

Materials and Methods

Ethics

This retrospective observational study was reviewed and approved by the Ethics Committee of Tokushima University Hospital (approval number; 3853-1) and publicized on our department website using an opt-out approach. The requirement for written informed consent from each patient or their legal guardian was waived for this retrospective study. This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.

Participants

We included adult patients aged 20 years and older who underwent acute ECTs using a pulse-wave stimulus at Tokushima University Hospital from November 1, 2010, to October 31, 2022. The study period was selected based on the time during which ketamine was used as a second-line anesthetic to augment seizure durations at our hospital. The exclusion criteria were as follows: patients who underwent maintenance ECTs, patients who received ketamine from the first session in an acute ECT course, patients with ECT interruption due to severe post-seizure complications, patients with sine-wave

ECTs, and patients who declined to participate in the study.

ECT protocol

ECT is usually performed using the following protocol in our hospital. Pulsed-wave ECT with bilateral electrode placement is performed using a Thymatron SYSTEM IV (Somatics LLC, Lake Bluff, IL, USA) with a pulse width of 0.5 ms and a pulse frequency of 70 Hz. In this configuration, Thymatron® outputs 504 mC of energy at 100% charge. The initial stimulus dose is determined using the half-age method, which indicates that the initial stimulus dose for a 60-year-old patient is 30% of the Thymatron maximum. [20] Seizure quality is evaluated by the attending psychiatrists using the following criteria. The primary requirement includes was (1) electroencephalogram (EEG)/motor seizure duration ≥ 25/20 sec (or ≥ 20/15 sec for patients aged ≥ 65 years). Additional supplementary factors utilized in the assessment include (2) symmetric waveforms with high amplitude, (3) postictal suppression, and (4) sympathetic activation; however, these factors lack defined, quantifiable records in this study.

The standard anesthetic protocol in our hospital is as follows: Propofol (1–1.5 mg/kg) and succinylcholine (1 mg/kg) are the first-line anesthetic and neuromuscular blocking agents, respectively, unless there are special circumstances, such as an allergy or drug rash. Adjunctive drugs, such as remifentanil or dexmedetomidine, are not included in the regimen. Anesthesiologists maintain respiration via mask ventilation; neither tracheal intubation nor the use of supraglottic devices are employed. Ventilation is regulated to ensure normocapnia, with no induction of intentional hyperventilation. Hypertension and tachycardia during an ECT session are treated with the calcium channel blocker, nicardipine, and the short-acting selective β1-blocker, landiolol, respectively.

The measures used to stabilize circulation are determined based on the discretion of the attending anesthesiologist. Notably, none of these medications are not administered prophylactically.

If the initial stimulus dose fails to produce a seizure of adequate duration, the stimulus dose is increased and the intensity is raised to 1.5–2.0 times the previous dose. When it is deemed that incrementally increasing the stimulus intensity, even up to nearly 100% of the maximum, is still insufficient to induce adequate seizures, switching to ketamine as an anesthetic is considered. Following the transition to ketamine, the stimulus dose is reduced based on the discretion of the attending psychiatrist.

Data collection and outcome measures

We collected the following patient information from electronic medical/anesthesia records: sex, age, diagnosis, medical history, American Society of Anesthesiologists Physical Status (ASA PS), anesthetic (type and dose), stimulus dose, EEG/motor seizure duration, systolic and diastolic blood pressure (SBP, DBP)/heart rate (HR) during the ECT session, pharmacotherapy for circulation during the ECT session, and occurrence of post-seizure headache/nausea.

For clinical question 1, we examined the data of patients who had experienced an anesthetic change and those who had not. For clinical question 2, paired analyses were performed to examine the ECT parameters and seizure duration between the last session before ketamine switching and the first session with ketamine in patients who experienced an anesthetic change. For clinical question 3, paired analyses were performed to examine the hemodynamic variability during ECT and post-seizure headache/nausea between sessions before and after the ketamine switch in patients who experienced an anesthetic

change. Since the data for circulation and post-seizure complications at the time of suboptimal seizures were deemed inappropriate, we targeted data from ECT with sufficient seizure durations for these analyses.

Statistical analysis

Data are presented as numbers (percentages), means (standard deviation, SD), or medians (interquartile range). Independent numerical variables between the two groups were compared using Student's t-test or the Mann–Whitney U test. Independent binary variables were compared between the two groups using the chi-square test or Fisher's exact test in cases with five or fewer cells. Dependent numerical variables were compared using a paired t-test or Wilcoxon signed-rank sum test. The dependent binary variables were compared using McNemar 's test.

Multivariate logistic regression analysis was performed to examine the factors associated with patients who experienced anesthetic changes, and the following factors were assessed: age, diagnosis, and dose of propofol. The number of explanatory variables was determined based on the number of events divided by 10.

Statistical analyses were performed using R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). A two-sided p-value < 0.05 was considered statistically significant.

Results

Of the 2181 ECT sessions identified during the study period, 766 maintenance ECT sessions were excluded. The remaining 1415 acute ECT sessions were performed

on 85 patients. An additional five patients were excluded due to use of ketamine from the first session, sine-wave ECT, and interruption of ECT due to a severe complication. A total of 80 patients were thus included in the analysis, Of these, 33 underwent anesthetic change to ketamine because of suboptimal seizures, while 47 patients did not. (Figure 1)

Patient characteristics are shown in Table 1. Patients who underwent anesthetic change to ketamine were significantly older than those who did not ($p = 0.008$). The distribution of diagnoses was also significantly different between groups ($p = 0.038$). Additionally, all patients who underwent anesthetic change had switched from propofol. In the multivariable logistic regression analysis, only age was significantly associated with patients who underwent anesthetic change (per-one year increase, odds ratio 1.05 [95% confidence interval, 1.00 to 1.10], $p = 0.040$; Table. 2)

A total of 33 patients required switching to ketamine due to suboptimal seizures despite the increased the stimulus dose for ECT with propofol from an initial dose of 179.5 (75.3) mC to 486.4 (48.2) mC. Of these patients, 32 (97.0%) patients experienced prolonged seizure durations under ketamine anesthesia. In these 32 patients, EEG (from 18.9 [14.9] s to 53.5 [21.0] s, mean difference: 34.6 s [95% CI, 26.4 to 42.7], $p < 0.001$) and motor (from 10.8 [9.6] s to 37.4 [16.7] s, mean difference: 26.6 s [95% CI, 19.6 to 33.6], $p < 0.001$) seizure durations were significantly extended after switching to ketamine. Upon switching to ketamine, the desired prolongation of seizure duration was achieved, despite a significant reduction in the stimulus dose (from 485.9 [48.8] mC to 276.4 [81.8] mC, mean difference: -209.5 mC [95% CI, -244.9 to -174.1], $p < 0.001$).

Hemodynamics during ECT, pharmacotherapy for circulation during ECT, and post-seizure complications were compared before and after ketamine administration (Table 3). Of the 33 patients considered, 26 patients were included in analysis and while

7 patients were excluded due to insufficient seizure durations with ECT using propofol, which would make comparison difficult. The maximum elevation in SBP (from 34.5 [28.8] mmHg to 61.7 [30.1] mmHg, mean difference: 27.2 mmHg [95% CI, 12.0 to 42.4], p = 0.001) and HR (from 26.5 [21.2] bpm to 52.2 [25.3] mmHg, mean difference: 25.7 bpm [95% CI, 14.5 to 36.8], p < 0.001) during ECT significantly increased with ketamine. The extent of these increments was not influenced by patient characteristics, such as the presence or absence of hypertension (p = 0.758, p = 0.965, respectively). There was no significant difference in the maximum elevation in DBP (15.5 [21.9] mmHg versus 24.5 [18.6], mean difference: 8.9 mmHg [95% CI, -0.10 to 18.8], p = 0.076) before and after switching to ketamine, respectively. Additionally, the dose of nicardipine used during ECT significantly increased with ketamine (from 0.25 [0.00–1.00] mg to 1.00 [0.50–1.88] mg, p = 0.005). Twenty-four patients were included in the analysis of post-seizure complications; while two were excluded due to missing data. The incidence of headache significantly increased with ketamine (from 8.3% to 33.3%; p = 0.041).

Discussion

This retrospective study examined the risks and benefits of ketamine as a second-line anesthetic to augment seizure durations during acute ECTs. Older age was significantly associated with inadequate seizures during the acute course of ECT, which is consistent with the findings of previous studies. [7,20,21] Changing the anesthetic to ketamine induced significantly longer EEG and motor seizure durations (35 and 25 s, respectively) in patients experiencing suboptimal seizures in ECT with propofol. Moreover, ketamine requires significantly lower stimulus doses, saving approximately 200 mC. This indicates that a concurrent reduction in stimulus dose should be considered

when contemplating a transition from propofol to ketamine. However, ketamine significantly increased both the systolic blood pressure and heart rate during ECT and post-seizure headaches. Our results suggest that ketamine, as a second-line anesthetic, can augment seizure durations in patients experiencing suboptimal seizures in the course of acute ECTs. However, circulatory management and post-seizure complications require greater attention.

Traditionally, anesthetic changes have been attempted to improve seizure quality in patients experiencing suboptimal seizures during the course of acute ECT; however, few studies have examined the efficacy of switching anesthetics. [22] Most comparisons between different anesthetics have been performed in parallel-group RCTs. Our within-subject study targeted specific patients experiencing suboptimal seizures; this condition differs from previous between-subject RCTs that targeted unspecified patients. Although some RCTs have reported negative results regarding the superiority of ketamine for ECT, [13,23,24] our results emphasize that ketamine remains a promising option for specific patients who need seizure augmentation because of an elevated seizure threshold.

Ketamine successfully prolonged seizure duration; however, therapeutic efficacy as an improvement in patients' symptoms could not be assessed in this study. Comparable scores representing symptoms were not recorded regularly in the medical records. Even if the scores were available, the study design did not allow for the evaluation of whether seizure augmentation with ketamine contributed to improvement in patient symptoms because of the lack of a control group. Although shorter seizures may be related to therapeutic ineffectiveness, a longer total seizure duration through an acute ECT course may not contribute to maximizing therapeutic efficacy. [25-27] The ictal EEG, such as the amplitude, morphology, and postictal suppression, is also known to be related to treatment

efficacy, [28-30] however, this was not included in the analysis in this study. Previous study has indicated that ketamine produces superior seizure quality in terms of postictal suppression. [31] Further, well-designed prospective studies are needed to determine the therapeutic efficacy of ketamine as a second-line anesthetic in acute ECTs.

A major concern associated with ketamine is increased adverse events during or after ECT. Our results demonstrated that ketamine increased hemodynamic changes during ECT compared to propofol during sufficient ECT seizures. This could be attributed to ketamine's intrinsic sympathomimetic activity, which raises both blood pressure and heart rate.[32,33] Additionally, although it was beyond the scope of this study, it is worth noting that ketamine might impact circulatory dynamics by intensifying ECT seizures. Excessive sympathetic stimulation during ECT may increase the risk of ECT-induced complications, such as Takotsubo cardiomyopathy. [34] Another major concern is that ketamine may increase the incidence of post-seizure complications. In our study, ketamine significantly increased the incidence of post-seizure headache, while previous studies have suggested that ketamine increases hallucinations, nausea, vomiting, and dizziness. [8,35] These adverse events may cause higher subject dropout rates during ECT. [35,36] Therefore, considering the risks and benefits, ketamine may be recommended depending on the individual patient's condition rather than routine use.

This retrospective study aimed to investigate the efficacy of switching anesthetics during acute ECTs. However, it is crucial to note that both psychiatrists and anesthesiologists need not only a thorough understanding of the sedative drugs being used, but also a detailed insight into the modulation of anesthesia depth, application of adjunctive anesthetic agents, and management of ventilation. All these factors collectively influence the quality of convulsions.[37,38] Furthermore, hemodynamic

instability caused by increased sympathetic and parasympathetic activity during ECT necessitates efforts to stabilize the heart rate and blood pressure. Utilizing circulatory aids, such as calcium channel blockers and beta-blockers, can be instrumental in achieving this.[37] Our results suggest that ketamine-based ECT may increase the need for these circulatory aids.

This study had some limitations. First, seizure quality and anesthetic changes were assessed by an individual psychiatrist. Although our hospital uses algorithms for setting ECT parameters and treatment evaluations, the retrospective design is not as precise as the prospective criteria. Second, information on patient symptoms and post-seizure complications were missing from the medical records in several cases. Hence, this study may have had a low statistical power to detect possible post-seizure complications other than headaches. Third, baseline medication and changes in medication during ECT and hyperventilation may have affected seizure duration; however, these factors were not assessed in this study. A previous study suggested that most psychotropic medications had little effect on seizure duration and threshold. [39] Fourth, we analyzed seizure duration as an endpoint. While symmetric waveforms with high amplitude, postictal suppression, and sympathetic activation also seem important for evaluating seizure quality, these measures were not included in the analysis due to the absence of defined quantitative records and lack of relevant data in the medical records. Finally, propofol is the standard anesthetic for ECT in our hospital; consequently, all patients were switched from propofol to ketamine. Therefore, our results may not be applicable to other anesthetics such as thiopental/thiamylal, etomidate, and methohexital. Propofol may be associated with a short seizure duration, whereas etomidate may induce a longer seizure duration. [40] Etomidate and methohexital have not been approved in some countries, such as Japan,

limiting the options available for anesthetic changes to augment seizure durations. Thus, this study demonstrates that ketamine may be useful in these countries.

In conclusion, our results suggest that ketamine is an option for certain patients requiring seizure augmentation because of suboptimal seizures with other anesthetics. However, considering the greater hemodynamic changes and risk of post-seizure complications, ketamine use should be undertaken depending on the patient's condition. Further prospective studies are required to determine the therapeutic efficacy and superiority of ketamine as an alternative anesthetic for augmenting seizure durations.

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Figure legends

Figure 1: Flow diagram

ECT, electroconvulsive therapy; n, number.

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Table 1: Patient characteristics

	Without anesthetic changes **n = 47**	**With anesthetic changes to ketamine** **n = 33**	**p value**
Sex Male/Female [n, (%)]	20 (42.6) /27 (47.4)	14 (42.4)/19 (57.6)	1.000
Age (years)	54.6 (15.6)	63.2 (10.9)	0.008
ASA PS 1/2/3 [n (%)]	3 (6.4) /43 (91.5) /1 (2.1)	0 (0) /31 (93.9) /2 (6.1)	0.290
Diagnosis			0.038
Major depression [n, (%)]	25 (53.2)	25 (75.8)	
Bipolar disorder [n, (%)]	9 (19.1)	6 (18.2)	
Schizophrenia [n, (%)]	13 (27.7)	2 (6.0)	
Anesthetics			0.509
Propofol [n, (%)]	45 (95.7)	33 (100.0)	
Thiamylal [n, (%)]	2 (4.3)	0 (0.0)	
Dose of propofol (mg/kg)	1.17 (0.16)	1.25 (0.39)	0.182

Data are given as mean (standard deviation) or number (%).

n, number; ASA PS, American Society of Anesthesiologists Physical Status.

Table 2: Multivariable logistic regression for factors associated with anesthetic changes to ketamine

	Odds ratio (95% CI)	p value
Age (years)	1.05 (1.00 to 1.10)	0.040
Diagnosis		
Major depression	1.10 (0.31 to 3.90)	0.885
Bipolar disorder	Reference	
Schizophrenia	0.34 (0.05 to 2.23)	0.259
Dose of propofol (mg/Kg)	3.83 (0.59 to 25.10)	0.161

CI, confidence interval.

Table 3: Paired analysis for hemodynamics, pharmacotherapy, and post-seizure complications before/after anesthetic changes (n = 26)

	Before changes to ketamine	After changes to ketamine	p value
Maximum hemodynamic change during ECT session			
Δ SBP (mmHg)	34.5 (28.8)	61.7 (30.1)	0.001
Δ DBP (mmHg)	15.5 (21.9)	24.5 (18.6)	0.076
Δ HR (bpm)	26.5 (21.2)	52.2 (25.3)	< 0.001
Pharmacotherapy for circulation during ECT session			
Dose of nicardipine (mg)	0.25 (0.00–1.00)	1.00 (0.50–1.88)	0.005
Dose of langiolol (mg)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.115
Post-seizure complication (n = 24)			
Headache [n (%)]	2 (8.3)	8 (33.3)	0.041
Nausea [n (%)]	1 (4.2)	4 (16.7)	0.371

Data are given as mean (standard deviation), median (interquartile range) or number (%). Postoperative complications were analyzed in 24 patients because of missing values.

ΔSBP, maximum degree of elevation in systolic blood pressure; ΔDBP, maximum degree of elevation in diastolic blood pressure; ΔHR : maximum degree of elevation in heart rate; bpm, beat per minute.