

Factors associated with post-electroconvulsive therapy delirium

A retrospective chart review study

Young Tak Jo, MD^a, Sung Woo Joo, MD^b, Jungsun Lee, MD, PhD^a, Yeon Ho Joo, MD, PhD^{a,*}

Abstract

Although electroconvulsive therapy (ECT) is generally a safe therapeutic method, unexpected adverse effects, such as post-ECT delirium, may occur. Despite its harmful consequences, there has been little discussion about the predictors of post-ECT delirium. Thus, the current study aimed to clarify the factors associated with post-ECT delirium by reviewing electronic medical records of 268 bitemporal ECT sessions from December 2006 to July 2018 in a university hospital.

Demographic and clinical characteristics of sessions involving patients with or without post-ECT delirium were compared. Multiple logistic regression analysis was applied to analyze the correlation between variables and post-ECT delirium.

Post-ECT delirium developed in 23 sessions (8.6%). Of all the demographic and clinical variables measured, only etomidate use was significantly different between delirium-positive and delirium-negative groups after Bonferroni correction. The regression model also indicated that etomidate use to be significantly associated with post-ECT delirium.

In this study, etomidate was associated with a higher risk of developing post-ECT delirium, an association that appeared unrelated to other possible measured variables. Practitioners should take into account the risk of post-ECT delirium while choosing anesthetics, so as to prevent early discontinuation before sufficient therapeutic gain is achieved.

Abbreviations: ECT = electroconvulsive therapy, VIF = variance inflation factor.

Keywords: delirium, electroconvulsive therapy, etomidate

1. Introduction

Since its first use in 1938,^[1] electroconvulsive therapy (ECT) has been one of the most efficient therapeutic methods in the field of psychiatry. Even after the introduction of various pharmacological interventions, ECT remains widely used for almost all psychiatric disorders,^[2,3] primarily owing to its rapid relief of symptoms.^[4] ECT is especially effective for catatonia^[5] and depression with severe psychotic symptoms^[6] and high suicide

risk,^[7] and a well-established alternative therapeutic method for treatment-resistant mood disorders.^[8]

Considering that ECT artificially induces a seizure, seizure-related adverse effects are the most likely to occur and should be considered in clinical practice. Although clinicians train carefully to prevent them, adverse effects, such as post-ECT delirium,^[9,10] occur unexpectedly and require further management. Post-ECT delirium, characterized by clouding of consciousness, disorientation, agitation, and even violent behavior, is one of the most common adverse effects of ECT, which can occur in up to 12% of patients who receive ECT.^[11] It typically lasts between 5 and 45 minutes immediately following the procedure,^[12] with some cases even requiring intravenous sedatives to be properly stabilized.^[13]

Post-ECT delirium not only causes premature discontinuation of treatment,^[14] but also leads to various harmful consequences. Delirious behaviors cause falls,^[15] which can be fatal in the elderly, and uncontrolled behaviors can cause multiple traumas. Long-term retrograde amnesia has also been reported with post-ECT delirium.^[16] Furthermore, post-ECT delirium causes a hazard to medical staff such as nurses in the intensive care unit.^[12] However, there has been little discussion about the predictors of post-ECT delirium in the current literature. Reti et al^[9] reported that seizure length is a significant predictor of post-ECT delirium, and Kikuchi et al^[17] found that the presence of catatonic features before ECT is a significant predictor of post-ECT delirium. However, these studies have limitations of small sample sizes and an insufficient number of studied variables, which are obstacles for drawing a clear conclusion regarding predictors of post-ECT delirium.

The aim of the current study is therefore to clarify the factors associated with post-ECT delirium by a retrospective chart

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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review of 268 bitemporal ECT sessions from December 1, 2006, and November 30, 2019 in the ECT unit of the Department of Psychiatry in the Asan Medical Center. We also compared the demographic and clinical characteristics of sessions involving patients with or without post-ECT delirium. Multiple logistic regression analysis was applied to analyze the correlation between variables and the post-ECT delirium.

2. Methods

2.1. Study population

The study population comprised all patients treated in the ECT unit of the Department of Psychiatry in Asan Medical Center, Seoul, Korea, between December 1, 2006, and November 30, 2019. A total of 268 patients, excluding patients younger than 19 years, were treated with ECT during the study period. In the case of a single patient receiving several ECT series during the study period, only the first ECT series was included. Moreover, for each series, only the first session was studied because the subsequent series/sessions might be affected by a change in the treatment protocol owing to post-ECT delirium.^[9] Specifically, we intended to exclude the effect of additive intravenous sedatives, which were used to control post-ECT delirium in the first session, and lowered electrical parameters in the subsequent series/sessions. Therefore, a total of 268 ECT sessions, with each patient contributing once, were included in this study. This is a retrospective chart review study, conducted in compliance with the principles of the Declaration of Helsinki. The study was approved by the Asan Medical Center Institutional Review Board (File number: 2018-1099) and exempted from the requirement of written informed consent.

2.2. ECT procedure

Patients were treated with ECT under inpatient or outpatient settings. Each patient completed a medical check-up before the procedure, including blood tests, chest X-ray, electrocardiogram, anesthesiologist's clearance, and brain imaging if required. Written informed consent for the treatment was obtained from all patients or the legal representatives in the case of patients lacking mental capacity to make their own decision.

ECT was performed 3 times a week. Vital signs were carefully monitored and recorded during the procedure. All psychotropic medications which alter seizure threshold, such as benzodiazepines or clozapine, were discontinued as much as possible after midnight on the day of treatment. The MECTA Spectrum 5000Q device (MECTA Corporation, Tualatin, OR) was used to deliver the stimulation.

General anesthesia was induced by a single anesthetic drug selected by an experienced anesthesiologist according to the individual patient's general condition and clinical circumstance. The following anesthetics were used: pentobarbital (1.5–6.0 mg/kg), etomidate (0.1–0.5 mg/kg), or propofol (0.8–1.5 mg/kg). After the loss of responsiveness to verbal command, 0.5 to 3.0 mg/kg of succinylcholine was administered to patients for muscle relaxation during the seizure. The cuff method was applied to allow practitioners to estimate the motor seizure duration readily, and a 2-channel electroencephalogram was also applied^[18] for collateral information on the seizure. The motor seizure duration is determined by the observation of clonic movements on the left lower extremity.

Table 1

Electrical parameters at the first treatment.

Age (yr)	Sex	Pulse width (ms)	Frequency (Hz)	Duration (s)	Current (mA)
<30	Female	1.4	60	1	700
	Male	1.4	70	1	700
30–60	Female	1.4	70	1.25	750
	Male	1.4	80	1.25	750
60>	Female	1.4	80	1.5	750
	Male	1.4	90	1.5	750

Once the patients were under the adequate depth of anesthesia and prepared for the electrical stimulation, standard bitemporal ECT was administered. As previously described by Joo et al,^[19] electrical parameters for the first treatment were set using the preselected-dose method according to MECTA Corporation. This method determines electrical parameters according to the sex and age of the patient, based on previous studies.^[20–23] The electrical parameters used are presented in Table 1. However, these parameters were occasionally modified by an experienced psychiatrist according to the individual patient's clinical circumstance. After the treatment, the patients were closely observed by registered nurses until awakening. Nursing records were documented in detail, including patients' orientation, level of consciousness, and behavioral changes, which allowed practitioners to determine the presence of postictal delirium.

2.3. Data collection

We obtained the following information by reviewing electronic medical records: age, sex, body mass index, psychiatric diagnosis, concomitant psychotropic medications, type and dosage of anesthetic, motor seizure duration, and stimulus parameters (charge, energy, pulse width, frequency, stimulus duration, and total current).

Concomitant medication was defined as the medication prescribed for the day before the first session. In detail, we determined whether psychotropic medications, such as lithium, valproate, lamotrigine, and clozapine, that can alter the seizure threshold, were prescribed. The dosage of each medication was also evaluated. In the case of divalproex, valproate equivalent doses were estimated according to the Oxford Health NHS Foundation Trust Formulary (<http://www.oxfordhealthformulary.nhs.uk/>).

It was determined whether each patient developed post-ECT delirium by thoroughly reviewing recovery room nursing records. We defined post-ECT delirium as severe agitation with irritable and violent behavior requiring physical or chemical restraint immediately after the treatment. Thus, patients whose nursing records had explicit comments of physical restraint or antipsychotic/benzodiazepine injections were considered as having post-ECT delirium.

2.4. Statistical analyses

Either the Chi-squared or Fisher exact test was used for categorical variables, and independent *t*-test or Mann–Whitney *U* test was used for continuous variables according to the normality of each variable was determined by the Shapiro–Wilk test. For comparisons of electrical parameters between sessions

with or without post-ECT delirium, subgroup analyses were performed using sessions in which only 1 electric stimulus was applied. This was because it was necessary to increase parameters for subsequent electric shots when seizure duration was insufficient, or seizure induction failed. In this subgroup analysis, sessions with incomplete data on electrical parameters were excluded. For multiple testing correction, Bonferroni correction was applied.

For an analysis of correlations between variables and post-ECT delirium, multiple logistic regression analysis was applied. Before the multiple logistic regression analysis, we used the variance inflation factor (VIF) to deal with multicollinearity among variables and excluded the variables with high VIF in the regression model. Moreover, after constructing a regression model with all possible predictor variables, we constructed another regression model with variables that were selected using backward stepwise selection based on the Wald statistic to complement the original regression model. In this additional regression model, the level of variable elimination was determined using unchanged Nagelkerke R-square. The goodness of fit for the regression model was estimated using the Hosmer–Lemeshow test. All statistical analyses were performed using the Statistical Package for the Social Sciences software for Windows Ver. 26 (IBM Corporation, Armonk, NY), and a result of $P < .05$ was considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics

Of the total 268 sessions, 23 sessions (8.6%) developed post-ECT delirium. Among 23 sessions involving patients with postictal delirium, 14 (13.5%) included men, whereas 9 (5.5%) included women. One session (0.4%) resulted in the development of rhabdomyolysis causing early termination of the treatment. Although the male to female ratio was higher in delirium positive-group than delirium-negative groups ($\chi^2=5.158$, $df=1$, $P=.027$), it was not statistically significant after multiple testing correction by the Bonferroni method. There were no significant differences between delirium-positive and delirium-negative groups with respect to other baseline demographics including age ($U=2637.5$, $P=.612$) and body mass index ($U=2296.5$, $P=.143$). Moreover, the youngest and oldest patients included in this study were 20 and 82 years old.

There was no significant difference in the delirium-positive case ratio by psychiatric diagnosis ($\chi^2=0.627$, $df=4$, $P=.972$). It was revealed that the delirium-positive group had taken 2.43 ± 1.31 psychotropic medications, which were slightly fewer than 2.64 ± 1.42 in the delirium-negative group. However, it did not reach statistical significance ($U=2635.5$, $P=.600$). In terms of psychotropic medications (lithium, valproate, lamotrigine, and clozapine), there was no statistically significant difference in the use and dosage of the psychotropic medications between the delirium-positive and delirium-negative groups. In terms of anesthetics, there was a statistically significant difference between delirium-positive and delirium-negative groups ($\chi^2=20.033$, $df=2$, $P < .001$). Sessions where patients were anesthetized with etomidate showed a higher ratio of delirium-positive to delirium-negative sessions than sessions where patients were anesthetized with pentobarbital or propofol. Meanwhile, the dose of muscle relaxant by weight was not significantly different between delirium-positive and delirium-negative groups ($U=2425.5$,

$P=.295$). The number of electric stimuli was also not significantly different between these groups ($U=2445.5$, $P=.139$). The average motor seizure duration in the sessions with post-ECT delirium was 52.8 ± 26.4 seconds, which was longer than 41.6 ± 22.4 seconds in the sessions without post-ECT delirium, but not statistically significant ($U=2142.5$, $P=.057$). The comparisons of all studied variables between the delirium-positive and delirium-negative groups are shown in Table 2.

3.2. Electrical parameters

In order to compare electrical parameters, a subgroup analysis using sessions with a single electric stimulus was performed. In the delirium-positive group, electrical charge, energy, pulse width, frequency, and stimulus duration were higher or longer than those in the delirium-negative group, though this was not statistically significant (charge: 211.1 ± 78.9 mC vs 190.6 ± 73.8 mC; energy: 32.3 ± 13.6 J vs 30.7 ± 12.0 J; pulse width: 1.35 ± 0.15 Hz vs 1.34 ± 0.14 Hz; frequency: 74.0 ± 11.8 Hz vs 70.1 ± 16.1 Hz; stimulus duration: 1.42 ± 0.51 seconds vs 1.31 ± 0.27 seconds). There was also no significant difference in current between the 2 groups. All results of the subgroup analysis are shown in Table 3.

3.3. Multiple logistic regression model

Multiple logistic regression model was applied for correlations of variables with post-ECT delirium. Because electrical parameters only except current showed multicollinearity ($VIF \geq 3$), all variables except electrical parameters were included. Only etomidate use was again found to be significantly associated with post-ECT delirium (odds ratio of delirium=12.335; 95% confidence interval, 3.076–49.468; $P < .001$). No other variables were statistically significant predictors of post-ECT delirium. The regression model indicated a Nagelkerke R^2 of 0.204, and the Hosmer–Lemeshow test statistic was $\chi^2=10.965$, $df=8$, and $P=.204$. Further details on the results of the regression model are presented in Table 4.

In addition, another regression model was constructed with variables selected using backward stepwise selection. The level of variable elimination was determined as nearly unchanged Nagelkerke R^2 of 0.204 at first, which was 0.203 until level 4 of the regression model. In this model, etomidate use alone was significantly associated with post-ECT delirium ($P < .001$). The result of the Hosmer–Lemeshow test was $\chi^2=4.711$, $df=8$, $P=.788$.

4. Discussion

This study was based on a retrospective chart review of a total of 268 bitemporal ECT sessions, and investigated the factors associated with post-ECT delirium. Among all sessions, 23 sessions (8.6%) were associated with the development of post-ECT delirium. In demographic, clinical variables, and electrical parameters, only etomidate use was significantly different between delirium-positive and delirium-negative groups. The multiple logistic regression model also indicated that etomidate use was significantly associated with post-ECT delirium, regardless of the variable inclusion method.

Etomidate, an ultrashort-acting nonbarbiturate anesthetic, is 1 of the 3 most common anesthetics used for ECT.^[24] Since etomidate can prolong seizure duration, it is often considered as

Table 2
Demographic and clinical characteristics of sessions*

	Delirium (+) N = 23	Delirium (-) N = 245	U or χ^2	df	P-value
Sex [†]			5.158	1	.027
Male	14 (13.5)	90 (86.5)			
Female	9 (5.5)	155 (94.5)			
Age (yr) [‡]	44.5[13.6]	46.4[16.0]	2637.5		.612
BMI [‡]	24.4[4.2]	23.2[4.3]	2296.5		.143
Diagnosis ^{§,}			0.627	4	.972
Major depressive disorder	8 (9.1)	80 (90.9)			
Bipolar disorder	6 (10.5)	51 (89.5)			
Schizoaffective disorder	3 (12.0)	22 (88.0)			
Schizophrenia	4 (7.5)	49 (92.5)			
Others	2 (4.4)	43 (95.6)			
Number of concomitant psychotropics ^{¶,}	2.43[1.31]	2.64[1.42]	2635.5		.600
Specific medication [§]					
Lithium	1 (16.7)	5 (83.3)	0.511	1	.419
Valproate	0 (0.0)	10 (100.0)	0.975	1	1.000
Lamotrigine	0 (0.0)	15 (100.0)	1.492	1	.626
Clozapine	4 (15.4)	22 (84.6)	1.698	1	.256
Anesthetics [§]			20.033	2	.001
Pentobarbital	16 (6.6)	225 (93.4)			
Propofol	1 (8.3)	11 (91.7)			
Etomidate	6 (40.0)	9 (60.0)			
Relaxant dosage (mg/kg)	1.23[0.29]	1.29[0.30]	2425.5		.295
Number of electric stimuli [‡]	1.35[0.49]	1.26[0.57]	2445.5		.139
Seizure duration (s) [‡]	52.8[26.4]	41.6[22.4]	2142.5		.057

All variables are presented as "mean [standard deviation]" or "number (percentage)." In case of time-varying data of individual patients, the data shown is from the closest day to the initial treatment session. BMI = body mass index, ECT = electroconvulsive therapy.

* The first ECT session of each ECT series.

† Chi-squared test.

‡ Man-Whitney U test.

§ Fisher exact test; statistical significant $P < .05$ is in **bold**.

|| All psychiatric diagnoses after May 2013 were made according to DSM-5 and others according to DSM-IV-TR.

¶ Number of psychotropic medications taken during a single day before the first day of treatment.

an alternative to pentobarbital in cases of insufficient seizure duration.^[25] However, there have been some reports that etomidate is correlated with delirium after anesthesia.^[26,27] In addition, even post-ECT agitation after etomidate administration in patients who previously showed no adverse response to methohexital has been reported.^[28] In this context, our study replicated the results from the current literature. Furthermore, since there was no significant multicollinearity between all studied variables, it was suggested that the correlation between

etomidate use and post-ECT delirium was not mediated by other variables, such as prolonged seizure duration.

Meanwhile, total delivered electrical charge, which is the most frequently used summary metric for the dosage of ECT,^[29] was not predictive of post-ECT delirium in our study. This is inconsistent with Selvaraj et al,^[30] who showed that a higher stimulus dose relative to the seizure threshold could increase the severity of delirium following ECT. However, Sackeim et al^[31] mentioned that adverse effects of ECT are associated with the amount by which the electrical dosage exceeds the threshold, not the absolute electrical dosage. Therefore, further research considering the seizure threshold is needed, since we only considered absolute electrical charge, not the seizure threshold.

The current study also showed that motor seizure duration had no predictive value for post-ECT delirium, which is inconsistent with the results of a previous study by Reti et al^[9] who reported that longer seizure duration is strongly related to post-ECT delirium. While the previous study monitored seizure length by electroencephalography, the current study determined seizure duration primarily by the cuff method whereby persistence of clonic movements on the left extremity was measured. This might be a reason for inconsistencies with the previous result.

Although it is a well-known risk factor,^[32] age had no significant predictive value for post-ECT delirium. This discrepancy may be due to the difference that this study specifically focused on post-ECT delirium, unlike most other studies

Table 3
Comparisons of electrical parameters between sessions with or without post-ECT delirium.

Treatment variables	Delirium (+) N = 15	Delirium (-) N = 197	U	P-value*
Charge (mC)	211.1[78.9]	190.6[73.8]	792.5	.311
Energy (J)	32.3[13.6]	30.7[12.0]	885.0	.520
Pulse width (ms)	1.35[0.15]	1.34[0.14]	1260.0	.618
Frequency (Hz)	74.0[11.8]	70.1[16.1]	1105.5	.204
Stimulus duration (s)	1.42[0.51]	1.31[0.27]	1253.5	.498
Current (mA)	757.1[51.4]	765.2[46.9]	1187.0	.562

All continuous variables are presented as "mean [standard deviation]." ECT = electroconvulsive therapy.

* Mann-Whitney U test.

Table 4
Multiple logistic regression model for post-ECT delirium.

Variables	Odds ratio	95% Confidence interval		P-value
		Lower	Upper	
Sex				
Male	Ref.			Ref.
Female	0.498	0.182	1.361	.174
Age (yr)	0.987	0.948	1.027	.506
BMI	1.047	0.934	1.175	.430
Diagnosis				
Major depressive disorder	Ref.			Ref.
Bipolar disorder	1.104	0.295	4.136	.883
Schizophrenia	0.206	0.025	1.672	.139
Schizoaffective disorder	0.362	0.046	2.838	.333
Others	0.594	0.124	2.859	.516
Number of concomitant psychotropic	0.981	0.686	1.402	.915
Specific medication				
Lithium	1.657	0.141	19.431	.688
Clozapine	4.201	0.674	26.202	.124
Anesthetics				
Pentobarbital	Ref.			Ref.
Propofol	0.963	0.092	10.094	.975
Etomidate	12.335	3.076	49.468	<.001*
Relaxant dose (mg/kg)	0.353	0.060	2.083	.250
Number of electric stimuli	0.963	0.354	2.616	.941
Seizure duration (s)	1.013	0.993	1.033	.194

BMI=body mass index, ECT=electroconvulsive therapy.

*Statistically significant $P < .05$.

considered delirium due to general medical conditions. Our result supports the general safety of ECT even in the elderly. Because delirium can cause falls,^[15] which can be fatal in the elderly, as well as cognitive dysfunction,^[16] post-ECT delirium is an important consideration in the elderly. However, this study advocates the usage of ECT even in the elderly in terms of clinical efficacy and also safety, as recommended in a recent study.^[33]

We found no significant predictive value of whether taking lithium affected post-ECT delirium. This finding is inconsistent with those of a few studies^[34,35] that show that lithium can aggravate post-ECT delirium. Although few past studies^[36,37] suggested that the relationship between lithium use and adverse effects of ECT was insignificant or controversial, it has been generally considered that lithium aggravates post-ECT delirium in recent days.^[38] Several possible mechanisms have been suggested for lithium causing postictal delirium, including increased permeability of sodium channels^[39] and blood-brain barrier disruption.^[40] The contradictory result from this study might be due to the small sample sizes. Because we generally reduce specific medications that can complicate ECT before beginning treatment, the number of ECT sessions under concurrent use of lithium was significantly small. Thus, there were only 6 sessions with lithium out of 268 sessions, which resulted in insufficient statistical power.

This study showed no significant correlation between psychiatric diagnosis and post-ECT delirium. In a previous study by Kikuchi et al,^[17] the presence of catatonic features was determined to be a predictor of post-ECT delirium. Although we did not investigate the presence of catatonic symptoms, it could be postulated that post-ECT delirium was associated with major depressive disorder or bipolar disorder because catatonia is more likely to occur in the course of mood disorders.^[41] However, there was no significant association of mood disorders with post-ECT

delirium. Future studies with an investigation for the presence of catatonia are needed to confirm these negative findings.

This study has several strengths compared to previous studies, such as a larger number of investigated ECT sessions and the ruling out of multicollinearity problems. However, several limitations of this study should be considered. First, there is a limitation of incomplete data quality due to the retrospective study design. Thus, false-positive and false-negatives could not be entirely ruled out. We defined post-ECT delirium narrowly as irritable behavior requiring physical or chemical restraints after the treatment, resulting in significantly lower false-positive cases. Second, we did not consider the severity of post-ECT delirium. The retrospective chart review only allows us to determine the presence of post-ECT delirium. It might be possible that the factors associated with post-ECT delirium differed by the severity of post-ECT delirium. Therefore, future prospective studies using quantitative scales such as DRS-R-98^[42] are required to confirm this issue. Third, we only included concomitant medication prescribed within a day before the first session. Since most medications have half-lives of more than a day, defining concomitant medication as the medication taken during a single day could be inaccurate. More precise estimation with therapeutic drug monitoring is recommended to derive an affirmative conclusion. Moreover, although this study was based on a large number of ECT sessions, there were still only 23 cases of post-ECT delirium. Thus, the statistical power could be insufficient to detect differences between delirium-positive and delirium-negative groups. In this regard, statistically nonsignificant differences between groups should not be completely disregarded as negative findings. Lastly, there have been a few studies regarding ECT as a possible treatment option for delirium,^[43,44] which might contradict the presence of delirium as an adverse effect of ECT. However, we believe that this paradoxical phenomenon can happen due to the unknown physiologic mechanism of ECT.

In conclusion, we found the use of etomidate as the only significant variable associated with post-ECT delirium. Thus, in terms of choosing anesthetics for ECT, practitioners should take into account not only the effect on seizure threshold and treatment efficacy, but also the risk of post-ECT delirium to necessitate early discontinuation of ECT before sufficient therapeutic gain is achieved.

Author contributions

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