Psychiatry Research 273 (2019) 759–766

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Long-term clinical efficacy of maintenance electroconvulsive therapy in patients with treatment-resistant schizophrenia on clozapine

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ARTICLE INFO

Keywords:
Schizophrenia
Clozapine
Acute electroconvulsive therapy
Maintenance electroconvulsive therapy
Treatment-resistant schizophrenia

ABSTRACT

Electroconvulsive therapy (ECT) has been suggested as a treatment for augmenting the response to clozapine in patients that do not respond well to clozapine alone and maintenance ECT (M-ECT) had also been recommended to sustain improvement. This retrospective study of up to 2 years of observation was conducted to explore whether M-ECT is beneficial for long-term maintenance of the symptom remission elicited by acute ECT. Positive and Negative Syndrome Scale (PANSS) were plotted for each patient and compared using a linear mixed-effect model. A total of thirty-eight patients were followed and classified into three groups: (1) clozapine alone (CZP, $n = 15$), (2) acute ECT only (A-ECT, $n = 11$), and (3) acute ECT with M-ECT (M-ECT, $n = 12$). The mean number and interval of ECT sessions during the maintenance period in the M-ECT group were 39.0 ± 26.7 and 15.6 ± 8.4 days, respectively. The slope of the M-ECT group eventually declined, but that of the A-ECT group gradually increased back to the pre-ECT level. No persistent or serious adverse effects were observed. In conclusion, A-ECT augmented the effect of clozapine, but M-ECT was required for sustaining symptom improvement.

1. Introduction

Electroconvulsive therapy (ECT) has been shown to exert swift and safe effects on psychotic symptoms in patients with schizophrenia (Kho et al., 2004; Havaki-Kontaxaki et al., 2006; Petrides et al., 2015; Kim et al., 2018). However, the improvement attributed to ECT is short-lived, with rapid psychotic relapse occurring following abrupt cessation of acute ECT (Lisanby et al., 2008; Kellner et al., 2016). The 1-year relapse rate was reported at 42.7~63.6% in patients with schizophrenia, with most recurrences occurring within the first 6 months post-treatment (Suzuki et al., 2004; Shibasaki et al., 2015; Ward et al., 2018). Since there is evidence that the administration of additional ECT sessions after acute ECT is successful in sustaining mood improvement or preventing relapse of mood disorders (Trevino et al., 2010; Sienaert and Peuskens, 2006; Kellner et al., 2016; Santos Pina et al., 2016), maintenance electroconvulsive therapy (M-ECT) for patients with treatment-resistant schizophrenia (TRS) is recommended (Weiner and Reti, 2017).

Although clozapine is the recommended drug for treating TRS, it fails to elicit a response in 40~70% of patients (Kane et al., 1988; Meltzer et al., 1989; Muscatello et al., 2014). A range of adjunctive strategies administered in conjunction with clozapine have been implemented with modest or inconclusive results, except for ECT augmentation (Kerwin and Bplonna 2005; Remington et al., 2005; Porcelli et al., 2012; Galling et al., 2016). The combined administration of ECT and clozapine has been shown to be beneficial (Ward et al., 2018; Grover et al., 2018) based on a reported response rate of 47.4~72.7%, the highest response rate of the various augmentation options for TRS patients (Porcelli et al., 2012; Miyamoto et al., 2014; Petrides et al., 2015; Lally et al., 2016; Kim et al., 2017, 2018; Kaster et al., 2017). In contrast, Melzer-Ribeiro et al. (2017) recently reported no significant difference between real and sham ECT as an augmentation strategy for patients with a partial response to clozapine. Thus, further placebo-controlled studies with larger samples are warranted (Grover et al., 2018).

Studies of the concomitant use of antipsychotic drugs and M-ECT have reported that it is superior to drug-only treatment for preventing relapse and improving cognitive function (Ward et al., 2018). According to the Prolonging Remission in the Depressed Elderly (PRIDE) study (Kellner et al., 2016), after tapering off during 6 months of post-

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https://doi.org/10.1016/j.psychres.2019.02.008
Received 29 December 2018; Received in revised form 4 February 2019; Accepted 4 February 2019
Available online 05 February 2019
0165-1781/

treatment ECT following the initial acute ECT course, M-ECT should be performed regularly at least once every 2 months to prevent symptom recurrence (Sackeim et al., 2001; Iancu et al., 2015; Santos Pina et al., 2016). However, no data are available regarding the persistence of these effects following the discontinuation of ECT or describing how long combined treatment with M-ECT and clozapine should be continued (Moeller et al., 2017; Grover et al., 2018). Recently, Braga et al. (2017) reported that the administration of continuation ECT to patients with clozapine-resistant schizophrenia for up to 24 weeks following a randomized controlled trial (RCT) (Petrides et al., 2015) was not associated with clinical worsening of psychotic symptoms or any additional side effects. However, further studies on the combined effects of M-ECT and clozapine in TRS patients, as well as additional reports and/or guidelines for the administration of M-ECT aimed at sustaining the clinical improvements induced by acute ECT in TRS patients, are required.

Thus, the present retrospective observational study, which extended previous studies from our research group that focused on acute ECT in patients with schizophrenia on clozapine (Kim et al., 2017; 2018), assessed whether M-ECT would be beneficial for the long-term maintenance of the symptom remission elicited by acute ECT. Because the measurements were not consistent throughout the observation period, patients with schizophrenia who were treated with clozapine were classified into three groups according to whether acute and/or M-ECT sessions were performed in order to track the individual and group trajectories of psychotic symptoms for 2 years using a linear mixed-effect (LME) model.

2. Methods

2.1. Subjects

Patients aged 20 to 65 years who had been diagnosed with schizophrenia from March 2012 to June 2018, in accordance with the DSM-IV-TR criteria and treated continuously with clozapine were identified in the electronic medical records (EMR) of the ECT center at Dongguk University International Hospital. Patients who had been treated with clozapine for at least 12 weeks, and who simultaneously maintained plasma clozapine levels of greater than 350 ng/ml during the observation period, were selected to rule out those with pseudo-resistance to clozapine. Patients who had comorbid physical illnesses, substance addiction, intellectual quotients under 80, or inadequate clinical information, were excluded, as were those who had been assessed for psychotic symptoms and plasma clozapine levels less than twice. Patients who underwent acute ECT and subsequently received ECT regularly for more than 6 months (up to 2 years) were classified as the M-ECT group. Those who had undergone no additional ECT sessions after acute ECT or who ceased ECT within 6 months of the tapering period were classified as the A-ECT group. Finally, patients who were treated with clozapine alone and who did not undergo ECT during the same observation period were selected from the EMR using the same inclusion criteria and classified as the CZP group for reference purposes.

2.2. Procedure

Demographic and clinical characteristics, including ECT history and scores on the Positive and Negative Syndrome Scale (PANSS), were collected for up to 2 years during the observation period. All data regarding patients' clozapine and norclozapine plasma levels and daily clozapine doses on sampling days were also collected.

The ECT sessions were performed on individuals with inpatient status throughout the entire acute ECT course. For the M-ECT sessions, patients were hospitalized the day prior to ECT and discharged in the afternoon, after completing ECT in the morning. An acute ECT course was defined as two or three sessions per week with no more than 20 sessions that ended with the cessation of sessions or with tapering to once a week. The effects of acute ECT were evaluated according to score changes and the reduction of the mean PANSS total score, both before and after acute ECT. However, during the post-treatment follow-up period, the interval and frequency of clinical measurements were irregular and inconsistent for each patient. All collected data were plotted to obtain mean trajectories using the locally weighted scatterplot smoothing (LOWESS) method, individually for all three groups to compare their long-term courses.

Any reported adverse events and cognitive effects that may have been caused by ECT were collected from patients' progress notes and nursing records during the observation period. Data were also gathered from the Mini-Mental State Examination, the Korean version of the Consortium (MMSE-KC), and the Korean Version of the Montreal Cognitive Assessment (MoCA-K). This study protocol was approved by the Institutional Review Board of Dongguk University International Hospital.

2.3. ECT sessions

The ECT sessions were conducted using bilateral electrode placement and brief pulse stimuli (800 mA; 1 ms) with a MECTA spECTrum 5000Q system (MECTA Corp, Lake Oswego, OR, USA). An adequate seizure duration was deemed to be at least 25–30 s as monitored by an electroencephalogram (EEG) and/or at least 20 s as assessed by an optical motion sensor (OMS). Seizure quality was evaluated based on polyspike activity patterns, three spikes and wave activity, and postictal suppression (Rattehalli et al., 2009). After determining the initial seizure threshold (IST) during the first session, an electric charge 2.5-fold greater than the IST was administered from the following sessions. During the M-ECT period, the ECT parameters in each M-ECT session, including electric charge, session interval, seizure duration, psychotropic drug use, and psychotic symptoms, were monitored to determine the appropriate dose of electricity and the interval before the next session. The anesthesia and muscle relaxation procedures are described in detail in a previous report from our research group (Kim et al., 2017).

2.4. Statistical analysis

The demographic and clinical characteristics of the three groups were compared using one-way ANOVA for continuous variables and the chi-squared test for categorical variables (Tables 1 and 2). Changes in the mean PANSS total scores attributed to the effects of acute ECT were analyzed with the paired *t* test (Table 2). Since this was a retrospective study based on real-world clinical practice, the frequency and intervals of measurements for the PANSS and clozapine plasma levels were irregular and inconsistent among the participants. Therefore, neither pointwise comparisons between groups nor repeated-measures ANOVA tests were feasible. Instead, a LME model was used to compensate for this irregularity. In accordance with the LME framework, the longitudinal trajectories of the mean PANSS total scores of the three patient groups were approximated to linear curves and compared. From the base model with the simplest terms, a series of incrementally more complex models were built and compared. From this stepwise regression, the most perfunctory, albeit significant model, was developed and interpreted. The obtained *p*-values were adjusted for multiple comparison using the method developed by Holm (1979). Statistical significance was set at a *p*-value of less than 0.05. All statistical analyses were performed using SPSS for Windows software (ver. 23.0; SPSS, Inc., Chicago, IL, USA) and the open-source statistical program R version 3.5. (R Core Team , 2016).

3. Results

3.1. Demographic and clinical characteristics

Sixty-six patients with TRS who used clozapine were identified in

Table 1
Demographic characteristics in patients with schizophrenia using clozapine.

	Acute ECT + CZP				
	Total	A-ECT	M-ECT	CZP	*p*-value[†]
Number of participants	23	11	12	15	
Sex					0.330
Male	11 (47.8)	7 (63.6)	4 (33.3)	8 (53.3)	
Female	12 (52.2)	4 (36.4)	8 (66.7)	7 (46.7)	
Age (yrs.)	37.8 ± 10.7	38.5 ± 14.0	37.2 ± 7.2	33.6 ± 8.4	0.430
Age of onset	20.2 ± 7.1	20.6 ± 8.9	20.0 ± 5.4	18.6 ± 6.6	0.749
Male	17.8 ± 5.2	17.9 ± 5.6	17.6 ± 5.3	18.2 ± 6.0	
Female	22.5 ± 8.0	25.3 ± 12.4	21.1 ± 5.4	19.0 ± 7.7	
Duration of Illness (yrs.)	17.6 ± 8.6	18.0 ± 9.0	17.2 ± 8.5	15.1 ± 6.7	0.624
Male	19.6 ± 10.0	18.7 ± 10.8	21.1 ± 9.9	14.6 ± 6.3	
Female	15.8 ± 6.9	16.8 ± 5.7	15.3 ± 7.7	15.6 ± 7.6	
Duration of clozapine treatment (yrs.)	6.4 ± 6.1	8.0 ± 6.9	4.9 ± 5.1	7.1 ± 4.7	0.389
Education (yrs.)	13.5 ± 2.2	13.5 ± 2.0	13.6 ± 2.5	14.5 ± 2.1	0.397
Family history					0.786
Absent	10 (43.5)	4 (36.4)	6 (50.0)	6 (40.0)	
Present	13 (56.5)	7 (63.6)	6 (50.0)	9 (60.0)	

[†] *p*-values were obtained using one-way ANOVA for continuous variables and chi-squared test for categorical variables. Continuous variables are summarized as means ± standard deviation and categorical variables as frequencies (percentage). ECT, electroconvulsive therapy; CZP, clozapine; A-ECT; acute ECT without additional ECT, M-ECT, maintenance electroconvulsive therapy.

the EMR during the 6-year observation period (Fig. 1). Of these patients, 25 did not have available baseline PANSS data or had a significant comorbid disorder and were excluded from the study. Most patients for whom there were no baseline PANSS data were too excitable, irritable, or severely catatonic to allow for proper assessments. Thus, 41 patients were defined as treatment resistant because they showed at least moderately severe symptoms and a lack of symptom reduction following the administration of several antipsychotics within a therapeutic dose range for at least 6 weeks (Howes et al., 2017). Of these 41 patients, 26 received ECT after being referred to the ECT center, whereas the remaining 15 patients did not undergo ECT. Three of the 26 patients who completed acute ECT were excluded from the study analyses because they were lost to follow-up. Of the 23 patients who completed the acute ECT course and were followed thereafter, 12 were classified into the M-ECT group, and the other 11 were classified into the A-ECT group. The 15 patients who did not undergo ECT were classified to the CZP group. The gender distributions of the A-ECT and M-ECT groups appeared to differ (Table 1), but this difference was not statistically significant. Similarly, although males had an earlier age of onset (17.8 ± 5.22 years) than females (22.5 ± 8.03 years), this difference was not statistically significant. In the A-ECT group, the most common reason for not receiving M-ECT was that the patient refused further ECT after acute ECT. The age of onset and duration of illness did not differ among the three groups. The mean durations of clozapine treatment in the ECT group and the CZP group were 6.4 ± 6.1 and 7.1 ± 4.7 years, respectively. For the 23 patients who underwent ECT, the most common indications for ECT were persistent psychotic symptoms and moderate functional impairments as determined by the charged psychiatrists. No significant differences in demographic characteristics were observed between the 38 patients included in the

Table 2
Clinical information associated with ECT in patients with clozapine-treated schizophrenia.

	Acute ECT + CZP				
	Total (n = 23)	A-ECT (n = 11)	M-ECT (n = 12)	CZP (n = 15)	*p*-value[†]
Acute ECT					
duration (d)	45.4 ± 17.3	42.2 ± 19.4	48.3 ± 15.5		0.408
number of sessions	15.0 ± 4.6	14.3 ± 4.6	15.8 ± 4.6		0.452
M-ECT or observation					
duration (d)	566.0 ± 229.4	629.5 ± 210.3	507.8 ± 239.5	623.1 ± 187.1	0.290
number of sessions	24.0 ± 25.8	7.6 ± 10.7	39.0 ± 26.7		0.002
mean interval (d)	24.7 ± 18.8	46.6 ± 19.2	15.6 ± 8.4		0.000
PANSS total score					
baseline	102.0 ± 15.9***	101.9 ± 15.2**	102.2 ± 17.3***	82.3 ± 17.2	0.004
after acute ECT	81.2 ± 14.4	83.4 ± 16.9	79.3 ± 12.1		0.507
reduction rate (%)	19.6 ± 13.4	17.8 ± 13.4	21.1 ± 13.7		0.567
Chlorpromazine-equivalent (mg)	760.3 ± 293.5	678.2 ± 275.5	835.5 ± 264.6	737.6 ± 242.6	0.380
Daily dose of clozapine (mg)					
baseline	288.0 ± 102.5[‡]	272.7 ± 108.7	302.1 ± 99.1	268.3 ± 61.6	0.508
after acute ECT	252.2 ± 83.9	234.1 ± 87.5	268.8 ± 80.6		0.334
Plasma clozapine level (ng/ml)					
baseline	561.2 ± 278.4	530.3 ± 252.7	592.1 ± 312.5	587.4 ± 191.9	0.757
after acute ECT	453.2 ± 221.9	445.7 ± 277.3	459.9 ± 173.2		0.894

[†] *p*-values were obtained using Student's *t*-test to compare two ECT groups (M-ECT and A-ECT) and one-way ANOVA to compare three groups.
** $p < 0.01$.
*** $p < 0.001$, compared between baseline and after acute ECT by paired *t*-test.
[‡] compared between baseline and after acute ECT, t = -2.198, p = 0.039 by paired *t*-test. Variables are summarized as means ± standard deviation. ECT, electroconvulsive therapy; CZP, clozapine; A-ECT, acute ECT without maintenance ECT; M-ECT, maintenance electroconvulsive therapy; PANSS, Positive and Negative Syndrome Scale.

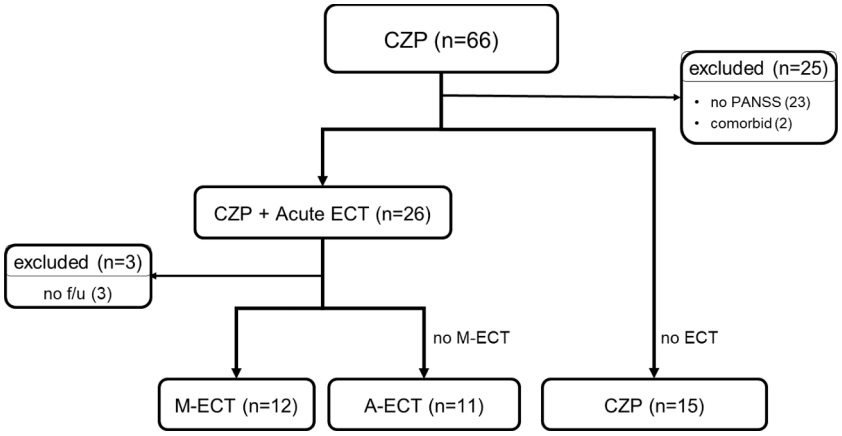

Fig. 1. Flowchart of patients with schizophrenia using clozapine. CZP, clozapine; PANSS, Positive and Negative Syndrome Scale; ECT, electroconvulsive therapy; A-ECT; acute ECT without maintenance ECT, M-ECT, maintenance ECT.

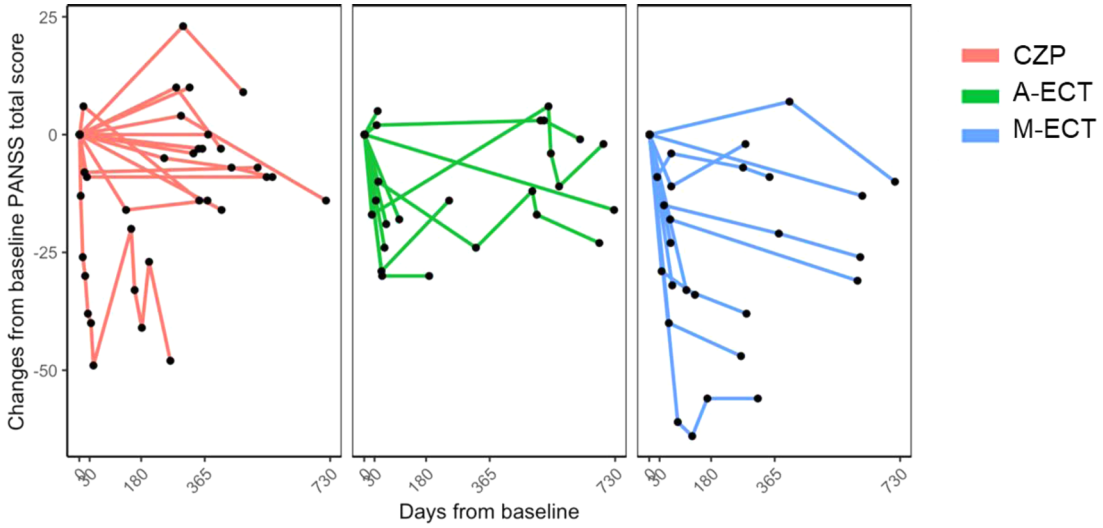

Fig. 2. Individual trajectories of changes in the baseline PANSS total score in the three groups (CZP, A-ECT and M-ECT) of patients with schizophrenia on clozapine
PANSS, Positive and Negative Syndrome Scale; ECT, electroconvulsive therapy; CZP, clozapine; A-ECT, acute ECT without maintenance ECT; M-ECT, maintenance ECT.

analyses and the 28 patients excluded from them or among the three groups in the analysis.

A comparison of the mean PANSS total scores at baseline among the three patient groups revealed that this score was significantly lower in the CZP group (82.3 ± 17.2) than in the A-ECT (101.9 ± 15.2) and M-ECT (102.2 ± 17.3) groups ($p = 0.004$ by one-way ANOVA; Table 2). The daily dose of clozapine and the chlorpromazine-equivalent dose of all antipsychotics did not differ among the three patient groups.

3.2. Effects of acute ECT

There were no significant differences in mean PANSS total score, chlorpromazine-equivalent dose, or daily dose of clozapine between the A-ECT and M-ECT groups (Table 2). Of the 23 patients who completed acute ECT, the mean duration and number of acute ECT sessions were 45.4 ± 17.3 days and 15.0 ± 4.6, respectively. The mean PANSS total score was significantly reduced from 102.0 ± 15.9 at baseline to 81.2 ± 14.4 after acute ECT ($t = -6.203$, $p < 0.001$ by paired t-test). The mean reduction in the PANSS total score was 19.6 ± 13.4%, and 47.8% of the patients (i.e., 11 of 23) exhibited clinical remission based on a 20% reduction in PANSS total score. The mean daily clozapine dose of these 23 patients significantly decreased from 288.0 ± 102.5 at baseline to 252.2 ± 83.9 following acute ECT ($t = -2.198$, $p = 0.039$ by paired t test), but no significant change was detected in the mean plasma clozapine level.

3.3. Effects of M-ECT

The observation periods for the A-ECT and M-ECT groups were 629.5 ± 210.3 and 507.8 ± 239.5 days, respectively (Table 2). The mean numbers of sessions for the A-ECT and M- ECT groups were 7.6 ± 10.7 and 39.0 ± 26.7, respectively ($p = 0.002$ by Student's t-test). In the A-ECT group, five patients underwent periodic ECT sessions during the first 6 months of the tapering period after acute ECT, and the remaining six patients received no additional ECT after completing acute ECT. The mean interval between ECT sessions was 15.6 ± 8.4 days in the M-ECT group.

A visual inspection of the individual and group trajectories of the mean PANSS total scores in the three groups revealed several tendencies (Figs. 2 and 3-a). The trajectories in the A-ECT and M-ECT groups steeply declined during the acute ECT course, but this improvement was followed by gradual returns to previous levels; the return in the A-ECT group was more marked. Meanwhile, the CZP group showed some exacerbation of symptoms during the earlier part of the observation period, but the overall pattern was of a gradual and steady recovery.

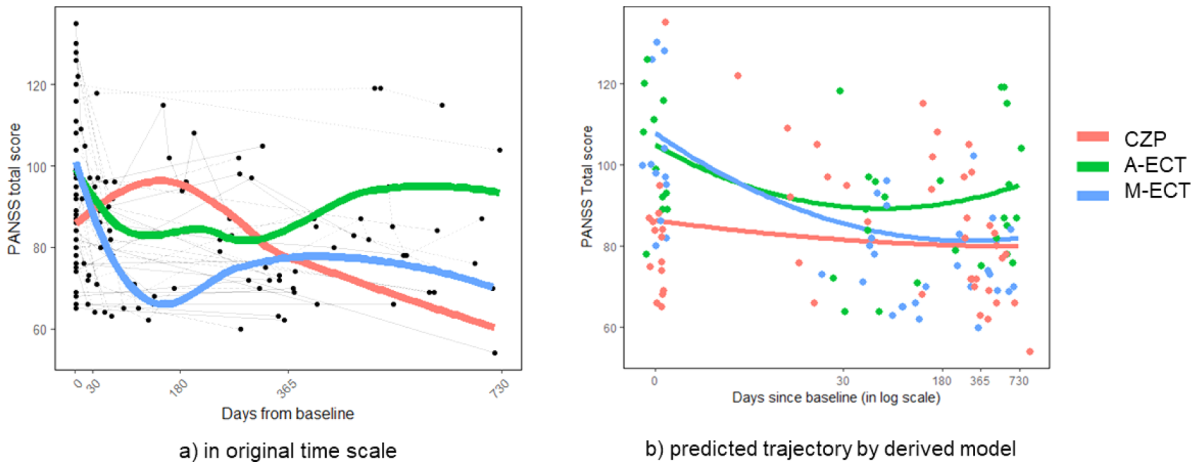

Fig. 3. Individual and hypothetical trajectories of PANSS total scores in the three groups (CZP, A-ECT and M-ECT) of patients with schizophrenia on clozapine (a) Raw data in original time scale. (b) Predicted trajectory according to the final linear mixed-effect model in log-transformed time scale. The final model was obtained through a series of hierarchical stepwise regression procedures. The plotted curves were parabolic because the final model contained a second-degree polynomial term for time. The colored lines represent the locally weighted scatterplot smoothing (LOESS) smoothed mean lines for each group. PANSS, Positive and Negative Syndrome Scale; ECT, electroconvulsive therapy; CZP, clozapine; A-ECT, acute ECT without maintenance ECT; M-ECT, maintenance ECT.

Although the mean PANSS scores at baseline did not differ among the three groups, the mean score of the A-ECT group was much higher than those of the other groups at the end of the observation period (Table 2).

Prior to formally testing the above tendencies, an appropriate transformation of the time axis was necessary to compensate for the skewed distribution of measurement timepoints and the curvilinear relationship between time and PANSS total score. For this purpose, a preparatory analysis was performed to determine the best transformation strategy. A series of models with increasingly complex transformations was constructed and compared to less complex ones using a likelihood-ratio test (Table 3). Based on this procedure, it emerged that a second-degree polynomial regression with a log-transformed time scale using ECT type as a covariate was a suitable modeling strategy.

A subsequent analysis focused on testing the significance of the interaction between the main effects of time and ECT type (Table 4). Similar to previous analyses, two nested models were constructed: one that ignored the interaction and another that included the interaction. The results showed that the ECT type × time interaction was statistically significant (likelihood ratio test: Chi-squared = 14.1, df = 4, $p < 0.01$). A post hoc analysis of the interaction effect verified that the pairwise difference between the linear slopes of the CZP and M-ECT groups was significant even after *p*-value adjustment (Wald test with Kenward-Roger correction: *z* value = 3.53, $p < 0.001$ before adjustment and $p = 0.001$ after adjustment; Table 5). The pairwise difference between the slopes of the A-ECT and M-ECT groups was also significant after *p* value adjustment (Wald test with Kenward-Roger correction: z

Table 3
Summary of hierarchical stepwise regression analysis for predicting PANSS total score with time (days since baseline) and the ECT type as the main predictors (CZP, A-ECT and M-ECT).

Model description	Model 1 Baseline model (random intercept effect)	Model 2 Model 1 + log transformation of time	Model 3 Model 2 + second degree polynomial regression	Model 4 Model 3 + random slope effect
Model coefficients				
Type: A-ECT	13.77 ± 5.15†**	13.83 ± 5.17**	14.79 ± 5.23**	14.02 ± 5.09*
Type: M-ECT	5.40 ± 5.00	6.29 ± 5.02	7.48 ± 5.08	5.44 ± 4.91
Days since baseline (untransformed)	-0.02 ± 0.01***			
Days since baseline (log-untransformed)		-5.59 ± 0.89***		
Log(Days): first degree polynomial			-66.48 ± 10.32***	-68.82 ± 13.13***
Log(Days): second degree polynomial			36.69 ± 11.50**	29.84 ± 9.66**
Model summary				
Number of observations	122	122	122	122
Number of participants	38	38	38	38
AIC	1010.47	989.01	981.51	974.68
Log likelihood	-499.23	-488.51	-483.76	-478.34
chi-square		21.46	9.5	10.84
Degrees of freedom		0	1	2
p-value of improvement over previous model		<0.001	0.002	0.004

A series of models of increasing complexity were constructed and compared with less complex models using the likelihood ratio test. The model demonstrating the most significant advantage over less complex models and the lowest Akaike information criterion (AIC) was selected as the best model (= model 4). PANSS, Positive and Negative Syndrome Scale; ECT, electroconvulsive therapy; CZP, clozapine; A-ECT, acute ECT without maintenance ECT; M-ECT, maintenance electroconvulsive therapy.

† unstandardized model coefficients ± standard error. Note: *p*-values for model coefficients were calculated using the Wald test with Kenward-Roger correction of degree of freedom.

*** $p < 0.001$.

** $p < 0.01$.

* $p < 0.05$.

Table 4
Comparison between a model based on the independent effects of ECT type and time (without interaction) and a model based on the interaction between the two effects.

Model description	Model 1 Model with independent effects of ECT type and time	Model 2 Model allowing interaction between ECT type and time
Model coefficients		
Sex	-9.03 ± 4.32†,*	-8.62 ± 4.24*
Type: A-ECT	12.45 ± 5.17*	13.34 ± 5.08**
Type: M-ECT	6.88 ± 5.29	8.28 ± 4.98
Log(Days): 1st degree	-68.73 ± 13.23***	-29.84 ± 18.07
Log(Days): 2nd degree	29.49 ± 9.66**	5.62 ± 17.89
A-ECT x Log(Days):1st degree		-28.94 ± 20.06
M-ECT x Log(Days):1st degree		-95.15 ± 27.99***
A-ECT x Log(Days): 2nd degree		33.82 ± 23.66
M-ECT x Log(Days): 2nd degree		29.26 ± 24.57
Model summary		
Number of observations	122	122
Number of participants	38	38
AIC	941.35	903.01
Log likelihood	-460.67	-437.51
chi-square		14.12
Degree of freedom		4
p-value of model improvement		<0.01

Both models were compared with the likelihood ratio test and the latter model demonstrated significant improvement ($p = 0.007$). This result implied that the time-dependent trajectory of PANSS score change may differ among the three groups (CZP, M-ECT, and A-ECT). ECT, electroconvulsive therapy; CZP, clozapine; A-ECT, acute ECT without maintenance ECT; M-ECT, maintenance electroconvulsive therapy; AIC, Akaike information criterion.

† unstandardized model coefficients ± standard error. Note: *p*-values for model coefficients were calculated using the Wald test with Kenward-Roger correction of degree of freedom.

*** $p < 0.001$.

** $p < 0.01$.

* $p < 0.05$.

value = 2.12, $p = 0.034$ before adjustment and $p = 0.067$ after adjustment).

The model-based prediction of the hypothetical trajectory of the PANSS total score is presented in Fig. 3-b. Since the final models included second-degree polynomials of time, the hypothetical trajectories were quadratic curves with one inflection point. The trajectories of the CZP and A-ECT groups appeared to be nearly parallel, whereas the trajectory of the M-ECT group was clearly distinguishable from the other slopes. The effects of acute ECT were apparent in both the A-ECT and M-ECT groups, but the trajectory of the A-ECT group indicated that symptoms worsened immediately after the cessation of acute ECT. In contrast, this exacerbation of symptoms was not observed in the trajectory of the M-ECT group.

3.4. Adverse events

Some patients suffered mild postictal agitation, headaches, or nausea that were successfully managed with conventional measures, analgesics, and/or benzodiazepines within a few minutes to hours according to the progress notes and nursing records of each patient. Although cognitive function was not evaluated sufficiently, systematically, or regularly using the standard MMSE-KC and MOCA-K assessment tools, the group trajectories of the cognitive scale scores, which were obtained in a manner similar to that of the group trajectories of the PANSS total scores, exhibited no changes over the 2-year observation period. No persistent or serious adverse effects, such as memory disturbance, were recorded in the EMR.

4. Discussion

This retrospective observational study expanded on our previous reports (Kim et al., 2017; 2018) to again demonstrate that an acute course of ECT effectively augmented clozapine treatment in TRS patients. Additionally, the present study showed that M-ECT maintained acute ECT-induced improvements in psychotic symptoms, which could be reduced to a level observed in patients using clozapine alone during a long-term observation period. However, the psychotic symptoms gradually deteriorated to pre-ECT levels if additional ECT sessions were not conducted. Furthermore, the administration of acute ECT significantly lowered the daily dose of clozapine, but plasma clozapine levels were maintained above at least 350 ng/ml throughout the entire observation period. The mean PANSS total score at baseline in the CZP group, including patients who were not clinically indicated for ECT, was significantly lower than those of the ECT groups. Overall, the present findings indicate that patients with severe and persistent psychotic symptoms despite clozapine treatment can be effectively treated with ECT. No specific record of adverse events related to ECT or general anesthesia was present in this study.

The acute ECT alleviated severe psychotic symptoms swiftly and safely in TRS patients who were using clozapine. This indicates that ECT possesses additional, or different, therapeutic properties to those of clozapine, although the patients' plasma clozapine levels were within the therapeutic range of 350 ~ 600 ng/ml. The mean reduction of PANSS total scores in the ECT group was 19.6 ± 13.4%, that is, identical to that reported in our previous studies (Kim et al., 2017; 2018). The responder rate in the acute ECT group was 47.8% (i.e., 11 of 23 patients), which was within the range of 47.4 to 72.7% reported previously for combined ECT and clozapine therapy (Havaki-Kontaxaki et al., 2006; Lally et al., 2016). It is noteworthy that the mean daily clozapine dose in the ECT groups was also significantly reduced, suggesting that the occurrence of adverse events associated with clozapine use may be reduced by maintaining therapeutic plasma clozapine levels.

The most notable finding from the comparison of long-term trajectories of psychotic symptoms among the three groups was that the M-

Table 5
Post-hoc analysis of the interactions between the ECT type and time.

Pairwise comparison	Estimated Slope difference	Standard error	*z*-value	*p*-value	
				before adjustment	after adjustment†
CZP vs. A-ECT	2.65	2.36	1.12	0.261	0.261
CZP vs. M-ECT	8.00	2.27	3.53	<0.001	0.001
A-ECT vs. M-ECT	5.35	2.54	2.12	0.034	0.067

† *p*-value adjustment for multiple comparisons was carried according to the method described by Holm. This analysis aimed to find, in which pair of different ECT types, the slopes of the PANSS score changes differ from each other. The estimated slope difference represented the pairwise difference in the linear slopes of PANSS score change. ECT, electroconvulsive therapy; CZP, clozapine; A-ECT, acute ECT without maintenance ECT; M-ECT, maintenance electroconvulsive therapy.

ECT group significantly differed from the A-ECT and CZP groups. More specifically, the changes in the psychotic symptoms of the M-ECT group were continuously maintained, and these patients exhibited improvements compared to those observed in the A-ECT group, even decreasing to the level of the symptoms in the CZP group at the end of the 2-year observation period. Taken together, the present results regarding the long-term trajectory of psychotic symptoms demonstrated that M-ECT efficiently maintained the improvement in psychotic symptoms and eventually allowed patients to attain the same symptom levels as clinically stable patients using clozapine (i.e., the CZP group). However, patients who did not receive M-ECT gradually regressed to their pre-ECT psychotic states. This may indicate the administration of M-ECT to patients with severe psychotic symptoms that are resistant to clozapine.

The mean interval between sessions in the M-ECT group was 15.6 ± 8.4 days; this group exhibited at least maintenance of symptom improvements and showed no adverse cognitive effects. A systemic review of M-ECT in TRS patients indicated that most treatment regimens began with weekly sessions that gradually tapered to biweekly or monthly sessions (Ward et al., 2018). Stiebel (1995) recommended more frequent M-ECT for patients with thought disorders (every 1–2 weeks) than for those with mood disorders (every 3–4 weeks). Increased intervals between M-ECT sessions may allow the brain sufficient time for recovery (Iancu et al., 2015) from the temporary cognitive decline associated with repeated sessions. Further study is required to determine the optimal interval between sessions for the maintenance of improved mental state and the minimization of adverse cognitive effects during M-ECT.

Despite increasing evidence that M-ECT helps to prevent relapse and recurrence in TRS patients (Chanpattana, 1999; Koen et al., 2008; Ward et al., 2018), reports of the concomitant administration of M-ECT with clozapine are scarce, and the results of RCTs are not accessible (Bannour et al., 2014; Moeller et al., 2017). Most current reports are based on retrospective observations. Iancu et al. (2015) reported 20 patients with schizophrenia or schizoaffective disorder who received a mean of 91.3 ECT sessions, with a mean interval of 2.5 weeks between sessions; the patients exhibited significant improvements in Global Assessment of Functioning scores and a reduction of Clinical Global Impression-Severity scores. Moeller et al. (2017) reported a patient with paranoid schizophrenia who had been diagnosed with TRS due to lack of response to antipsychotics, including clozapine, and was administered 24 ECT sessions over a 1-year period. The severity of the patient's symptoms declined significantly, as reflected in various scales, including the Psychotic Symptom Rating Scales (PSYRATS), remained stable with neuroleptic treatment, and the patient required no additional hospitalization during their M-ECT course. Retrospective analyses of M-ECT that included mirror analyses before and after treatment revealed a reduction in hospitalization rate (Shelef et al., 2015; Cosculluela et al., 2017; Choi et al., 2018), and Desarkar et al. (2018) reported the successful use of concomitant (acute and long-term [>18 months]) ECT and clozapine treatment of a patient with TRS, catatonia, and intellectual disability. A prospective RCT of M-ECT administered in combination with clozapine could corroborate retrospective findings concerning the efficacy of M-ECT.

This observational study has several limitations. Firstly, retrospective analyses are inevitably associated with problems such as sampling bias and data insufficiency. However, this study was the first of its kind to explore the effects of M-ECT on clozapine-treated patients over a 2-year period. Secondly, the numbers of patients in each of the three groups were small, and the frequency of and intervals between the clinical measurements were irregular and inconsistent. Despite these limitations, both acute ECT and M-ECT were associated with apparent therapeutic effects in the context of clozapine augmentation. Thirdly, the effects of concomitant antipsychotics or other medications, including drugs used to manage the side effects of clozapine, were not considered in the present study, but the chlorpromazine-equivalent dosages did not influence the effects of clozapine. Fourthly, due to the retrospective observational design used in the present study, the patient grouping was not randomized, and ECT could not be compared to a placebo effect, such as sham ECT. As an alternative, a patient group treated with clozapine alone was included as a reference group, even though it was not precisely a control group. Nonetheless, ECT induced a marked reduction in psychotic symptoms, at least in comparison with the level of patients treated with clozapine alone. It is important to note that there might be a subgroup of clozapine-treated patients who would require augmentation strategies concomitant with clozapine treatment, but the present study did not identify the predicating factors. Fifthly, the evaluations of adverse effects and of memory and cognitive functions using standardized scales in the present study were inconsistent and were not performed on a regular basis; hence, they could not be analyzed statistically. However, the progress notes and nursing records in the EMR did not reveal any outstanding problems other than some mild adverse effects immediately after the ECT sessions that were mostly relieved with conventional interventions and medications. One of the primary issues of the present study concerned the definition of M-ECT. Thus, more research is needed regarding the efficacy of M-ECT when started after acute ECT and regarding the optimal administration intervals and duration.

In conclusion, this retrospective observational study demonstrated the benefits of both acute ECT and M-ECT in TRS patients using clozapine. Earlier improvements attributed to acute ECT were similar to the level of symptoms associated with clozapine responsiveness and were well maintained by M-ECT until later in the course of treatment. On the other hand, there was a trend toward regression to pre-ECT levels of psychopathology in patients who did not undergo M-ECT. A prospective study investigating the effects of M-ECT on TRS patients using clozapine is needed.

Conflicts of interest and source of funding

Dr. Kim YS received grants, research support and honoraria from Janssen, Otsuka, and Dainippon Sumitomo. Dr. Chung IW received research and educational grants from Janssen, Otsuka, Hanmi, Mecta, and Hwanin. Dr. Youn T received research and educational grants from Otsuka, Eisai, Hanmi, Lundbeck, and Mecta. The others have nothing to declare.

The overall research design, data acquisition, statistical analyses, and interpretation of the study results were conducted without input from any pharmaceutical company and institution.

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