Brief Report
https://doi.org/10.9758/cpn.2018.16.3.339 pISSN 1738-1088 / eISSN 2093-4327
Clinical Psychopharmacology and Neuroscience 2018;16(3):339-342

The Effects of Continuation-Maintenance Electroconvulsive Therapy on Reducing Hospital Re-Admissions in Patients with Treatment-Resistant Schizophrenia

Kyung Mook Choi[1,*], Soo-Hee Choi[1,2,*], Jung Kyung Hong[1], Mi Hyun Lee[1], Joon Hyung Jung[1], Sang Hoon Oh[1], Dong Chung Jung[1], Sung Nyun Kim[1]

[1]Department of Neuropsychiatry, Seoul National University Hospital, [2]Department of Psychiatry and Institute of Human Behavioral Sciences, Seoul National University College of Medicine, Seoul, Korea

Objective: Continuation-maintenance electroconvulsive therapy (C/M-ECT) is used to prevent relapse or recurrence in patients with severe mental illnesses. We aimed to investigate the effect of C/M-ECT on reducing hospital re-admissions in patients with treatment-resistant schizophrenia.
Methods: We applied a mirror-image design by retrospectively examining re-hospitalization rates of 18 patients with schizophrenia spectrum disorders. We compared the numbers of psychiatric admissions during the actual period over which C/M-ECT was administered with the same period prior to the beginning of C/M-ECT.
Results: The number of psychiatric admissions was reduced significantly during C/M-ECT (0.33±0.77) compared with that of the same period prior to C/M-ECT (2.67±1.33) (Wilcoxon signed rank $Z=-3.663$; $p<0.001$).
Conclusion: This finding shows that C/M-ECT augmentation could successfully reduce the re-hospitalization rates in patients with treatment-resistant schizophrenia.

KEY WORDS: Electroconvulsive therapy; Schizophrenia; Treatment-resistance; Recurrence; Hospitalization.

INTRODUCTION

Schizophrenia is a chronic disabling psychiatric illness that as many as 20-30% of patients do not respond to antipsychotic medications.[1,2] Patients who do not respond to two or more adequate treatment of antipsychotics are regarded to have treatment-resistant schizophrenia (TRS).[3] Clozapine is the treatment of choice proven to be effective in these treatment-resistant patients, which symptoms are still resistant to clozapine in approximately 45-70% of patients.[4] Various pharmacological augmentation strategies for clozapine-resistant patients have been explored with no robust evidence.[1]

Electroconvulsive therapy (ECT) is one key of various augmentation strategies for TRS patients since 1990s,[5,6] and previous studies consistently demonstrated the initial effect of ECT augmentation.[4] A recent systematic review and meta-analysis included data of total 192 TRS patients from previous studies, and reported the response rate of ECT-clozapine combination to be 54-66%.[1] In addition, a randomized controlled study showed that the augmentation of clozapine with ECT is effective and is a safe treatment option in TRS patients who do not respond to clozapine.[4] The study showed that 50% of patients on clozapine-ECT combinations responded to the treatment during single-blind 8-week period.[4] However, there is paucity of evidence on the long-term effect of ECT augmentation for TRS patients. One exception is the study of Lally *et al.*,[1] which reviewed the long-term follow-up data for 62 TRS patients with clozapine-ECT combination and identified a high relapse rate of 32% in the weeks to months after ECT discontinuation. Therefore, further evidence is needed for the long-term treatment of TRS pa-

Received: May 25, 2017 / **Revised:** May 26, 2017
Accepted: May 29, 2017
Address for correspondence: Sung Nyun Kim, MD, PhD
Department of Neuropsychiatry, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-4930, Fax: +82-2-744-7241
E-mail: snkim@snu.ac.kr
ORCID: https://orcid.org/0000-0001-9399-2595
*These authors contributed equally to this study as co-first authors.

tients who recur or relapse after ECT augmentation.

One approach to reduce the relapse after the initial treatment of ECT (index ECT) is "continuation" or "maintenance" ECT (C/M-ECT). The frequency of C/M-ECT is reduced after the index ECT, lengthening the intervals between treatments from weekly to fortnightly, then monthly to prevent relapse (continuation) or recurrence (maintenance).[7,8] Most of previous studies on C/M-ECT for TRS schizophrenia were limited by the nature of the study design[9] or the usage of qualitative outcome measures.[10] Meanwhile, one study reported the effectiveness of maintenance ECT by retrospective analysis of 19 patients which showed that the mean duration of yearly hospitalization was decreased by 80% in chronic schizophrenia.[11] However, whether C/M-ECT augmentation to pharmacotherapy in TRS patients would prevent psychiatric admission or reduce the number of admission was not well known in the long-term follow up. The aim of this study was to examine the long-term effect of C/M-ECT augmentation by the measure of the number of the psychiatric admissions in TRS patients, compared with the same time-duration of C/M-ECT beforehand the start of C/M-ECT. We hypothesized that C/M-ECT would decrease the number of psychiatric admissions which could represent recur or relapse.

METHODS

Participants

In this retrospective study, we reviewed the electronic medical record of treatment-resistant patients with schizophrenia spectrum disorder, who were treated with C/M-ECT at Seoul National University Hospital, Seoul, South Korea from December 2009 to September 2016. The inclusion criteria were diagnosis of schizophrenia or schizoaffective disorder by Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) or DSM fifth edition (DSM-5); age 18 to 65 years; duration of illness less than 2 years; resistance to at least two antipsychotics; augmentation therapy with ECT, and C/M-ECT duration less than 4 months. C/M-ECT was defined as treatment that followed an index ECT course with the purpose of preventing relapse and/or recurrence.[7] The present study was approved as a retrospective study by Institutional Review Board of Seoul National University Hospital.

ECT Procedure

Prior to the ECT procedure, patients signed a separate informed consent for ECT according to the institutional procedures for ECT. ECT was administered with a bilateral electrode placement using a MECTA Spectrum 5000Q device (MECTA Corp, Tualatin, OR, USA). Propofol and etomidate were used for medication during the general anesthesia. Succinylcholine (0.5-1 mg/kg) was injected to induce muscular relaxation. Seizure was followed up with electroencephalography, electrocardiography, and visual observation.

Standard C/M-ECT algorithm was 4 times for 4 weeks (M1-M4), 4 times for 8 weeks (M5-M8), 4 times for 16 weeks (M9-M12), and 4 times for 24 weeks (M13-M16), which was respectively performed at 1, 2, 4, and 6 week-interval. As a result, the patients were scheduled to receive 16 times-ECT for total 52 weeks, however the actual algorithm of patients was modified depending on clinical situations.

Statistical Analysis

The duration of C/M-ECT was varied according to patients; therefore we applied a "mirror-image design" using the duration of C/M-ECT in each patient. We compared the numbers of psychiatric admissions for the actual period over which C/M-ECT was administered with exactly the same number of days beforehand the beginning of C/M-ECT. Wilcoxon signed rank tests for non-parametrical variables were performed by using IBM SPSS Statistics (version 22; IBM Co., Armonk, NY, USA).

RESULTS

Clinical Characteristics of Participants

Eighteen treatment-resistant patients were included. The mean age at index ECT was 30.7 years (standard deviation [SD], 9.8; range, 19-61 years). Sixteen (88.9%) patients were treated with clozapine during C/M-ECT. Chlorpromazine-equivalent dose of antipsychotics was 875.3 mg (SD, 464.8) at the beginning of C/M-ECT, and 883.1 mg (SD, 416.2) at the end of C/M-ECT, respectively.

C/M-ECT was administered 36.9 times on average (SD, 27.2), and the mean duration of C/M-ECT was 28.6 months (SD, 19.1; range, 9-71 months) (Table 1).

Table 1. Demographic and clinical characteristics of participants

Characteristic	Data
Gender	
Male	7 (38.9)
Female	11 (61.1)
Diagnosis	
Schizophrenia	15 (83.3)
Schizoaffective disorder	3 (16.7)
Age at index ECT (yr)	30.7±9.8 (19-61)
Number of C/M-ECT	36.9±27.2 (7-115)
Duration of C/M-ECT (mo)	28.6±19.1 (9-71)

Values are presented as number (%) or mean±standard deviation (range).
ECT, electroconvulsive therapy; C/M-ECT, continuation-maintenance ECT.

Table 2. Difference in number of psychiatric admissions before and after continuation-maintenance ECT

Variable	Data	Z value†	*p* value
Number of admissions before C/M-ECT*	2.67±1.33 (1-6)	−3.663	<0.001
Number of admissions after C/M-ECT	0.33±0.77 (0-3)		

Values are presented as mean±standard deviation (range).
ECT, electroconvulsive therapy; C/M-ECT, continuation-maintenance ECT.
*During the same period of C/M ECT duration prior to the beginning of C/M- ECT.
†Based on positive ranks on Wilcoxon signed rank test.

Hospital Re-admissions

Statistical analysis showed that the number of psychiatric admissions decreased significantly during C/M-ECT compared with the same time-period before C/M-ECT (Wilcoxon signed rank Z=−3.663; $p<0.001$) (Table 2). The mean number of psychiatric admissions was 2.67 (SD, 1.33) and 0.33 (SD, 0.77), before and during C/M-ECT respectively. The patients of 94.4% had been hospitalized during the same period prior to C/M-ECT and four patients (22.2%) had been hospitalized during C/M-ECT.

DISCUSSION

The result of this study showed that C/M-ECT in TRS patients was effective for reducing the number of admissions. The participants were treatment resistant to two or more antipsychotics and treated with high dose of medication (mean chlorpromazine equivalent dose, 875.3 mg) including clozapine (88.9%). However, 22.2% of patients were re-admitted to psychiatric ward even during C/M-ECT augmentation.

In an inclusive review, treatment with ECT was significantly more likely to result in fewer relapses and increased rates of hospital discharge than sham ECT in schizophrenia.[12] More specifically, Kristensen *et al.*[10] evaluated the efficacy of ECT augmentation in 66 TRS patients, and 18 patients also received the maintenance ECT for periods ranging from 3 months to 12 years (mean, 2.2 years). Most of the participants were evaluated as excellent or good response. Another study reported the reduction of 80% of the average hospitalization duration as well as the effect on mood, anxiety, delusional symptoms and suicidal ideation by examining 19 TRS patients.[11] In the review of Lally *et al.*,[1] a high relapse rate of 32% in the weeks to months after ECT discontinuation was reported in patients with clozapine-ECT combination, whereas 22.2% of patients experienced re-admission in this study. Although we are unable to directly compare the results of our study to these previous studies due to the difference of the study design, participants, and the criteria of relapse, this result is in line with previous studies reporting the effectiveness of C/M-ECT in TRS patients. The mechanism of C/M-ECT augmentation is not well understood. It is postulated that ECT changes the permeability of blood-brain barrier and modulates the crossing of antipsychotic medication,[13] or potentiates the effect of neurotransmitters.[14]

We employed the mirror-image design in this study and investigated the re-admissions during C/M-ECT. In schizophrenia patients, re-admission rate is reported to associate with lowering the quality of life and the satisfaction with the treatment.[15] The present result may indicate that the C/M-ECT treatment can help the TRS patients adapt to their daily life without depending on the admission of hospital.

Several limitations of the present study should be noted. First, there were no data for the adverse events during C/M-ECT. Second, the change of medication during C/M-ECT was not considered, which may have influence the clinical course of the patients including re-admission. Third, this was a retrospective study. Further studies are required to delineate the influence of these factors on the effectiveness of C/M-ECT in a longer follow up period. Lastly, as this is an uncontrolled study without a comparison group, the number of admission observed may be a reflection of background variations occurring irrespective

of treatment.

The present study has an important implication in that C/M-ECT demonstrated a useful effect on re-hospitalization of TRS patients. Further research with prospective design is needed for clarification of long-term effect of C/M-ECT treatment.

■ **Acknowledgments**

All authors report no financial relationship with any commercial interest. This study was funded by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (2014R1A1A1004553) and grant no. 04-2016-0480 from the SNUH Research Fund. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

REFERENCES

1. Lally J, Tully J, Robertson D, Stubbs B, Gaughran F, MacCabe JH. *Augmentation of clozapine with electroconvulsive therapy in treatment resistant schizophrenia: a systematic review and meta-analysis. Schizophr Res 2016;171:215-224.*
2. Brenner HD, Dencker SJ, Goldstein MJ, Hubbard JW, Keegan DL, Kruger G, *et al. Defining treatment refractoriness in schizophrenia. Schizophr Bull 1990;16:551-561.*
3. Kane J, Honigfeld G, Singer J, Meltzer H. *Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45: 789-796.*
4. Petrides G, Malur C, Braga RJ, Bailine SH, Schooler NR, Malhotra AK, *et al. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. Am J Psychiatry 2015;172:52-58.*
5. Kim HS, Kim SH, Lee NY, Youn T, Lee JH, Chung S, *et al. Effectiveness of electroconvulsive therapy augmentation on clozapine-resistant schizophrenia. Psychiatry Investig 2017; 14:58-62.*
6. Yoshino Y, Ozaki Y, Kawasoe K, Ochi S, Niiya T, Sonobe N, *et al. Combined clozapine and electroconvulsive therapy in a Japanese schizophrenia patient: a case report. Clin Psychopharmacol Neurosci 2014;12:160-162.*
7. O'Connor DW, Gardner B, Presnell I, Singh D, Tsanglis M, White E. *The effectiveness of continuation-maintenance ECT in reducing depressed older patients' hospital re-admissions. J Affect Disord 2010;120:62-66.*
8. American Psychiatric Association. *The practice of electroconvulsive therapy: recommendations for treatment, training, and privileging (a task force report of the American Psychiatric Association). 2nd ed. Washington, D.C.:American Psychiatric Association;2001. 368 p.*
9. Bannour S, Bouhlel S, Krir MW, Amamou B, Ben Nasr S, El Kissi Y, *et al. Combination of maintenance electroconvulsive therapy and clozapine in treating a patient with refractory schizophrenia. J ECT 2014;30:e29-e30.*
10. Kristensen D, Bauer J, Hageman I, Jørgensen MB. *Electroconvulsive therapy for treating schizophrenia: a chart review of patients from two catchment areas. Eur Arch Psychiatry Clin Neurosci 2011;261:425-432.*
11. Lévy-Rueff M, Jurgens A, Lôo H, Olié JP, Amado I. *Maintenance electroconvulsive therapy and treatment of refractory schizophrenia. Encephale 2008;34:526-533.*
12. Tharyan P, Adams CE. *Electroconvulsive therapy for schizophrenia. Cochrane Database Syst Rev 2005;(2):CD000076.*
13. Kales HC, Dequardo JR, Tandon R. *Combined electroconvulsive therapy and clozapine in treatment-resistant schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 1999;23:547-556.*
14. Havaki-Kontaxaki BJ, Ferentinos PP, Kontaxakis VP, Paplos KG, Soldatos CR. *Concurrent administration of clozapine and electroconvulsive therapy in clozapine-resistant schizophrenia. Clin Neuropharmacol 2006;29:52-56.*
15. Schmidt-Kraepelin C, Janssen B, Gaebel W. *Prevention of rehospitalization in schizophrenia: results of an integrated care project in Germany. Eur Arch Psychiatry Clin Neurosci 2009; 259 Suppl 2:S205-S212.*