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ORIGINAL RESEARCH

One-Year Clinical Outcomes Following Electroconvulsive Therapy for Patients with Schizophrenia: A Nationwide Health Insurance Data-Based Study

Sung Woo Joo[1], Harin Kim[1], Young Tak Jo[1], Soojin Ahn[1], Young Jae Choi[1], Woohyeok Choi[1], Soyeon Park[2], Jungsun Lee[1]

[1]Department of Psychiatry, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Department of Psychiatry, Medical Foundation Yongin Mental Hospital, Yongin, Republic of Korea

Correspondence: Jungsun Lee, Department of Psychiatry, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-Ro 43-Gil, Songpa-Gu, Seoul, 05505, Republic of Korea, Tel +82-2-3010-3422, Fax +82-2-485-8381, Email js_lee@amc.seoul.kr

Background: Although the use of electroconvulsive therapy (ECT) in the treatment of schizophrenia has decreased since the advent of antipsychotic drugs, ECT is still implemented in several clinical indications. However, a few population-based studies have examined its real-world effectiveness in schizophrenia.

Methods: We used data from 2010 to 2019 from the Health Insurance Review and Assessment Service database in the Republic of Korea. We selected 380 schizophrenia patients having more than six ECT sessions and 1140 patient controls matched for age, sex, calendar year at entry, and the number of psychiatric hospitalizations before the time point of start of psychiatric hospitalization for ECT. Antipsychotic treatment discontinuation, psychiatric hospitalization, and direct medical costs were used as measures of clinical outcomes. Multiple regression analysis was used for any group-by-time interaction effect, and 1-year pre- and post-ECT periods were compared within and between the groups.

Results: We found a significantly lower number of antipsychotic treatment discontinuations in the ECT group during the 1-year post-ECT period ($t=2.195$, $p=0.028$). A larger decrease was found in the number of psychiatric hospitalizations in the ECT group, with a group-by-time interaction effect ($p=0.043$). The direct medical costs in the 1-year pre- ($t=-8.782$, $p<0.001$) and post-ECT periods ($t=-9.107$, $p<0.001$) were higher in the ECT group than in the control group, with no significant change across both periods.

Conclusion: We found that the ECT group had a larger decrease in the number of psychiatric hospitalizations in the 1-year post-ECT period than the control group.

Keywords: schizophrenia, electroconvulsive therapy, population-based

Introduction

Despite the declining use of electroconvulsive therapy (ECT) after the development and acceptance of pharmacological treatment of schizophrenia, ECT is still an important treatment option in managing patients with schizophrenia along with antipsychotic medications. Several studies have reported the additive effectiveness of ECT augmentation to antipsychotic treatment in terms of the improvement of positive symptoms and amelioration of negative symptoms in treatment-resistant schizophrenia.[1,2] The clinical indications for ECT in patients with schizophrenia include catatonia, suicidal risk, severe agitation/violence, and poor oral intake,[3] which suggests that ECT still plays an indispensable role in the treatment of schizophrenia in real-world clinical practice.[4] Despite enormous efforts to reduce the stigma surrounding ECT, its utilization rate is still low worldwide,[5,6] including the Republic of Korea. According to a previous study, the utilization rate of ECT for the treatment of schizophrenia during psychiatric hospitalization was estimated to be approximately 0.3% in the Republic of Korea, which is notably lower than that in other Asian countries.[7]

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Although ECT is not associated with the risk of incidental dementia and a detrimental effect on cognitive functions,[8,9] it is usually considered the last treatment option.[10] Clinicians opt to initiate ECT when several trials of pharmacotherapy and non-pharmacotherapy fail. Therefore, patients indicated for ECT are likely to be treatment-refractory or have a severe suicidal or violence risk, which could limit the enrollment of patients in randomized controlled trials (RCTs), probably owing to a lack of their ability to provide informed consent.[11] Most previous studies regarding the effectiveness and safety of ECT in schizophrenia are retrospective observational studies with a relatively small number of participants, which cannot provide good-quality evidence.[3] With regard to the generalization of results from RCTs, it should be considered that participants in RCTs are more likely to be selective and compliant than patients in real-world clinical practice. Therefore, it is important to evaluate the real-world effectiveness of ECT in schizophrenia with a large amount of real-world data.

All South Koreans are obligated to register in a nationwide health insurance service, except for those in special circumstances, resulting in an insurance coverage rate of 98%. The Health Insurance Review and Assessment Service (HIRA) is responsible for reviewing claims generated from medical institutions and maintaining a claim database. Information on the use of medical services by all South Koreans, such as diagnoses, prescriptions of medications, and direct medical costs, is encoded in the claim database.[12] Our research team has conducted several studies using this nationwide claim database;[13,14] these studies have a notable strength of utilizing a large sample size and being able to observe patients without follow-up loss because of nationwide coverage and the compulsory nature of the national health insurance service. Given the low utilization rate of ECT for the treatment of schizophrenia in the Republic of Korea,[7] the availability of data for a large number of patients with schizophrenia who had received ECT may be a remarkable strength of the HIRA database.

In this study, we aimed to investigate the real-world effectiveness of ECT in patients with schizophrenia using the HIRA database. The number of antipsychotic treatment discontinuations and psychiatric hospitalizations, as well as direct medical costs, were used as measures of the clinical outcomes. Abundant evidence has emphasized the importance of the continuation of antipsychotic treatments for the prevention of relapses and improvement in social and occupational functions of patients.[15,16] Psychiatric hospitalization has been considered a marker for relapse in previous studies using claim databases.[17,18] Direct medical costs are reflective of the economic burden to patients, families, and society and may be associated with the severity and clinical course of the disease.[19,20] We compared the 1-year pre- and post-ECT periods within and between two groups of patients who had received ECT and of matched controls who had not received ECT. We examined whether schizophrenia patients who had received ECT had better clinical outcomes than the matched controls in terms of the number of antipsychotic treatment discontinuations and psychiatric hospitalizations, as well as the direct medical costs.

Materials and Methods

Study Population

We utilized data from January 2010 to December 2019 from the HIRA database to include patients with schizophrenia who had received ECT. Initially, we identified patients with schizophrenia using the following criteria: 1) The main diagnostic code for schizophrenia (F20) was recorded at least twice for outpatients or once for inpatients during the total observation period; 2) the observation period started from the first antipsychotic prescription, and the patient's age at the start of the observation period was between 18 and 65 years; and 3) medications for dementia, including acetylcholine esterase inhibitors (eg, donepezil, rivastigmine, and galantamine) and memantine, were not prescribed before and within 1 year after the start of the observation period. Among them, we initially included patients who had received at least one ECT session during the total observation period. An ECT course was defined as at least more than two ECT sessions per week during psychiatric hospitalization. We only included the patients who had received only one ECT course during the total observation period, resulting in the exclusion of patients who had received ECT courses several times or received maintenance/continuation ECT during the total observation period. The main diagnostic code for psychiatric hospitalization during which ECT had been performed was to be F20–29 (schizophrenia, schizotypal, and delusional disorders), and the number of ECT sessions during the psychiatric hospitalization was to be more than six. With the abovementioned criteria, we included 380 patients with schizophrenia in the ECT group. We selected patient controls matched for age at entry, sex, calendar year at entry, and the number of psychiatric hospitalizations before the time point of start of psychiatric hospitalization for ECT at a ratio of 1:3.

This study was approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB No. 2021–0556). The need for informed consent was waived owing to the use of anonymous and de-identified data.

Definitions of the Clinical Outcomes

Antipsychotic treatment discontinuation was defined as a lapse of more than 30 days from the expected date of the next antipsychotic prescription. Supplementary Table 1 shows a list of antipsychotic drugs included in the analyses. When more than two antipsychotic drugs were prescribed in the same treatment period, we used the highest prescription duration among the drugs. The hospitalization episodes were reconstructed by adopting the methods described in a previous study.[21] When the type of hospitalization was general medical or psychiatric, and the main diagnostic code for hospitalization was F00–99 (mental and behavioral disorders), we labeled it as a psychiatric hospitalization. When rehospitalization occurred within 30 days after the end of the prior hospitalization, we disregarded it when calculating the number of psychiatric hospitalizations. Direct medical costs were calculated using information indicating the total medical costs for visits (RVD_RPE_TAMT_AMT) in the claim database. The total medical costs include inpatient and outpatient care costs, as well as pharmacy costs, but not non-covered costs by the insurance provider. To extract the costs associated with psychiatric illness, we applied the condition that the main diagnostic code for visits should be F00-99.

Statistical Analysis

All statistical analyses were performed using the R software, version 3.5.1 (R Development Core Team, Vienna, Austria). A two-tailed p-value of <0.05 was used to determine statistical significance.

Continuous and categorical variables (demographic and clinical characteristics of the study population) were presented as means and standard deviations (SD) or numbers (%). Group comparisons were performed using an unpaired *t*-test or the chi-square test. We examined the number of antipsychotic treatment discontinuations and psychiatric hospitalizations and the direct medical costs in the 1-year pre- and post-ECT periods. Group-by-time interaction effects were evaluated using multiple regression analysis. An unpaired *t*-test was used to compare the outcome variables between the two groups in the 1-year pre- and post-ECT periods. Within each group, a paired *t*-test was used to compare the outcome variables in the 1-year pre- and post-ECT periods.

Results

Demographic and Clinical Characteristics of the Study Population

A total of 380 patients with schizophrenia who had received ECT and 1140 matched controls were included in the analysis. In the ECT group, the mean (SD) age at entry was 33.2 (11.2) years, and 44.5% were men. The mean (SD) number of psychiatric hospitalizations from entry to the start of psychiatric hospitalization for ECT was 1.9 (1.9). There were no significant group differences in age at entry, sex, and the number of psychiatric hospitalizations between the ECT and the control groups. The patients in the ECT group had received a mean (SD) number of 12.2 (4.2) ECT sessions during psychiatric hospitalization. During the 3 months before psychiatric hospitalization for ECT, the patients in the ECT group had been prescribed a mean (SD) number of 2.6 (1.5) antipsychotics, and the proportions of patients with monotherapy and polypharmacy were 22.6% and 77.4%, respectively. Further details on the demographic and clinical characteristics of the study population are presented in Table 1.

Within- and Between-Group Comparisons of the Clinical Outcomes in the 1-Year Pre- and Post-ECT Periods (Table 2 and Figure 1)

Within-Group Comparisons

The number of antipsychotic treatment discontinuations significantly decreased in the 1-year post-ECT period in both groups (ECT group: $t=-3.628$, $p<0.001$; control group: $t=-2.271$, $p=0.023$). The number of psychiatric hospitalizations in the 1-year post-ECT period also decreased in the ECT ($t=-5.302$, $p<0.001$) and control groups ($t=-6.952$, $p<0.001$). There was no significant change in the direct medical costs in the 1-year post-ECT period in both groups.

Table 1 Demographic and Clinical Characteristics of the Study Population

Variable	ECT Group (n=380)	Control Group (n=1140)	P-value
Age at entry, mean (SD), years	33.2 (11.2)	33.4 (11.2)	0.76
Age group at entry, n (%), years			1.00
18–19	32 (8.4)	96 (8.4)	
20–29	136 (35.8)	411 (35.8)	
30–39	95 (25.0)	288 (25.0)	
40–49	80 (21.1)	243 (21.1)	
50–59	30 (7.9)	90 (7.9)	
60–65	7 (1.8)	21 (1.8)	
Male, n (%)	169 (44.5)	507 (44.5)	1.00
Duration from entry to the time point of start of psychiatric hospitalization for ECT, mean (SD), years	4.4 (2.3)	4.4 (2.3)	1.00
Number of psychiatric hospitalizations from entry to the time point of start of psychiatric hospitalization for ECT, mean (SD)	1.9 (1.9)	1.8 (1.8)	0.36
Length of psychiatric hospitalization for ECT, mean (SD), days	56.2 (26.6)		
Number of ECT sessions, mean (SD)	12.2 (4.2)		
Antipsychotic treatment during the 3 months before psychiatric hospitalization for ECT			
Number of prescribed antipsychotics, mean (SD)	2.6 (1.5)		
Monotherapy, n (%)	86 (22.6)		
Polypharmacy, n (%)	294 (77.4)		
With clozapine	125 (32.9)		

Abbreviations: ECT, electroconvulsive therapy; SD, standard deviation.

Table 2 Group Comparisons of the Clinical Outcomes in the 1-Year Pre- and Post-ECT Periods

	Group		Between-Group, t-value (P-value)	Within-Group, t-value (P-value)		Group × Time P-value
	ECT	Control		ECT	Control	
Number of antipsychotic treatment discontinuations, mean (SD)						
Before	0.31 (0.61)	0.29 (0.61)	−0.317 (0.752)	−3.628	−2.271	0.083
After	0.17 (0.48)	0.25 (0.60)	2.195 (0.028)*	(<0.001) ***	(0.023)*	
Number of psychiatric hospitalizations, mean (SD)						
Before	0.84 (0.79)	0.45 (0.64)	−9.766 (<0.001)***	−5.302	−6.952	0.043*
After	0.58 (0.79)	0.30 (0.57)	−7.493 (<0.001)***	(<0.001) ***	(<0.001) ***	
Direct medical costs, KRW, mean (SD)						
Before	8,850,888 (7,799,587)	5,340,390 (6,360,241)	−8.782 (<0.001)***	0.475 (0.635)	−1.854 (0.064)	0.433
After	9,052,569 (8,888,967)	5,078,276 (6,785,412)	−9.107 (<0.001)***			

Note: *p<0.05, ***p<0.001.
Abbreviations: ECT, electroconvulsive therapy; KRW, Korean won; SD, standard deviation.

Between-Group Comparisons

While there was no significant difference in the number of antipsychotic treatment discontinuations in the 1-year pre-ECT period, the ECT group had a significantly lower number of antipsychotic treatment discontinuations than the control

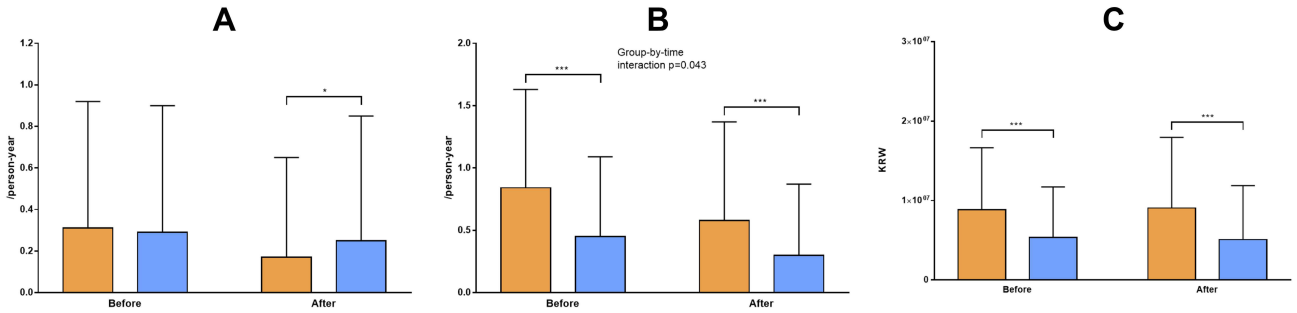

Figure 1 Comparisons of (**A**) the number of antipsychotic treatment discontinuations, (**B**) psychiatric hospitalizations, and (**C**) the direct medical costs between the ECT and control groups in the 1-year pre- and post-ECT periods. The Orange and blue bars indicate mean and standard deviations of the values in the ECT and control groups, respectively. * p<0.05, *** p<0.001. KRW, Korean won.

group in the 1-year post-ECT period (t=2.195, p=0.028). The group-by-time interaction effect for the number of antipsychotic treatment discontinuations was not significant (p=0.083). The ECT group had a significantly increased number of psychiatric hospitalizations in the 1-year pre- (t=−9.766, p<0.001) and post-ECT periods (t=−7.493, p<0.001) compared with the control group. A significantly larger decrease in the number of psychiatric hospitalizations was found in the ECT group than in the control group, with a significant group-by-time interaction effect (p=0.043). There was a consistent pattern of significantly increased direct medical costs in the ECT group compared with that in the control group in the 1-year pre- (t=−8.782, p<0.001) and post-ECT periods (t=−9.107, p<0.001).

Discussion

In this study, we used the HIRA database to investigate the real-world effectiveness of ECT in patients with schizophrenia. We compared the number of antipsychotic treatment discontinuations and psychiatric hospitalizations and the direct medical costs in the 1-year pre- and post-ECT periods within and between the groups. We found that there was a significantly lower number of antipsychotic treatment discontinuations in the 1-year post-ECT period in the ECT group than in the control group. Although the number of psychiatric hospitalizations in both periods was higher in the ECT group than in the control group, there was a significantly larger decrease in the number of psychiatric hospitalizations across both periods in the ECT group than in the control group. No significant difference in the direct medical costs between the 1-year pre- and post-ECT periods was found in either group; the direct medical costs in the ECT group were consistently higher in both periods than those in the control group.

Most practice guidelines for the treatment of schizophrenia recommend 1–2 years of antipsychotic treatment for first-episode schizophrenia and long-term antipsychotic treatment for multiple-episode schizophrenia.[22] The continuation of antipsychotic treatment has been considered an essential part of the treatment of schizophrenia to prevent relapses and improve the long-term outcomes and functioning of patients. Several previous studies have reported the low continuation rate of antipsychotic treatment in patients with schizophrenia.[23] A systematic review showed that familial support and the level of insight are highly predictive of treatment adherence.[24] It was reported that poor insight exists even at the onset of psychosis among patients with schizophrenia.[25] Several treatment strategies, such as long-acting injectable antipsychotic drugs and cognitive behavioral therapy for psychosis, have been developed to enhance treatment adherence; however, their effectiveness is limited.[25] In this study, the ECT group showed a lower number of antipsychotic treatment discontinuations in the 1-year post-ECT period than the control group. To the best of our knowledge, there is no existing evidence related to this observation. The promising effects of ECT on antipsychotic treatment continuation in this study should be validated in future studies with a larger sample and longer observation period.

Although we used matched controls in the group comparisons, an increased number of psychiatric hospitalizations in the l-year pre-ECT period was found in the ECT group compared with the control group. This might be related to the severe psychiatric symptoms or treatment resistance among the patients in the ECT group, considering that 32.9% of these patients had received polypharmacy with clozapine during the 3 months before psychiatric hospitalization for ECT. We observed a larger decrease in the number of psychiatric hospitalizations in the 1-year post-ECT period in the ECT group than in the

control group. Given that the severity of psychiatric symptoms dictates whether schizophrenia patients should be managed in inpatient or outpatient settings, the initiation of psychiatric hospitalization suggests that the psychiatric symptoms of the patients are severe enough to require intensive care or management. Based on that psychiatric hospitalization has been used as a surrogate for relapse in previous studies,[17,18] our results may also indicate the usefulness of ECT in reducing relapses. In line with the current findings, a previous study by Lin et al demonstrated that their ECT group had a decreased rate of rehospitalization in the 1-year post-ECT period compared with their control group.[26]

Despite the low incidence of schizophrenia, it is a tremendous economic burden for patients, their families, and society across the world.[20] Previous studies have reported that a substantial proportion of the total costs is associated with indirect costs, which include caregiving, premature mortality, and unemployment.[20,27] Direct medical costs usually include expenditure for inpatient care, outpatient care, diagnostic tests, and prescription drugs. In our study, there was no significant change in the direct medical costs between the 1-year pre- and post-ECT periods in both groups. However, the direct medical costs were consistently higher in the ECT group than in the control group across both periods. Given that a substantial proportion of direct medical costs related to schizophrenia is related to inpatient care,[28,29] the increased direct medical costs in the ECT group might be related to the higher number of psychiatric hospitalizations in the 1-year pre- and post-ECT periods. In the within-group comparison, the direct medical costs in the ECT group did not decrease in the 1-year post-ECT period, while the number of psychiatric hospitalizations decreased in the 1-year post-ECT period. A possible explanation for the lack of any significant change in the direct medical costs is a more regular follow-up in the 1-year post-ECT period supported by the lower number of antipsychotic treatment discontinuations. Contrary to our study, Lin et al reported that the total medical expenses increased significantly in their control group in the 1-year post-ECT period but not in their ECT group.[26] This could be attributed to a few methodological differences. While we aimed to focus on the effects of ECT on psychiatric symptoms specific to schizophrenia by restricting the main diagnostic code to F20-29, the previous study did not consider schizophrenia specific symptoms to be the main indication for ECT. In the previous study, the authors had selected control patients who had at least one psychiatric hospitalization during the observation period and used the duration of hospitalization in the matching procedure. In contrast, we utilized the number of psychiatric hospitalizations during the period from entry to the start of psychiatric hospitalization for ECT in selecting matched controls.

One notable strength of our study is the utilization of information from a relatively large number of patients with schizophrenia who had received ECT, despite the low utilization rate of ECT in the Republic of Korea. However, some limitations should be considered. First, because this study was based on a claim database, we could not assess the severity of the psychiatric symptoms of the patients. Although antipsychotic treatment discontinuation and psychiatric hospitalization are important indicators of clinical course, they only have an indirect association with the clinical symptoms. Second, our results suggest that ECT may have a beneficial effect in reducing psychiatric hospitalization. However, it is still uncertain how ECT exerts its positive effects and which clinical and therapeutic factors are associated with them. Third, we included patients who received more than six ECT sessions during psychiatric hospitalization for ECT to ascertain an adequate administration of ECT. However, the minimum criterion of at least six ECT sessions was still arbitrary, given that more than six ECT sessions are recommended in general, and a higher number of ECT sessions may be needed for patients with schizophrenia than for those with mood disorders.[30] Fourth, the current study has a retrospective observational study design, which is an inherent limitation in evaluating the effectiveness of ECT on clinical outcomes in schizophrenia. Our results indicate the associations of ECT with clinical outcomes but not the causal relationship between them. A prospective RCT with a large sample size is needed to validate the current results.

Conclusions

We investigated the real-world effectiveness of ECT in patients with schizophrenia in terms of the number of antipsychotic treatment discontinuations and psychiatric hospitalizations, as well as direct medical costs. A lower number of antipsychotic treatment discontinuations was observed in the ECT group than in the control group in the 1-year post-ECT period. Further, there was a larger decrease in the number of psychiatric hospitalizations in the ECT group than in the control group. The direct medical costs in the 1-year pre- and post-ECT periods were significantly higher in the ECT group than in the control group, but there was no significant change in the direct medical costs across both periods in

both groups. Based on these nationwide health insurance data, we suggest that ECT may be beneficial in reducing psychiatric hospitalizations in patients with schizophrenia. However, further investigations are needed to collect more evidence.

Data Sharing Statement

The datasets used in this study are available from the Health Insurance Review and Assessment service on reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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