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Reduced risk of stroke among psychiatric patients receiving ECT: A population-based cohort study in Taiwan

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ABSTRACT

Electroconvulsive therapy (ECT) as well as the diseases it treats have been associated with stroke and cognitive impairment. We investigate the relationship between ECT and the subsequent development of stroke in patients with different severe mental illnesses. Tapping Taiwan's National Health Insurance Research Database, we identified patients diagnosed with severe mental illnesses who had received ECT between Jan 1, 2002 and Dec 31, 2007. A comparison cohort was constructed of patients who were matched by age, gender, and diagnosis but did not receive ECT. The patients were then followed up for occurrence of subsequent new-onset stroke. We identified 6264 patients had been diagnosed with mental illness and had received ECT. They were matched with 18,664 mentally ill patients who had not. The study cohort had a lower incidence of subsequent stroke than the matched controls, after controlling for age, diabetes, hypertension, coronary heart disease and enrollee socio-demographic category, risk factors for stroke in both study and control cohorts. ECT is associated with reduced risk of subsequent stroke in patients with severe mental illnesses in Taiwan. Therefore, clinicians should not let risk of stroke stop them from suggesting ECT to physically healthy patients who might benefit from this therapy.

1. Introduction

First introduced in 1938, electroconvulsive therapy (ECT), one of the oldest treatment methods in the field of psychiatry, uses electric current to elicit a seizure to treat mental illness (Gazdag and Ungvari, 2019). While ECT is considered an effective and safe treatment, it has been associated with several adverse effects, including muscle soreness and cognitive impairment (Rose et al., 2003; Verwijk et al., 2015; Zheng et al., 2018).

ECT has been used successfully to treat clozapine-resistant schizophrenia (Petrides et al., 2015), bipolar disorder (Medda et al., 2014), and treatment-resistant depressive disorder (Kellner et al., 2012). There are several theories regarding how ECT achieves its effect. One theory is that it works via its effects on neurotransmitters, particularly the serotonin and dopamine systems (Baldinger et al., 2014). Another theory is that ECT treats inflammation, which has been associated with depression, by acting on cytokines (Guloksuz et al., 2014). Another study has found hypertensive surge induced by ECT increases transient blood-brain barrier permeability stimulating neurogenesis (Andrade and Bolwig, 2014). Still, another theory is that ECT works by increasing brain plasticity, promoting the proliferation of stem cells (Bouckaert et al., 2014; de Jong et al., 2014).

During the ECT seizure period, there are sudden increases in both blood pressure and heart rate, which may affect the brain blood circulation, conceivably leading to ischemic or hemorrhagic stroke. However, ECT has been associated with a low mortality rate as 0.001–0.00025% (Torring et al., 2017), and seventy-five percent of subsequent deaths in ECT patients have been attributed to cardiovascular defects (Chandra et al., 2009), though one study has reported a case of ECT-related myocardial stunning (Chandra et al., 2009). In a systematic review and meta-analysis, major adverse cardiac events and death after ECT occur in about 1 of 50 patients and after about 1 of 200 to 500 electroconvulsive therapy treatments (Duma et al., 2019). Thus, mentally ill patients receiving ECT can also have heart diseases, which may further increase their risk of stroke.

Schizophrenia can be found in about one percent of the general population (Freedman, 2003). Patients with schizophrenia are known to be at higher risk of stroke than those in the general population

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(Curkendall et al., 2004; Lin et al., 2008; Sacchetti et al., 2010) The typically unhealthy lifestyles associated with schizophrenia (e.g. smoking and consumption of unhealthy diets) as well as use of antipsychotics have been related to the development of coronary heart disease and stroke (McCreadie, 2003; Sacchetti et al., 2010). Thus, patients with schizophrenia often have comorbid physical illnesses that also increase risk of stroke (Leucht et al., 2007). People with mental disorders are often less likely to be aware of various risks to their health, less able to prevent their own risk behaviors, and less likely to seek treatments than those without mental disorders (Druss et al., 2000) For these reasons, they are at increased risk of mortality and have shorter life expectancies than the general population (Newman and Bland, 1991; Saha et al., 2007).

ECT, itself, may increase in endothelial cell proliferation leading to structural changes that might increase risk of stroke (Hellsten et al., 2004). Case reports have found ECT patients to be at increased risk of reversible ischemic neurologic deficit and ischemic stroke (Bruce et al., 2006; Lee, 2006; Miller and Isenberg, 1998). However, their sample sizes were small, their study groups consisted of local patients, they lacked well-matched control groups, and they did not control for comorbid physical illnesses. Therefore, in this study we investigated the association between ECT and the subsequent stroke in patients with different severe mental illnesses. To do this, we identified severely mentally ill patients receiving ECT in a nationwide health insurance database and followed these for subsequent new-onset stroke for six years, until occurrence of stroke, or until death, comparing them with a control cohort of age-, gender-, and diagnosis-matched patients who did not receive ECT.

2. Patients and methods

2.1. Study design and data sources

Taiwan's National Health Insurance program is a compulsory health insurance program covering the cost of medical care and prescriptions of all Taiwan's legal residents. It covers outpatient, inpatient, emergency and dental care and has had a coverage rate of up to 98% since 1995. The NHI Research Database (NHIRD) contains comprehensive information on its enrollees, their diagnoses (International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-9-CM), medical services rendered, and medications prescribed. Taiwan's National Health Research Institute manages the NHIRD and releases its data for research purposes. Confidentiality is maintained according to the directives established the National Health Insurance Bureau. The data used in this study came from the Longitudinal Health Insurance Database, a subset of the NHIRD. The longitudinal database consists of a systematically collected and random sample of data contained from the NHIRD for certain periods of time (2002–2007). There are no significant differences in distribution of gender, age, or income level between the patients in the Longitudinal Health Insurance Database and the patients whose data are maintained in the NHIRD, itself.

2.2. Ethical statement

This study was approved by the Institutional Review Board of Kaohsiung Municipal Kai-Syuan Psychiatric Hospital, Taiwan (Ethical code: KSPH-2013-34). Review board requirements for written informed consent were waived because all personal identifying information had been removed from the dataset prior to analysis.

2.3. Study population

In this retrospective cohort study, we identified all patients who were newly hospitalized with psychiatric illnesses between January 1, 2002 and December31, 2007. In the database, patients with the psychiatric illness were identified by the ICD-9-CM code 290 to 319 listed on their claims submissions. Patients receiving ECT without previous stroke or transient ischemic attack were enrolled into the study cohort. ECT was used as a time-dependent variable by splitting the data-set according to time of first ECT. We excluded patients who received diagnosis of stroke or ischemic attack before the first session of ECT. Other patients with these diagnoses who did not receive ECT were first age-, sex-, and diagnosis-matched and then randomly selected to be enrolled into our comparison cohort at a ratio of three controls to one ECT patient. Random assignment was performed using SAS statistical software. All patients in both cohorts were followed until the occurrence of our primary outcome diagnosed stroke (ICD-9-CM code 430-438) or until death, withdrawal from the NHI system, or December31, 2007, the end of the study period.

We also collected data on parameters such as age, gender, socioeconomic status (SES), level of urbanization, physical illnesses such as hypertension, diabetes mellitus, dyslipidemia and coronary artery disease and severity of comorbidity (, for both cohorts. The recoding of SES and urbanization of residence in the insurance is based on income in Taiwan and several urbanization variables. Enrollee category, which defines workplace, is an important risk factor for stroke (Jakovljevic et al., 2001). In Taiwan, the NHRID categorizes enrollees into four subgroups: EC 1 (civil servants, full-time, or regularly paid personnel with a government affiliation), EC 2 (employees of privately owned institutions), EC 3 (self-employed individuals, other employees, and members of the farmers' or fishermen's association), and EC 4 (veterans, members of low-income families, and substitute service draftees). We used these EC categories to classified patients in both of our cohorts into four subgroups: EC 1(Higher SES), EC 2 (Middle SES), EC 3 (Moderate SES), and EC 4 (Lower SES).

Severity of comorbidity was based on the modified Charlson Comorbidity Index Score (CCIS) recorded on the claims database for the last six months of each patient's life. The CCIS is a widely accepted scale used for risk adjustment in administrative claims data sets (Deyo et al., 1992; Li et al., 2008), and already proved to be associated with mortality (Fine et al., 1996). This index incorporates 19 different medical categories and each weighted according to its potential to impact on mortality. Those with a relative risk below 1.5 were assigned a weight of 1; conditions with a risk of 1.5 to <2.5 a weight of 2; conditions with a risk of 2.5 to <3.5 a weight of 3. The final score was calculated for each patient by taking into account all comorbid conditions present when the index was applied. Both cohorts in our study were classified into three subgroups: CCIS 0 (no comorbidity), CCIS 1 (mild comorbidity) and CCIS 3 (moderate comorbidity).

2.4. Statistical analysis

Patient characteristics were analyzed descriptively and group differences tested using independent t tests and Chi-squared test. Cox proportional hazards regression was used to identify the risk factors associated with stroke in the whole sample. SAS statistical software for Windows, Version 9.3 (SAS Institute, Cary, NC), was used for data extraction, computation, linkage, processing, and sampling. All other statistical operations were performed using SPSS statistical software for Windows, Version 17 (IBM, Armonk, NY). A P-value < 0.05 was considered significant.

3. Results

In total, we identified and enrolled 6264 patients who were diagnosed as having a mental illness and who had received ECT. From the remaining patients diagnosed with mental illnesses who had not received ECT, we enrolled 18,664 age-, gender-, and diagnosis-matched controls. As can been seen in Table 1, a comparison of the study and control subjects' characteristics, there was no significant difference between the two matched groups with regard to age (both slightly above 36 years old), gender (around 50 percent), or mental illness

Table 1
Socio-demographic characteristics and stroke-related illnesses of psychiatry patients with electro-convulsion therapy and matched control subjects.

	ECT n = 6264 (Mean)	% (SD)	Non-ECT n = 18,664 (Mean)	% (SD)	P
Socio-demographic characteristics					
Age (Mean ± SD)	(36.47)	(11.49)	(36.24)	(11.42)	0.169
Gender					0.981
Male	3173	50.70	9451	50.60	
Female	3091	49.30	9213	49.40	
Diagnosis					0.950
Schizophrenic disorders	4156	66.40	12,407	66.50	
Episodic mood disorders	1812	28.90	5364	28.70	
Other psychiatry disorders	296	4.70	893	4.80	
Socioeconomic status					< 0.0001
Upper	258	4.10	895	4.80	
Middle	1188	19.00	4229	22.70	
Moderate	1301	23.92	3984	21.30	
Low	2730	52.95	7694	41.20	
Missing	787	12.50	1862	10.00	
Level of urbanization					0.020
Urban	5936	94.80	17,544	94.00	
Suburban	325	5.20	1092	5.90	
Rural	3	0.00	28	0.10	
Charlson Comorbidity Index Score					0.009
0	5190	82.90	15,861	85.00	
1	783	12.50	1987	10.60	
≥2	291	4.60	816	4.40	
Stroke related illnesses					
Diabetes					0.500
Yes	313	5.00	893	4.80	
Hypertension					0.454
Yes	435	6.90	1245	6.70	
Hyperlipidemia					0.025
Yes	254	4.10	643	3.40	
Coronary Heart Disease					0.064
Yes	167	2.70	421	2.30	
Status after 10 years of follow-up					
Stroke					0.001
Yes	432	6.90	1530	8.20	

(schizophrenic disorders, 66%; episodic mood disorders 28%; other 4.8%). Patients receiving ECT had lower socioeconomics statuses than those who had not (Moderate SES: 23.92% vs. 21.30% and Lower SES: 52.95% vs. 41.20%, respectively; both $p < 0.0001$). They also had higher level of urbanization (94.8% vs. 94.0%, $p = 0.020$) and a higher prevalence of comorbidity (Mild: 12.5% vs. 10.60%; Moderate: 4.6% vs. 4.40%, respectively; both $p < 0.009$). Comparing patients by type of comorbidity, we found the two groups to only have a statistical difference with regard to dyslipidemia (4.10% vs. 3.40, respectively; $p = 0.025$). Four hundred thirty-two (6.9%) of study patients and 1530 (8.2%) control patients were later diagnosed with newly diagnosed stroke ($p < 0.001$).

Table 2 summarizes the results of our Cox proportional hazards regression analysis conducted to calculate the hazards ratio (HR) of the newly diagnosed stroke for the patients receiving ECT compared with the matched controls. Patients that had received ECT were found to be at a markedly reduced risk for subsequent stroke (HR 0.816, 95% confidence interval [CI] 0.734–0.909, $p \leq 0.001$). Other risks factors for subsequent stroke were age (HR 1.050, 95% CI 1.046–1.054), diabetes (HR 1.340, 95% CI 1.136–1.579), hypertension (HR 1.462, 95% CI 1.272–1.680), coronary heart disease (HR 1.517, 95% CI 1.256–1.832) and score 2 or more Charlson comorbidity index (HR 1.455, 95% CI 1.225–1.728). A low SES appeared to be a protective factor for the subsequent stroke. Compared to schizophrenic disorders, patients with episodic mood and other psychiatry disorders were at higher risk of subsequent stroke (HR 1.186, 95% CI 1.071–1.313 and HR 1.507, 95% CI 1.270–1.788, respectively).

Table 2
Adjusted hazard ratios for stroke within the follow-up period (n = 24,141).

	Exp(B)	95% CI	P
Patient characteristics			
Age	1.050	1.046–1.054	≤0.001
Diabetes	1.340	1.136–1.579	≤0.001
Hypertension	1.462	1.272–1.680	≤0.001
Coronary heart disease	1.517	1.256–1.832	≤0.001
Socioeconomic status			
Upper	reference		
Middle	0.750	0.613–0.917	0.005
Moderate	0.853	0.701–1.038	0.112
Low	0.791	0.654–0.957	0.016
Diagnosis			
Schizophrenic disorders	reference		
Episodic mood disorders	1.186	1.071–1.313	0.001
Other psychiatry disorders	1.507	1.270–1.788	≤0.001
Charlson Comorbidity Index Score			
0	reference		
1	1.143	0.996–1.313	0.057
≥2	1.455	1.225–1.728	≤0.001
Having ECT	0.816	0.734–0.909	≤0.001

787 subjects with missing data were excluded from this analysis.
Adjusted for age, gender, diagnosis, socioeconomic status, level of urbanization and Charlson comorbidity index score.

4. Discussion

This nationwide retrospective cohort study found that psychiatric patients receiving ECT in Taiwan were significantly less likely to have a stroke than those not receiving this therapy and that age, diabetes, hypertension and coronary heart disease are risk factors for stroke in those patients receiving ECT. Compared with previous studies, we found a higher incidence of stroke in mentally ill patients in our study and comparison cohorts (6.9% and 8.2%, respectively) than in the general population Taiwan (0.33%, 330/100,000 person-years), as reported in a review study by (Venketasubramanian et al., 2017).

Although our cohorts were matched by age, sex, and psychiatric diagnosis, we found group differences with regard to SES, urbanization, and prevalence of hyperlipidemia. Our study cohort of those receiving ECT had lower SES than the comparison cohort (Table 1; $p < 0.0001$). They also had a higher level of urbanization (Table 1, $p = 0.020$). Urbanization is a risk factor for schizophrenia (Lederbogen et al., 2011). One previous study of a Taiwanese population has also reported an increased risk of stroke in more urbanized groups and suggested that increased risk of stroke may related increase air pollution, life pressure, depression, all of which have associated with urbanization level (Lin et al., 2007).

Our analysis took into account several physical illnesses known to be risk factors of stroke such as diabetes, hypertension and coronary heart disease (Guzik and Bushnell, 2017). Our ECT cohort had a significantly higher prevalence of hyperlipidemia than the comparison cohort (Table 1, 4.10% vs. 3.40, $p = 0.025$). There were no differences in distribution of diabetes, hypertension and coronary heart disease. Our ECT cohort had lower incidence of stroke (Table 1, 6.90% vs. 8.20%, $p < 0.001$). While it would easy to conclude that ECT is safe based on this finding, the reduced risk of stroke associated in this study may also be related to the fact that doctors considering the use of ECT to treat a patient request comprehensive physical and lab examinations

prior to making this treatment decision to avoid subjecting patients with poor physical conditions to this stress-inducing treatment. It would be reasonable to assume that many patients receiving ECT are in better physical condition than those who do not. However, ECT patients have a higher comorbidity by a significantly higher CCI-S and are still at lower risk of stroke as we demonstrated in Table 1.

Most studies of the relationship between ECT and subsequent stroke do not control for comorbid disease (Elmaadawi et al., 2017; Rozing et al., 2018). We controlled for comorbid diseases reported to be associated with stroke (Guzik and Bushnell, 2017). Our Cox proportional hazards regression model revealed age, diabetes, hypertension and coronary heart disease to be risk factors for stroke in the ECT cohort. However, after controlling for these comorbid diseases, this study found ECT to remain significantly associated with a reduced risk of subsequent stroke in Taiwan. How might ECT reduce risk of stroke? It is well-known that a psychiatric disease can influence a patient's cognitive ability and thus his or her ability to maintain healthy lifestyles (Shahab et al., 2018; Zuckerman et al., 2018). Although ECT, itself, has previously been reported cause memory disturbance (Semkovska and McLoughlin, 2010). A more recent meta-analysis has revealed that this effect is not usually long-term (Zheng et al., 2018). Thus, ECT may improve cognition, an improvement that could then lead to the better maintenance of a healthier lifestyle, reducing risk of stroke as well as other cardiovascular diseases.

Compared to a similar cohort study in Demark which showed ECT was not associated with an elevated risk of new stroke or recurrent stroke, our study showed ECT was associated with reduced risk of subsequent stroke in patients with severe mental illnesses. The difference may come from age, level of education, comorbid alcohol misuse, diagnosis, and previous history of stroke or transient ischemic attack. The group treated with ECT were relatively young in our study compared to a previous ECT and later stroke in Denmark (Rozing et al., 2018). Age itself is a risk factor of stroke (Boehme et al., 2017). However, there was higher stroke risk in our study group than the Denmark study despite of younger age. We proposed doctors practicing ECT in other countries should considering the protect effect of ECT in stroke especially in young patients.

This study has several limitations inherent to the use of claims databases. First, Taiwan's national health insurance claims do not contain patient lifestyle and behavior data, so we could not include it in our analysis. We didn't not include pharmacological and psychotherapy in this study. Antipsychotics were report to increase the risk of metabolic syndrome which is a risk factor of stroke (Newcomer, 2007). The reduced incidence of stroke in patients with lower SES might be related to pre-stroke deaths, as lower SES and mental illness have both been associated unhealthy lifestyles and risk-taking behaviors (Krueger and Chang, 2008). The reduced incidence of stroke in patients with lower SES might also be related to a very rough and uncommon definition of SES, which is also a limitation of SES related results. Second, the diagnosis and severity of the stroke listed in claims data may not always be completely accurate, though the accuracy of the diagnosis has been studies and validated (Hsieh et al., 2015). Third, we didn't include the intervals between ECT and stroke. Survival analysis about the intervals between ECT and stroke may be need in further study.

In conclusion, this nationwide cohort study found that there is a reduced risk of stroke among psychiatric patients receiving ECT in Taiwan. It also found that in patients receiving ECT, as in the general population, age, diabetes, hypertension and coronary heart disease are risk factors for stroke. Therefore, psychiatrists need not let risk of stroke prevent them from recommending ECT to physically healthy patients who might benefit from this therapy. Further prospective studies taking in account lifestyle factors, pharmacological therapies and psychotherapy may be needed to confirm our findings.

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Conflict of interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Kuan-Ying Hsieh: Conceptualization, Visualization, Formal analysis, Data curation, Writing - original draft. **Kuan-Yi Tsai:** Formal analysis, Data curation, Validation. **Frank Huang-Chih Chou:** Conceptualization, Visualization, Formal analysis, Data curation, Validation, Funding acquisition, Supervision. **Yu-Mei Chou:** Conceptualization, Visualization, Formal analysis, Data curation, Validation, Funding acquisition, Supervision.

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