Original article

Evaluation of the efficacy of the continuation electroconvulsive therapy in treatment-resistant schizophrenia

Avaliação da eficácia da eletroconvulsoterapia contínua para esquizofrenia resistente ao tratamento

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Abstract

Background: Electroconvulsive therapy (ECT) has been reported being a safe and effective treatment in schizophrenia. However, there are a limited number of studies assessing continuation ECT utilization in patients with schizophrenia giving partial response to pharmacological treatment. **Objective:** The aim of this study is to evaluate the effectiveness of continuation ECT in preventing relapse in patients with treatment-resistant schizophrenia. **Methods:** In this retrospective analysis, schizophrenia patients (n = 73) were defined in three groups such as patients who received only AP treatment (only AP), patients who received acute ECT only during hospitalization (aECT+AP), patients who received acute ECT and continuation ECT (a-cECT+AP). Three groups were compared according to positive and negative syndrome scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) scores. **Results:** As per comparison of only AP group, aECT+AP group and a+cECT+AP groups in terms of after discharge PANSS and after discharge BPRS scores for 1st month, 3rd month and 6th month; 3rd and 6th month's PANSS scores of a+cECT+AP group were statistically significantly lower than other two groups. **Discussion:** Although this study suffers the limitations of retrospective medical chart analysis, results suggest that, in patients with a diagnosis of schizophrenia who have responded to an acute course of ECT, continuation ECT in combination with antipsychotics is more effective than antipsychotics alone in preventing relapse.

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Keywords: Continuation ECT, schizophrenia treatment-resistant, PANSS, BPRS.

Resumo

Contexto: A eletroconvulsoterapia (ECT) tem mostrado ser um tratamento seguro e eficaz para esquizofrenia. No entanto, o número de estudos que avaliam a utilização contínua de ECT em pacientes com esquizofrenia e a resposta parcial ao tratamento farmacológico é limitado. **Objetivo:** O objetivo deste estudo é avaliar a eficácia da ECT de continuação na prevenção de recaída em pacientes com esquizofrenia resistente ao tratamento. **Métodos:** Nesta análise retrospectiva, pacientes com esquizofrenia (n = 73) foram alocados em três grupos: pacientes que receberam apenas o tratamento AP (somente AP), pacientes que receberam um curso agudo de ECT durante a hospitalização (aECT+AP) e pacientes que receberam um curso agudo de ECT durante a hospitalização e ECT de continuação (a-cECT+AP). Esses três grupos foram comparados de acordo com a pontuação atribuída na *Positive and Negative Syndrome Scale* (PANSS) e na *Brief Psychiatric Rating Scale* (BPRS). **Resultados:** De acordo com a comparação dos grupos, somente em AP, aECT+AP e a+cECT+AP, em termos de PANSS e BPRS, após descarga no primeiro, terceiro e sexto mês, as pontuações na PANSS no terceiro e sexto mês no grupo a+cECT+AP foram estatística e significativamente menores do que nos outros dois grupos. **Conclusões:** Embora este estudo mostre limitações causadas pela análise retrospectiva de prontuários, os resultados sugerem que a continuação da ECT em combinação com antipsicóticos é mais eficaz do que somente os antipsicóticos, na prevenção da recaída em pacientes com diagnóstico de esquizofrenia que responderam ao curso agudo de ECT.

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Palavras-chave: ECT de continuação, esquizofrenia resistente ao tratamento, PANSS, BPRS.

Introduction

Electroconvulsive therapy (ECT) is one of the oldest biological treatment methods used in the field of modern psychiatry. This method based on the generation of generalized convulsions by stimulating the brain tissue with electrical current. ECT has been introduced into clinical use before the development of psychopharmacology at the end of the 1930s. Despite the avoidance and stigmatization of ECT caused by the negative reflection of some movies and novels, today, ECT is recognized as one of the most effective treatment options[1]. It is used in cases of severe depression and mania, and in catatonic patients who do not respond to other treatments or who require urgent solutions, many successful results were also obtained after ECT applications in many disorders other than those listed[2].

The exact mechanism of ECT is unclear, but there is a wide range of theories regarding its effectiveness. Some of them are amnestic theory, the theory of the autonomic nervous system, neurohumoral theory, anticonvulsant theory and the theory of the neuroendocrine system[3]. According to these theories, ECT increases receptor sensitivity in dopaminergic and noradrenergic pathways, and serotonin turnover; it also activates monoaminergic pathways extending from diencephalic centers to hypothalamus and limbic regions[4]. Elevation in plasma cortisol levels and prolactin secretion during ECT indicates an increase in hypothalamic activity and, an increase in neurotransmitter activity[5,6]. It is reported that ECT corrects the hemispheric dysfunction and provides synchronization between the left and right hemispheres[7]. According to the anticonvulsant theory, therapeutic effect depends on the brain's finalization process of the seizure, but not directly on ECT-induced convulsive seizures. In other word, although ECT causes seizure, it shows anticonvulsant effect in the long-term. It was reported that seizure threshold elevation was associated with a favorable clinical response[6,7]. In Turkey, the frequency of ECT applications in inpatients is 14%-16%, and it is about 5%-12% in the USA and many Asian countries[8-10].

According to the clinical situation and the response, ECT is implemented two or three times a week and 5-12 sessions in total[3].

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In the first years of use, ECT has been applied without intravenous anesthetics and muscle relaxants; it caused fractures and perceived as a fearful traumatic experience. Today, ECT is applied with intravenous anesthetics and muscle relaxants[11,12]. Continuation ECT is applied after acute ECT at least for six months in order to prevent relapse; Maintenance ECT is applied after a successful ECT course within the first six months at regular intervals ranging from a week to a month in order to prevent recurrence; the ones applied after 6 months are recommended to be called as "Preventive ECT"[13,14]. According to American Psychiatric Association, Maintenance ECT criteria: repetitive, episodic illness which respond to ECT; inability to tolerate maintenance drug treatment or ineffectiveness in preventing early exacerbations; being able to adapt to Maintenance ECT[15,16]. ECT has been reported being a safe and effective treatment in schizophrenia the first acute attack, and in patients with catatonia and suicide risks[17-19]. However, there are a limited number of studies assessing continuation ECT utilization in patients with schizophrenia giving partial response to pharmacological treatment[19-20]. In one of these studies, patients with schizophrenia were compared by dividing into three groups, patients receiving both continuation ECT and flupenthixol, patients receiving continuation ECT alone, and patients receiving flupenthixol alone. In this study, group of patients receiving both continuation ECT and neuroleptics had a relapse rate significantly lower than the other two groups[19]. In another study, it has been reported that a patient with catatonic schizophrenia and tardive dyskinesia has benefited from continuation ECT[21]. The aim of this study is to evaluate the effectiveness of continuation ECT in preventing relapse in patients with treatment-resistant schizophrenia.

Methods

Files of 255 patients who were diagnosed with schizophrenia according to DSM IV-TR between January 2012 and March 2013 after psychiatric assessment in Uskudar University NP Istanbul Psychiatry Hospital and hospitalized, and followed-up as an outpatient after discharge were evaluated retrospectively. The study continued with 73 patients with schizophrenia as patients using only a combination of 800-1400 mg/d chlorpromazine equivalent dose antipsychotic (AP) during their hospitalization and outpatient follow-up were included, and patients with comorbid psychiatric and neurological diagnoses and those with alcohol and substance abuse/dependence were excluded. These patients were defined in three groups such as patients who received only AP treatment (only AP), patients who received acute ECT only during hospitalization (aECT+AP), patients who received acute ECT and continuation ECT (a-cECT+AP). Only AP group, aECT+AP group, and a-cECT+AP group were compared according to positive and negative syndrome scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) scores. Scales applied to patients at the baseline, at time of hospitalization were hospitalization-PANSS (H-PANSS) and hospitalization BPRS (H-BPRS); scales applied to patients during discharge were discharge PANSS (D-PANSS) and discharge BPRS (D-BPRS).

PANS and BPRS scores of three groups followed-up during six months after discharged were compared for the 1st month, 3rd month and 6th month. Continuation ECT was defined as ongoing ECT that was administered after completion of the course of three times a week acute ECT, beginning with the administration of ECT on a weekly or less frequent basis. All data on demographic and clinical characteristics were abstracted from all patients' charts retrospectively.

ECT protocol

All ECT applications were short pulsed with continuous flow through MECTA-SPECTRUM brand ECT device brief pulse, square wave type, 500-800 mA (milliamps). All of the patients received bilateral bitemporal ECT application. For the formation of an effective convulsion, 20-60 joule current with the energy level of 3-8 was applied. ECT induced seizure duration was monitored with electroencephalography (EEG) (Thymatron System IV Somatics, IL, USA). ECT was applied three times in a week after 12-hour fasting and psychoactive medications were stopped 12 hours before ECT. Age-based method used as ECT stimulus dosing protocol[22]. This protocol was reviewed by the Uskudar University institutional review board and judged to be exempt from the requirement for written informed consent due to its retrospective design.

Statistical methods

SPSS (Statistical Package for Social Sciences) for Windows 16.0 software was used to analyze study data. Quantitative variables were expressed as mean ± standard deviation (SD) while qualitative variables were expressed as numbers and percentages. A normal distribution was found for quantitative variables by using the Shapiro-Wilk normalcy test ($p > 0.05$). Comparison of the Only AP group, aECT+AP group, and a-cECT+AP group was the Pearson chi-square analysis. The three-way comparison of the Only AP group, aECT+AP group, and a-cECT+AP group for PANSS and BPRS scores was with the one-way variance analysis (ANOVA) test and the two-way comparison with the Tukey method. The intragroup variables were tested with the Pearson Correlation Analysis. A p value < 0.05 was accepted as statistically significant.

Results

The study included 26 only AP patients with schizophrenia, 28 aECT+AP patients with schizophrenia, 19 a+cECT+AP patients with schizophrenia; a total of 73 patients with schizophrenia. The mean age of the only AP group was 31.92 ± 7.82 years, the mean age of the aECT+AP group was 31.82 ± 6.65 years, and the mean age of the a+cECT+AP group was 34.79 ± 9.80 years. There was no statistically significant difference in three groups in terms of socio-demographic characteristics ($p \geq 0.05$), (Table 1).

aECT+AP group received 9.71 ± 2.17 ECT, a+cECT+AP group received 21.89 ± 9.80 ECT. According to the comparison of the three groups in terms of H-PANSS, D-PANSS, H-BPRS, D-BPRS scores, a+cECT+AP group's H-BPRS, D-BPRS scores were statistically significantly higher than only AP group and aECT+AP group ($p < 0.01$). There were no differences between groups in terms of

Table 1. Comparison of the only AP group, aECT+AP group and a+cECT+AP group in terms of socio-demographic characteristics

	Only AP group (n = 26)	aECT+AP group (n = 28)	a+cECT+AP group (n = 19)	p
Age (year) (Mean ± SD)	31.92 ± 7.82	31.82 ± 6.65	34.79 ± 9.80	0.39[a]
Gender (n, %)				
Female	10 (38.5%)	13 (46.4%)	7 (36.8%)	0.76[b]
Male	16 (61.5%)	15 (53.6%)	12 (63.2%)	
Marital status (n, %)				
Married	11 (42.3%)	12 (42.9%)	11 (57.9%)	0.52[b]
Single	15 (57.7%)	16 (57.1%)	8 (42.1%)	
Education (n, %)				
Primary school	19 (73.1%)	21 (75.0%)	13 (68.4%)	0.88[b]
High school/+	7 (26.9%)	7 (25.0%)	6 (31.6%)	
Occupation (n, %)				
Working	4 (15.4%)	4 (42.6%)	3 (15.8%)	0.99[b]
Not working	22 (84.6%)	24 (85.7%)	16 (82.2%)	

[a]: one-way variance analysis (ANOVA) test used; [b]: chi-square test used.

other scales (p ≥ 0.05) (Table 2). Although the a+cECT+AP group had slightly longer mean duration of disease (10.89 ± 7.31 years), the mean length of disease did not differ statistically significantly between groups (p = 0.16)

Table 2. Comparison of only AP group, aECT+AP group and a+cECT+AP group in terms of numbers of ECT applied and H-PANSS, D-PANSS, H-BPRS, D-BPRS scores

	Only AP group (n = 26)	aECT+AP group (n = 28)	a+cECT+AP group (n = 19)	p
	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)	
Number of ECTs		9.71 ± 2.17	21.89 ± 9.80	**0.0001**[a]
				0.0001[c]
H-PANSS	107.12 ± 23.37	101.11 ± 22.90	110.00 ± 19.33	0.37[a]
				0.58[b]
				0.37[c]
				0.90[d]
D-PANSS	56.35 ± 9.47	51.11 ± 10.14	51.53 ± 12.36	0.15[a]
				0.17[b]
				0.99[c]
				0.29[d]
H-BPRS	45.35 ± 11.62	43.14 ± 15.85	60.32 ± 10.24	**0.0001**[a*]
				0.81[b]
				0.0001[c*]
				0.001[d*]
D-BPRS	19.27 ± 6.83	16.46 ± 6.63	31.37 ± 11.18	**0.0001**[a*]
				0.42[b]
				0.0001[c*]
				0.0001[d*]

*: statistically significant; [a]: between only AP group, aECT+AP group and a+cECT+AP groups; [b]: between only AP group, aECT+AP groups; [c]: between aECT+AP group and a+cECT+AP groups; [d]: between only AP group, and a+cECT+AP groups.

As per comparison of only AP group, aECT+AP group and a+cECT+AP groups in terms of after discharge PANSS and after discharge BPRS scores for 1st month, 3rd month and 6th month; 3rd and 6th month's PANSS scores of a+cECT+AP group were statistically significantly lower than other two groups (p < 0.01). 1st month's BPRS scores of a+cECT+AP group were statistically significantly higher than other two groups (p < 0.05). 6th month's BPRS of a+cECT+AP group were statistically significantly lower than only AP group (p < 0.05). There were no significant differences between 1st month's PANSS and 3rd month's BPRS scores of the three groups (p > 0.05) (Table 3).

In aECT+AP group and a+cECT+AP group (n = 47); in correlation analysis between numbers of ECT and PANSS and BPRS scores; rate of change of the number of ECT and PANSS during hospitalization (D-PANSS), between 3.month PANSS, 6.month PANSS and 6.month BPRS scores, a statistically significant negative correlation was found (respectively; p = 0.03, p = 0.0001, p = 0.0001, p = 0.001) (Table 4).

Table 3. Comparison of only AP group, aECT+AP group and a+cECT+AP group in terms of PANSS and BPRS scores for 1.month, 3.month and 6.month

	Only AP group (n = 26)	aECT+AP group (n = 28)	a+cECT+AP group (n = 19)	p
	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)	
1.month PANSS	54.81 ± 13.91	52.25 ± 10.83	51.16 ± 12.69	0.59[a]
				0.73[b]
				0.95[c]
				0.60[d]
3.month PANSS	68.35 ± 25.94	62.25 ±24.17	42.26 ± 12.12	**0.001**[a*]
				0.58[b]
				0.01[c*]
				0.001[d*]
6.month PANSS	73.50 ± 38.72	66.57 ± 37.46	33.37 ± 11.93	**0.0001**[a]
				0.73[b]
				0.004[c*]
				0.0001[d*]
1.month BPRS	18.88 ± 8.84	19.96 ± 13.64	29.84 ± 10.85	**0.004**[a*]
				0.94[b]
				0.01[c*]
				0.006[d*]
3.month BPRS	25.54 ± 13.90	25.54 ± 15.65	23.11 ± 9.94	0.80[a]
				1.00[b]
				0.82[c]
				0.83[d]
6.month BPRS	32.46 ± 23.32	28.29 ± 23.26	16.58 ± 8.57	**0.04**[a*]
				0.74[b]
				0.11[c]
				0.03[d*]

*: statistically significant; [a]: between only AP group, aECT+AP group and a+cECT+AP groups; [b]: between only AP group, aECT+AP groups; [c]: between aECT+AP group and a+cECT+AP groups; [d]: between only AP group, and a+cECT+AP groups.

Table 4. In aECT+AP group and a+cECT+AP group; correlation analysis between the numbers of ECT and PANSS and BPRS scores

	Number of ECT	Number of ECT
	(n = 47) (r)	(n = 47) (p)
D-PANSS	(-0.320)	**(0.03*)**
D-BPRS	(0.235)	(0.11)
1.month PANSS	(-0.219)	(0.14)
3.month PANSS	(-0.630)	**(0.0001*)**
6.month PANSS	(-0.655)	**(0.0001*)**
1.month BPRS	(0.231)	(0.12)
3.month BPRS	(-0.281)	(0.05)
6.month BPRS	(-0.464)	**(0.001*)**

Pearson correlation tests were used; *: statistically significant; PANSS-D: Y- PANSS and T-PANSS rate of change; BPRS-D: Y-BPRS and T-BPRS rate of change.

Discussion

Among the somatic treatments used in the practice of psychiatry, only ECT is started and stopped within a period of three or four weeks[3]. This situation has led to the occurrence of frequent relapses after ECT. Besides the use of ECT in the treatment of acute attacks, initiation of preventive treatment may be an appropriate approach in preventing relapses. One of the recommended approaches to reduce the rate of recurrence is to switch to protective pharmacotherapy following the termination of ECT[23]. However, it has been reported that protective pharmacotherapy did not provide an reasonable level of success in preventing recurrence[23]. Another strategy to prevent relapse after ECT is applying protective ECT for 4-12 months after the completion of the ECT implementation in the acute phase. However, lack of prospective, randomized study concerning the validity of this method and the fact that patients has to undergo general anesthesia for months restricts the applicability[23,24]. According to the findings of this study performed with the aim to evaluate the efficacy of continuation ECT on patients with schizophrenia who receive preventive pharmacotherapy; Y-BPRS, T-BPRS scores of the a+cECT+AP group were significantly higher than both only AP group and aECT+AP group. There were no differences between groups in terms of other scales. Scores of BPRS which is used to assess severity and changes of psychotic and depressive symptoms in schizophrenia and other

psychotic disorders were high in a+cECT+AP group, and it supports that the maintenance ECT has been an appropriate approach for this patient group[25]. Lately, Continuation and Maintenance ECT became a choice of treatment option for a group of treatment-resistant patients who do not benefit much from other treatment options[26].

According to another result of this study; when three groups were compared in terms of 1.month-3.month-6.month PANSS and BPRS scores; 3.month-6.month PANSS scores of a+cECT+AP group were significantly lower than other groups, 1.month-BPRS scores of a+cECT+AP group were significantly higher than other groups. 6.month-BPRS scores of a+cECT+AP group were significantly lower than Only AP group. There were no significant differences between 1.month-PANSS and 3.month-BPRS scores of the three groups. According to several studies, especially in patients with treatment-resistant schizophrenia, ECT combined with pharmacotherapy is more effective than just pharmacotherapy during the acute period[21-23]. However, for this advantage to be permanent, ECT implementation in intervals has been recommended, and maintenance ECT has been raised. Maintenance ECT has been reported to be a trustworthy option if drug therapy remains deficient in various situations, such as discontinuation, metabolic side effects, efficacy strength, duration of remission, and cost-effectiveness[26]. In a study on the use of maintenance ECT in schizophrenia; ECT and AP combination have been found to be superior than ECT alone or AP treatment alone in terms of preventing relapse[19]. In another study, 11 schizophrenia patients who received ECT during acute treatment and who did not receive neuroleptic drugs were applied continuation ECT after discharge for a period of six months – 1st month weekly, twice a week for two months, once in a month respectively. No deterioration was reported in 8 patients who completed the course[20]. In a case series, schizophrenia patients who do not respond to AP drug treatment were followed-up for a year after maintenance ECT, and it was reported that remission sustained only with chlorpromazine. According to these cases, it has been suggested that ECT either changes the course of the disease or increases the response to AP[27]. In this study, 3.month-6.month PANSS scores of a+cECT+AP group were lower than other groups, and that result supports the effectiveness of continuation ECT in preventing relapse and in sustaining remission. Additionally, 1.month-BPRS scores of a+cECT+AP group were significantly higher than other groups, and this might be related to the resistance of the patients who received maintenance ECT. Considering the literature, the maintenance ECT patients typically seem to be resistant to pharmacotherapy[19,20,26]. In a study, however, in terms of response to maintenance ECT in schizophrenia, good prognosis indicators are acute onset of the disease; less admission history; high education level; short-term use of the AP; less severe disease; better response to maintenance ECT and maintained memory functions. These results suggest that many factors need to be assessed when deciding on maintenance ECT[28]. Additionally in this study, decrease in 6th month's BPRS scores supports the efficacy of continuation ECT. Finally, in aECT+AP group and a+cECT+AP group, significant negative correlation between the number of ECT and PANSS rate of change (PANSS-D) and 3.month-PANSS, 6.month-PANSS, 6.month-BPRS scores suggest that the number of ECTs applied is associated with the maintenance of remission. Also, preventive ECT consisting of ECT applications after 6 months can be considered in patients with recurrent disease, responding to acute ECT, and accommodating maintenance ECT[29]. However, these results are required to be supported by further studies with larger patient groups. Additionally, it is probable that the promising outcome of cases in the continuation ECT group was a consequence of their more direct contact with medical staff. Patients in continuation ECT group were needed to see their clinicians at least twice a month to continue treatment. This close contact may have served as psychosocial support for the continuation ECT group.

Although this study gives relevant results about continuation ECT, it has some limitations. First this was a naturalistic, retrospectively designed study. Assignment of patients to treatment groups was not random, and assessments of outcome were not blind, but diagnostic and clinical data were all derived from structured instruments. The sample size was modest, possibly resulting in limited power to detect significant differences in the clinical characteristics of the groups. Another limitation of the study is the probable unreported medical characteristics of these patients that can influence the outcome such as use of clozapine, or refractoriness. Therefore, the results must be taken with caution as we can not clearly exclude that the difference in the outcomes are caused by a design bias. A method to partially control for such bias in future research would be the use of propensity score matching to perform group comparisons.

Conclusion

Despite the limitations of the method (retrospective study of medical files), this study suggests that, in patients with a diagnosis of schizophrenia who have responded to an acute course of ECT, continuation ECT in combination with antipsychotics is more effective than antipsychotics alone in preventing relapse. However, prospective longitudinal studies are needed to confirm these findings.

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The authors have no conflicts to disclose.

Conflicts of interest

There is no conflict of interest in this study.

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