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Effectiveness of the Combined Antipsychotic and Electroconvulsive Therapy (ECT) in Patients with First Episode Psychosis

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Keywords

Electroconvulsive therapy; treatment outcome; clinical competence; psychotic disorders

Abstract

Aim: This is a naturalistic controlled study to assess the efficacy of electroconvulsive therapy (ECT) as an augmentation strategy in patients with first episode psychosis (FEP). **Subjects and methods:** Sixty-five patients diagnosed with FEP according to DSM-IV -TR were included. Patients with affective psychosis and/or any other major psychiatric disorders or neurological disorders were excluded. Fifty patients were allocated to ECT group treated with combined antipsychotics and ECT therapy, with maximum 12 sessions, and 15 patients were allocated to non ECT group treated by antipsychotic medications only. Severity of symptoms and treatment response of the subjects in both groups were measured using Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS), and Clinical Global Impression (CGI) at admission and discharge, and the percentage of change in the scores of both groups were compared. **Results:** At baseline, the ECT group showed significantly higher severity of symptoms. At the endpoint both groups had a significant decrease from basal score, yet the ECT group showed highly statistically significant difference as regard the percentage of change as scored by the BPRS, CGI, and total PANSS and all its subscales. These differences were more pronounced in positive vs. negative symptoms. **Conclusion:** The combination of ECT and antipsychotic medications could be an effective early psychosis intervention and showed better results than antipsychotic drugs used alone. However, in contrast to our expectation it did not decrease the duration of hospitalization.

Introduction

Electroconvulsive Therapy (ECT) is the oldest psychiatric treatment. Its safety and tolerability are well-established in the treatment of severe psychiatric disorders in adults [1]. However, over the years the use of ECT in patients with schizophrenia has declined in developed countries, and its use is mostly restricted to treatment- resistant schizophrenia. However, it is still used frequently in low-income countries [2]. ECT is under-

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used due to stigma, in addition to the cognitive adverse effects. However, research has suggested that the ability to learn new information and non-memory cognitive functions are not affected, and that objective memory impairment occurring during a course of ECT is mostly reversible [3].

We are investigating the use of ECT in first-episode psychosis (FEP) as it is a potential effective treatment for "florid positive psychotic symptoms', like excitement, delusions and catatonia, or affective features commonly present in FEP, especially when rapid improvement is desired [4]. There is evidence that the use of ECT to augment antipsychotics may result in higher discharge rates than placebo or sham ECT. Moreover, many patients presented with moderate to severe impairment at the FEP, do not obtain full remission by pharmacotherapy alone, and eventually develop relapse [5]. The use of ECT in FEP was not systematically evaluated [6]. Indeed, 1985, a NIH Consensus Conference Panel recommended ECT for schizophrenia with acute onset. However, in 1990, the American Psychiatric Association (APA) sanctioned the use of ECT for schizophrenia with prominent affective features or catatonia during exacerbations [7]. This further supports that research is required to determine the usefulness of the ECT and antipsychotics combination in the treatment of acute psychosis [8].

The APA defined the FEP as the first manifestation of the disorder of full-blown psychotic symptoms, which are the prominent presence of delusions and/or hallucinations and/or disorganized speech and/or disorganized behaviour (including catatonia) with no insight and impairment in one's capacity for judgment [9]. At the time of first psychotic symptoms, neurobiological processes underlying schizophrenia have already been ongoing for many years. Although increased dopamine synthesis may be the final common pathway to psychosis, hypofunction of the NMDA, associated decreased GABA-ergic signalling and increased proinflammatory status of the brain are important underlying mechanisms [10].

The mechanism of action of ECT remains poorly understood [11]. Limited data suggest ECT shares some properties with atypical antipsychotic medications in the aspect that ECT enhances serotonergic neurotransmission and activation of the meso-cortico-limbic dopamine system [12]. They affect pro-inflammatory cytokine network and immune function in schizophrenia, possibly modifying the course of disease [11,13]. Evidence also suggests that ECT in schizophrenia patients alters cerebral blood flow in the prefrontal cortex [14] and increases brain-derived neurotrophic factor (BDNF) levels [15-17].

ECT could be a promising treatment strategy in FEP. In acutely agitated patients or patients showing severe disorganized behaviour, it would be extremely difficult to keep patients only on psychotropic drugs for 6-8 weeks as recommended by guidelines. Longer duration of hospitalization also has to be avoided [18]. Most previous studies of ECT have focused on pharmacotherapy-resistant conditions. The use of ECT in acute phases of schizophrenia remains controversial [19]. Accordingly, the aim of this study was to evaluate the usefulness of the antipsychotic and ECT combination among patients with FEP. We hypothesized, that improvement from baseline to discharge in clinical characteristics would be higher in the ECT group compared with patients treated with antipsychotics alone.

Subjects and Methods

This cross-sectional comparative naturalistic study was carried out in the tertiary care Ain Shams Hospital's psychiatry department, in the period from June 2015 until the end of December 2015, to assess the efficacy of ECT as augmentation strategy in patients with FEP. The institute of psychiatry is in Eastern Cairo and serves a catchment area of about the third of Greater Cairo with a population of 17.681 million. It serves both urban and rural areas.

The clinical sample of this study consisted of a convenient sample of 65 patients presented to the outpatient clinics of Ain shams Hospital's psychiatry department or admitted to the inpatients department with the diagnosis of FEP. FEP (Schizophrenia, Schizophreniform Disorder, Brief Psychotic Disorder) was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV-TR) criteria by means of the Structured Clinical Interview for DSM-IV (SCID I) with a duration of illness $\leq$ 6 months. Male patients only were included. We decided to include only male patients, because some studies report that gender may constitute a determining factor that affect the response to ECT, regardless of diagnosis [20]. Patients with an age between 18 and 40 years were included, and those who agreed to participate in the study. Patients with affective psychosis, any serious concomitant neurological disease or any major psychiatric disorders other than FEP were excluded, and also those who refused to sign the consent.

Procedures

The current study is a naturalistic one, where the FEP patients were divided into two groups based on the management treatment; the group of patients with FEP treated with ECT and antipsychotic combined therapy (ECT group) consisting of 50 patients and the group of FEP patients group treated with antipsychotic medications only without receiving ECT (non ECT group) consisting of 15 patients. Approval of the ethical committee of Faculty of medicine Ain Shams University was obtained. An informed written consent was signed from all participants in the study.

The database of the psychiatric institute showed that 70 patients were eligible to the criteria of the study during the period

of the study. Of these patients, 2 were excluded from the study due to having affective psychosis and there were 3 patients who refused to sign consent. There were no dropouts. Therefore, data of only 65 cases were included.

In Ain Shams university psychiatry department, ECT is administered to both outpatients and inpatients. ECT is commonly used among patients with psychosis; the usual indications are catatonia, FEP especially with severe symptoms, agitation/excitement, suicidality, and antipsychotic refractory symptoms. The decision to start ECT is usually made by a consultant psychiatrist (MD level) after detailed assessment. In complicated cases, a second opinion is usually sought from the head of unit. Once the treating-team decides that ECT is clinically indicated, written informed consent is sought from both patients and their relatives, after a detailed explanation of the process. ECT is administered only on a voluntary basis. Consenting patients undergo physical assessment and investigations as required and are also assessed by an anaesthetist.

The severity of symptoms and treatment response were assessed using Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI). Blind Assessment of the patients on admission and on discharge was done.

Electroconvulsive therapy

ECT was carried out by a team composed of an anaesthesiologist, a psychiatrist, a psychiatric nurse, and anaesthesia technician at the ECT division of the department of psychiatry, Ain Shams University. It was performed using a Thymatron DG (Somatics, Inc., Lake Bluff, IL, USA.) with standard settings. Energy dial was set according to patients' age and response. The registration of charge delivered (maximum of 504 mC), current (0.9 A), frequency (Hz), pulse width (ms), duration (max 8 seconds). The electrode placement was standard bilateral Frontotemporal.

After a period of fasting (8-12 hours) all patients received anaesthesia by sodium pentothal (3.5 mg/Kg) and a muscle relaxant (succinyl-choline chloride, 0.5 - 0.75 mg/Kg), atropine (0.2 - 0.4 mg) followed by oxygenation. The number of ECT sessions varied from 6 to 12. ECT was given three times per week, with proper monitoring of vital data, seizure parameters, and of the post-ECT period. Motoric seizure of at least 15 seconds is regarded as an effective treatment. ECT was discontinued if the clinical response reaches a plateau over two consecutive ECT treatments, if there is remission of target symptoms, or if patient develops complications during ECT, which contradict further use.

Tools

1. A neuro-psychiatric history and examination of cases using the standard Ain Shams University psychiatric sheet including socio-demographic data, past history of psychiatric and medical disorders was done.
2. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) was used to diagnose FEP (Schizophrenia, Schizophreniform disorder, and Brief Psychotic Disorder) and to exclude the presence of any other major psychiatric disorders. Arabic version was used [21,22]. Since the definition of the exact duration of FEP is controversial, patients with duration of illness ≤ 6 months were included in the study.
3. Positive And Negative Syndrome Scales (PANSS) [23].
   The PANSS is a 30-item rating scale that is specifically developed to assess individuals with schizophrenia and is used very widely in research settings. Of the 30 items included in the PANSS; 7 constitute a Positive Scale, 7 a Negative Scale, and the remaining 16 a General Psychopathology Scale [24,25].
4. Brief Psychiatric Rating Scale (BPRS) [26]. The BPRS was developed in the late 1960s as a short scale for measuring the severity of psychiatric symptomatology. An 18-item scale developed primarily to assess change in psychotic inpatients and to assess the effectiveness of treatment. It covers a broad range of areas including thought disturbance, emotional withdrawal and retardation, anxiety and depression, and hostility and suspiciousness. Its 18 items are rated on a seven-point item-specific Likert scale from 0 to 7, with the total score ranging from 0 to 108.

Clinical Global Impression (CGI)

The complete CGI – Clinical Global Impression Scale consists of three different global measures designed to rate the effectiveness of a particular treatment: CGI-S globally assess Illness Severity at baseline and CGI-C assessing Global Improvement or the change in the patient's clinical status, efficacy index or therapeutic response [27].

Statistics

The collected data were analysed to obtain results by using the computerized version of the Statistical Package for Social Sciences, 17th version (SPSS 17). Quantitative variables were described in mean–standard deviation (SD) and numbers and percentages if qualitative. For quantitative variables, group means were compared using Student t test (2-tailed). Correlations (two-tailed) were calculated using Pearson coefficient. For quantitative variables. The value of p was used to indicate the level of significance ($p = 0.05$ is considered significant, $p = 0.01$ is highly significant and $p = 0.001$ is very highly significant).

Results

This is a naturalistic cross-sectional comparative study, conducted in the institute of psychiatry, Ain shams university hospitals. During the period of the study, 65 patients met the eligibility criteria. Fifty FEP patients were treated by antipsychotic and ECT combined thera-

Table 1. Sociodemographic and clinical data of the studied samples

Socio-demographic and clinical data	ECT group N = 50	Non ECT group N = 15
Age (years) Mean ± SD	24.1 ± 4.4	23.2 ± 3.7
Education		
Illiterate	11 (22 %)	3 (20 %)
Primary	7 (14 %)	2 (13.3 %)
Secondary	20 (40 %)	6 (40 %)
Graduate	12 (24 %)	4 (26.6 %)
Occupation		
Unemployed	31 (62 %)	9 (60 %)
Employed	19 (38 %)	6 (40 %)
Marital status		
Unmarried	42 (84 %)	12 (80 %)
Married	8 (16 %)	3 (20 %)
Antipsychotic medications		
Olanzapine	19 (38 %)	7 (46.7 %)
Risperidone	11 (22 %)	6 (40 %)
Typical antipsychotics	12 (24 %)	2 (13.3 %)
Polypharmacy	8 (16 %)	0 (0 %)
Positive Family history	10 (20 %)	3 (20 %)
DUP (months) Mean ± SD	3.7 ± 2	3.5 ± 1.9
Duration of hospitalization (days) Mean ± SD	27.1 ± 5.5	30.3 ± 5.9

SD - standard deviation, ECT - electro-convulsive therapy, DUP - duration of untreated psychosis

py (ECT group) and the other fifteen FEP patients were treated with antipsychotic medications only.

Table 1 shows the average age of presentation of subjects was around 24 years old in both groups. The mean duration of untreated psychosis (DUP) was around 3.5 months in both groups.

Regarding the number of ECT Sessions required for improvement; 25 (50 %) of the patients (ECT group) had 8 ECT sessions, 13 (26 %) received 4 to 6 sessions and 12 (24 %) received 9 to 12 sessions. There were no significant reported adverse effects except for post ECT headache and short-term memory affection.

Comparing clinical response between both groups

Table 2 demonstrates high statistically significant differences in the clinical outcome in the ECT group vs non ECT group, with patients who received ECT having higher percentage of change before and after treatment than the non ECT group in; the BPRS, total PANSS, all PANSS sub-scores and CGI scores. The PSS percent of change was significantly higher than that of NSS.

Correlation between DUP with the clinical outcome and number of ECT sessions

In Table 3, the DUP (in FEP in both groups) had a statistically significant negative correlation with the percentage of change in BPRS, NSS and total PANSS and insignificant negative correlation with PSS. There was also a statistically significant positive correlation between DUP and number of ECT sessions.

Discussion

Although antipsychotic agents are the mainstay of the treatment of psychosis, some of the patients presented with moderate to severe impairment at onset, do not obtain full remission, and eventually follow a chronic course [5]. This calls for the development of alternative strategies to improve response in early psychosis [28].

Evidence about the efficacy of ECT on psychosis mostly comes from chronic patients and little known on FEP. The aim of this study is to evaluate short-term ef-

Table 2. Comparison of patients who received ECT combined with pharmacotherapy (ECT group) and those treated with antipsychotic medications only (non ECT group) regarding clinical response variables (BPRS, PANSS and CGI on admission and discharge and the percentage of change on treatment)

	ECT group N = 50 Mean ± SD	Non ECT group N = 15 Mean ± SD	P-value (t - test)
BPRS baseline	72.7 ± 9	50.8 ± 6.7	< 0.001**
BPRS on discharge	34.4 ± 6.6	33.3 ± 4.7	0.531
BPRS % of change	52.4 ± 8.8	34 ± 8.9	< 0.001**
PSS on admission	36.1 ± 4	25.2 ± 3.2	< 0.001**
PSS on discharge	17 ± 2.9	18 ± 2.5	0.178
PSS % of change	52.8 ± 8.2	28.2 ± 5.2	< 0.001**
NSS on admission	26.5 ± 5.7	18.2 ± 5.1	< 0.001**
NSS on discharge	18.2 ± 4.2	13.3 ± 2.8	< 0.001**
NSS % of change	30.9 ± 9.5	25.1 ± 11.5	0.049*
General psychopathology on admission	65 ± 8.6	46.3 ± 6.6	< 0.001**
General psychopathology on discharge	33.3 ± 6.3	33 ± 5.3	0.823
General psychopathology % of change	48.2 ± 10.1	28.4 ± 9.1	< 0.001**
Total PANSS on admission	127.5 ± 12.7	89.7 ± 11.5	< 0.001**
Total PANSS discharge	68.4 ± 10.9	64.3 ± 7.1	0.174
Total PANSS % of change	46.3 ± 7.4	28 ± 6.2	< 0.001**
CGI on admission	5.6 ± 0.5	4.4 ± 0.5	< 0.001**
CGI discharge	1.6 ± 0.6	2.4 ± 0.5	< 0.001**
CGI % of change	71.1 ± 11.7	44.7 ± 13.8	< 0.001**

DUP - Duration of untreated psychosis, BPRS - Brief Psychiatric Rating Scale, PANSS - Positive and Negative Syndrome Scale, PSS - positive symptom scale, NSS - negative symptom scale, CGI - Clinical Global Impression.

* = statistically significant < 0.05, ** = statistically highly significant < 0.01

ficacy of ECT in patients with FEP. Out of 65 inpatients and outpatients with FEP, 50 were given ECT sessions (ECT group) and 15 were put on antipsychotics alone (non ECT group).

It is worth noting that the ECT group had significantly higher BPRS, total PANSS together, with its 3 subscales, and CGI scores on admission. In agreement with our results, Flamarique and associates found that

Table 3. Correlation between DUP and clinical outcome (Percentage of change in BPRS, PANSS and its 3 sub-scores) and the number of ECT sessions needed (in the ECT group)

		BPRS % of change	PSS % of change	NSS % of change	General psychopathology % of change	PANSS % of change	Number of ECT sessions
DUP	R	-0.340*	-0.093	-0.321*	0.493**	-0.328*	0.493**
	p-value	0.015*	0.517	0.021*	0.000**	0.019*	0.000**

DUP - Duration of untreated psychosis, BPRS - Brief Psychiatric Rating Scale, PANSS - Positive and Negative Syndrome Scale, PSS - positive symptom scale, NSS - negative symptom scale, CGI - Clinical Global Impression.

*= statistically significant < 0.05, **= statistically highly significant < 0.01

patients in their ECT group presented with higher severity at baseline than non ECT patients [29].

Though the duration of hospitalization was shorter in ECT group (27 days) compared with the non ECT group (30 days), this difference did not reach statistical significance. This came in contrast to our hypothesis and to previous studies; Adhikari and Zhang and associates showed the average duration of hospitalization in non ECT group to be longer compared to ECT group [18,28]. This finding could be explained by the small sample in our study, which could undermine this effect from reaching statistical significance. Also, it is worth noting that the ECT group had higher severity scales ratings at the beginning of treatment, which may have taken more time to resolve than milder symptoms in the non ECT section. That is why, such finding should be replicated in larger samples. If this finding turns to be true, that will undermine the benefits of using ECT in FEP.

Improvements in the BPRS, total PANSS and its subscales and CGI percent of change scores in the ECT group between baseline and follow-up assessments were highly significant at discharge. Our results came in agreement with the findings of studies conducted on young adults with FEP [30,28].

Studies on FEP are scarce, however many studies, underwent on treatment resistant schizophrenia, report similar significant reduction in scores on different symptom rating scales with combined use of antipsychotics and ECT [2,18,19].

Our study showed highly significant difference between both groups in positive and general psychopathology subscales scores, and only significant difference regarding negative symptoms. Zhang and associates found comparable results regarding positive symptoms and general psychopathology percentage of change, which were significantly greater in ECT group compared to non ECT group, but there was statistically non-significant difference in negative symptom scores. The differences in the percentage of change in PANSS scores between the two studies may be explained that the assessment was done at week 2 in the study held by Zhang and colleagues, but in our study the assessment was done on discharge after an average duration of hospitalization between 25 and 30 days [28].

These findings corroborate those of other studies which also found no improvement in negative symptoms in patients treated either with antipsychotics and ECT combined therapy or antipsychotics alone and which reported these symptoms to be stable over time [30]. Chanpattana and Andrade also stated that the response to ECT was mainly predicted by less severe negative symptoms at baseline [31].

This lack of effectiveness on negative symptoms may not be specific to ECT. Antipsychotics are also less effective on negative symptoms, compared with positive symptoms. Moreover, as general psychopathology of PANSS represents a cluster of unspecific symptoms, including tension, anxiety, and depression, the greater improvement on general psychopathology in ECT group reflects ECT effectiveness in alleviating anxiety, depression, and other co-morbid symptoms.

Regarding DUP, the average DUP in the subjects was 3.67 months. The correlation between DUP and treatment response showed a statistically significant negative correlation with the percentage of change in BPRS, NSS, General Psychopathology and total PANSS, and an insignificant correlation with PSS. The results agree with other studies showing that, longer DUP is associated with longer time to treatment response in FEP [32-35]. Moreover, Grover and associates reported that response to ECT was mainly predicted by shorter duration of episode [2]. In addition, Perkins and associates reported that shorter DUP was associated with greater response to antipsychotic treatment. These results support the notion that the DUP may serve as an independent predictor of better response to treatment of psychosis in general [36]. Also, this research established that the number of ECT sessions was significantly predicted by DUP, with an average of 8 sessions. This concurs with Ucok & Sibel and Zhang and associates in their studies on ECT in FEP where the mean ECT sessions was 8 sessions and 6 sessions, respectively [19,28].

In conclusion, the results imply efficacy of ECT in the short-term showed in greater reduction in psychopathology in the ECT group, yet it did not shorten hospital stay. There is no doubt, that much more high-quality evidence is required to conclusively establish the usefulness of this combination in FEP. This study raises a further research question, does the efficacy of ECT augmented therapy in reducing symptoms worth implementing it as an early intervention for FEP, given that eventually it did not shorten hospitalization. And in addressing such a question, it should be put in mind the unique properties of ECT that might add to the therapeutic benefit of the treatment. For example, ECT's effectiveness in patients who are antipsychotic non-responders suggests a different or more potent mechanism of action, in addition, the antipsychotic effect of ECT in Parkinson disease highlights a particular divergence, where its application usually produces simultaneous improvement in both the motor and psychotic symptoms in contrast to antipsychotic medications [11,37]. Moreover, ECT can be considered early in cases of neuroleptic malignant syndrome that are refractory to pharmacological interventions [38].

Several limitations restrict the extent to which these results can be generalized. First: as a disadvantage of the

naturalistic study design, there was no control on assigning patients to the ECT group and non ECT group. So, patients were not randomized. And the antipsychotic medications were not unified in the non ECT group, as patients were treated as per unit protocol. Second: male patients only were included in our study. Results may vary for female patients with FEP. Third: Being a naturalistic study-both treatment groups differed significantly in clinical features represented in illness severity on admission. Third: because the study was set to take place in a specific period of time, only 65 patients were attainable at that period of time, which came at the expense of the number of non ECT control group. The small number of non ECT group may have weakened the power of study. Fourth: Higher number of controls and follow up design may have further strengthened the study results. Future studies on this research topic may be conducted on larger samples and in longitudinal study design. Nonetheless, given limited evidence from controlled trials on the FEP, such studies still have some value. Moreover, the inclusion of a pharmacotherapy only group adds to the usefulness of its findings.

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Conflict of Interest

None to declare.

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