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Short-Term Efficacy of Electroconvulsive Therapy in Treatment-Resistant Schizophrenia

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Abstract

Background: About one third of patients with schizophrenia are treatment-resistant. The treatment options for these patients are limited. Objectives: To study the short-term efficacy of electroconvulsive therapy in treatment-resistant schizophrenia. Methods: 30 patients with treatment-resistant schizophrenia were included. Patients were assessed at baseline, after 4, and after 6 sessions of electroconvulsive therapy using the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS). Global Assessment of Functioning (GAS) and Clinical Global Impression (CGI) scales were applied at baseline and at the end of ECT course. Results: As compared to baseline, the score on the BPRS changed significantly from 57.4 to 40.9 after 4 sessions (P<0.001) and further to 36.2 (P<0.001) at the end of 6 sessions. The score on the PANSS also showed a significant change from 86.7 at baseline to 70.7 after 4 sessions (P<0.001) and further to 65.6 at the end of 6 sessions (P<0.001). The significant change in score on the GAS and the CGI further shows that electroconvulsive therapy is effective in treatment-resistant Schizophrenia. Conclusions: A short course of electroconvulsive therapy leads to significant benefit in treatment-resistant schizophrenia (German J Psychiatry 2012; 15 (2): 44-49).

Keywords: treatment-resistant schizophrenia, electroconvulsive therapy, efficacy

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Introduction

Evidence from nearly a century of epidemiological research indicates that schizophrenia occurs in all populations with prevalence rates in the range of 1.4 to 4.6 per 1000 and an incidence rate in the range of 0.16-0.42 per 1000 (Jablensky, 2000). According to the Global Burden of Diseases Study, schizophrenia causes a high degree of disability, which accounts for 1.1% of the total Disability Adjusted Life Years (DALYs) and 2.8% of Years Lived with Disability (Rossler et al., 2005). Life expectancy in schizophrenia is reduced by approximately 10 years, mostly as a consequence of suicide and also due to complications of medical illnesses like cardiovascular disorders, cancer, metabolic syndrome, increased incidence of Human Immunodeficiency Virus and Hepatitis B and C (Hennekens, 2007; Hautecouverture et al., 2006; Hennekens et al., 2005; Marder et al., 2004; Newman & Bland, 1991; Hannerz et al., 2001). Even if the course of the illness today is considered more favorable than it was originally described, only a minority of those affected fully recover (Rossler et al., 2005).

Antipsychotic drugs are the mainstay of treatment for patients with schizophrenia. However, one fifth to one third patients derive little benefit from antipsychotic drug therapy (Chanpattana & Andrade, 2006). It has been reported that approximately 30% of patients with schizophrenia do not respond to antipsychotics. Recent studies suggest that this proportion may be as high as 50% (Chanpattana & Andrade, 2006). Patients who are resistant to even repeated trials of antipsychotic drugs pose a real challenge, as they usually require long periods of hospitalization, are frequently distressed by positive symptoms, and become extremely withdrawn.

Electroconvulsive therapy (ECT), either alone or in combination with antipsychotic drugs, has been shown to be effective in a certain percentage of patients with acute schizophrenia, particularly in the catatonic subtype (Gill & Lambourn, 1979; O'Connell, 1982; Rohland et al., 1993; Sato & Yamauchi, 1996; Awata & Matsuoka, 2003; Suzuki et al., 2004; Hayashi et al., 2006; Suzuki et al., 2006; Suzuki et al.,

2007) and also in schizoaffective disorder (Baghai & Moller, 2008; Swoboda et al., 2001; Milstein et al., 1990; Ries et al., 1981; Sajatovic & Meltzer, 1993). Off late, ECT has been used as a last resort in patients with chronic treatment-resistant schizophrenia (TRS), although its efficacy has not been systematically investigated. Anecdotal evidence in the form of case reports and case series suggest that ECT combined with antipsychotic drugs might be effective in TRS (Schott et al., 1992; Friedel, 1986). ECT combined with clozapine was effective in several cases of clozapine-resistant schizophrenia (Havaki-Kontaxaki et al., 2006; Kales et al., 1999; James & Gray, 1999; Bhatia et al., 1998; Safferman & Munne; 1992; Benatov et al., 1996). Recently, one study from India (Kumar et al., 2003) and two from Thailand (Tang & Ungvari, 2002; Tang & Ungvari, 2003) have also shown that ECT is effective in TRS. The present study was planned to examine the short-term therapeutic efficacy of ECT in treatment-resistant schizophrenia.

Material and Methods

Subjects

The study was conducted at a General Hospital Psychiatry Unit in a city in North India. Patients were inducted from those attending the outpatient clinic or those admitted to the inpatient services of the department of psychiatry. The sample consisted of 30 consecutive patients of TRS. *Inclusion criteria:* (1) Patients in the age group of 16 to 65 years. (2) Patients suffering from schizophrenia as per ICD 10 (WHO, 1992). (3) Patients who fulfilled the criteria for TRS. For the purpose of the study, TRS was defined according to the modified Kane et al. criteria (Kane et al., 1988), which defines TRS as: a) At least two prior drug trials of at least 4-6 weeks duration at 400-600 mg of chlorpromazine (or equivalent) without significant clinical improvement. b) Persistent psychotic symptoms defined as a score of > 45 on 18 item scale of Brief Psychiatric Rating Scale (Overall & Gorham, 1962) and score of >4 (moderate) on at least two items of positive symptoms. c) The duration of illness should be at least one year. (4) Patients who were accompanied by reliable informants. (5) Patients and informants who were willing to participate in the study and who were ready to give consent for ECT and anesthesia. *Exclusion criteria*: 1) Patients who had associated medical problems, which could affect the course of illness as well as their fitness for general anesthesia. 2) Patients of co-morbid substance dependence except nicotine dependence. 3) Patients who had received ECT in the past one-year. 4) Patients who had received at least 4 ECTs in the past without any significant improvement. We had planned to exclude patients who failed ECT previously so as not to expose them to a treatment that they were resistant to. However, no patients were excluded due to this reason. 5) Patients who were intellectually deficient. This was a longitudinal study with three assessments, one at baseline, second after 4 ECTs and third after 6 ECTs.

The defined guidelines of Central Ethics Committee for Biomedical Research on human subjects by Indian Council of Medical Research (ICMR) were adhered to, in addition to the principles enunciated in the 'Declaration of Helsinki'. The Ethics Committee of the Institution approved the study.

ECT technique

The patients were given ECT twice a week. The total number of sessions was not predetermined. The patients were given ECT as long as they showed improvement. ECT was stopped when patients showed no further improvement on 2 consecutive ECT sessions. However, the present paper reports improvement after up to six ECTs. After preparing the patients for ECT, bitemporal leads were applied, and parameters like current duration, frequency, and pulse width were selected on the ECT machine. Bitemporal ECT was used as per the protocol used in the department. Anesthesia was induced with thiopentone 4–5mg/kg body weight. Succinylcholine 1mg/kg body weight was used as muscle relaxant. The patient was ventilated manually with 100% oxygen using face mask with Magill's circuit connected to Boyle's anesthesia apparatus. The ECT machine used in the department is a Microprocessor Brief Pulse Constant Current machine. It delivers a brief pulse current whose duration can be varied. The current was delivered at a frequency of 70Hz and a pulse width of 1. The starting current duration was 0.8 sec to deliver brief pulse intensity at 50% to 200% of seizure threshold. The patients were shifted out of the ECT room after they became conscious, started breathing spontaneously and followed verbal commands.

Concurrent Medications

All the patients were continued on the same antipsychotic drugs at the same dose which they were taking at the time of inclusion in the study. If the patients responded to ECT, the same medication was continued after ECT. If they did not respond even to 6 ECTs, they were prescribed a different antipsychotic to which they were not resistant earlier and ECT was stopped. The concurrent use of non-antipsychotic drugs was allowed but was limited to trihexiphenidyl for extrapyramidal symptoms, benzodiazepines for sleep and anxiety and usual over the counter medications for problems like headache, body aches. None of the patient in the study was on antidepressants or psychotropic agent other than those mentioned above. None of the patients in the study were on any long-term medication for chronic medical illnesses.

Assessment

The rating scales used to assess the patients' status were the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962), the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Global Assessment of Functioning Scale (GAF) (Endicott et al., 1976) and the Clinical Global impression Scale (CGI) (Guy, 1976).

Statistical analysis

Descriptive statistics were used to characterize demographic and clinical data of the whole sample. The baseline and post

Table 1. Sociodemographic data of the participants

Variable		N (Total=30)	%
Age Category	Up to 25 Years	7	23.3
	26 – 35 Years	13	43.3
	> 35 Years	10	33.3
Sex	Males	21	70
	Females	9	30
Education	< 12 years of formal schooling	17	56.7
	More than 12 years of formal schooling	13	43.3
Occupation	Unemployed	26	86.7
	Govt. job	3	10
	Semiskilled	1	3.3
Income	< 3500	21	70
	3501 – 7000	3	10
	>7000	6	20
Family	Nuclear	25	83.3
	Joint	5	16.7
Location	Urban	22	73.3
	Rural	8	26.7
Marital status	Unmarried	20	66.7
	Married	7	23.3
	Divorced	1	3.3
	Separated	1	3.3
	Widower	1	3.3

treatment scores were analyzed by paired t test. Statistical significance was set at $P < 0.05$ level (significant) and $P < 0.01$ (highly significant).

Results

Socio-demographic data of the group is given in Table 1.The mean age of the patients was 31.5 years ranging from 21 to 45 years. The mean duration of illness was 9.7 ± 3.9 years (range 4–17 years). The mean number of ECTs given was 6.9 (range 6–14). The antipsychotics received prior to induction in the study are given in Table 2. Out of the 30 patients, the majority of the patients had taken risperidone (73.3%) and olanzapine (56.7%) in the past. 12 (40%) patients were resistant to clozapine. Before entry into the study, all the 30 patients had already received at least two antipsychotics in adequate dose and duration, and ten patients were resistant to more than two antipsychotics. The mean number of antipsychotics received was 2.8 (range 2–5). As can be seen from the table, many patients had been on antipsychotics for long periods despite being resistant to them. The reason is that many patients had remained well on a particular drug for a long time but then started deteriorating despite maintaining compliance. Another reason is that many patients had improved partially with the antipsychotics that they were taking but were not in remission and still fulfilled criteria for treatment resistance despite being on adequate dosage for an adequate duration.

The 9 patients who refused ECT were compared to the 30 patients who received ECT to look for any selection bias. Those patients who refused ECT were not different from those who consented for it on sociodemographic characteristics like age (mean 38.1; sd 12.3; p = .198), gender (5 females and 4 males; p = .238), marital status (5 married and 4 single; p = .102), education (< 12 years = 5, > 12 years = 4; p = 1.000) and family type. However, the patients who refused ECT were significantly different in terms of baseline scores on the BPRS and the PANSS. They had a significantly lesser score at baseline (mean score = 41.1 ± 9.4) than those who received ECT (mean 57.4; ± 9.42) on BPRS (p = <.0001). Similarly, they were significantly less ill as compared by the scores on PANSS (baseline scores ECT acceptors = 86.7± 14.0; ECT refusers = 67.4 ± 9.8; p <.0001). Throughout the course of ECT, the patients were continued on the same dose of the same antipsychotic that they were taking before induction into the study so that the treatment response could not be attributed to antipsychotic medications. 7 patients (23.3%) were on two antipsychotics (risperidone and haloperidol – 2 patients; risperidone and olanzapine – 2 patients; haloperidol and olanzapine – 1 patient; clozapine and risperidone – 1 patient; clozapine and trifluperazine – 1 patient) at the time of entry into the study. The remaining 23 patients (76.7%) were on a single antipsychotic. Out of these 23 patients, 9 (39.1%) were on clozapine, 4 (17.4%) were on risperidone and olanzapine each, 3 (13.0%) patients were taking quetiapine, 2 (8.7%) were taking chlorpromazine and 1 patient was on ziprasidone (4.4%).

Outcome measures

All the patients were assessed on BPRS and PANSS at baseline, after 4 ECTs and after 6 ECTs. The GAF and CGI scales were applied at baseline and at the end of the course

Table 2: Details of antipsychotics received prior to induction in the study (SD = standard deviation)

Drug	N	Mean dose ± SD	Dose range	Mean duration of use (months) ±SD	Duration range (months)
Clozapine	12	360 ± 117.8	150 – 600	10.3 ± 9.9	2 – 36
Risperidone	22	9.2 ± 1.7	6 – 12	8.3 ± 6.5	2 – 24
Olanzapine	17	28.8 ± 9.1	15 – 50	9.6 ± 10.8	2 – 36
Haloperidol	9	26.7 ± 7.6	15 – 40	16.6 ± 17.6	3 – 48
Quetiapine	5	510 ± 89.4	400 – 600	5.6 ± 3.4	2 – 12
Chlorpromazine	2	600	400 – 800	4	2 – 6
Ziprasidone	3	146.7 ± 23.1	120 – 160	3.3 ± 1.5	2 – 5
Aripiprazole	6	25 ± 7.8	15 – 30	7.7 ± 5.1	2 – 15
Trifluperazine	3	27.5 ± 11.9	20 – 45	17.3 ± 17.0	3 – 42
Loxapine	1	200	7	200	7

Table 3. Change in scores of BPRS and PANSS (BPRS = Brief Psychiatric Rating Scale; PANSS = Positive and Negative Syndrome Scale of Schizophrenia; SD = standard deviation)

Scores	Mean ± SD baseline	Mean ± SD after 4 ECTs	Mean ± SD after 6th ECT	P baseline vs 4 ECTs	P baseline vs 6 ECTs	P 4 ECTs vs 6 ECTs
BPRS score	57.4± 9.42	40.9± 13.1	36.2± 12.9	< .001*	< .001*	.678
PANSS total score	86.7± 14.1	70.7± 18.9	65.6± 19.1	.004*	<.001*	1
Positive syndrome scale	23.4± 3.7	18.5± 5.3	16.8± 5.7	< .0001**	< .0001**	1
Negative syndrome scale	18.7± 8.5	15.7± 7.5	14.5± 6.7	< .0001**	< .0001**	0.014**
General psychopathology scale	44.6± 8.3	36.4± 10.2	34.2 ± 10.3	< .0001**	< .0001**	0.004**

* significant, $p < 0.05$; ** highly significant, $p < 0.01$

of ECTs. The results showed significant change in total BPRS score and the total score on PANSS between all the assessments (Table 3). The change of score on three subscales of PANSS is also shown in the Table 3.

There was a significant change in mean score between baseline and at the end of ECT course on GAF from 26.3 ± 7.2 at baseline to 44.5 ± 15.7 ($p < 0.001$) and CGI from 5.6 ± 0.7 to 4.5 ± 1.2 ($p < 0.001$).

The improvement on the BPRS and PANSS scores over the ECT sessions was correlated with various sociodemographic and clinical variables of the patients. The change in score from baseline to the end of 6 ECT sessions was not significantly affected by the gender of the patients (mean score for males 21.3 ± 13.8, females 21.3 ± 13.2; p=0.993), age (p=0.796), education (mean for < 12 years 20.9 ± 12.6 mean for > 12 years 21.8 ± 14.9; p value – 0.870), marital status (mean for cohabiting 21.3 ± 17.3 for non-cohabiting 21.3 ± 12.4; p=0.997) and duration of illness (p = 0.839).

Discussion

The present study was a prospective, open trial carried out to study the efficacy of ECT in 30 severely ill TRS patients using standard rating instruments over a short period. Though, there was no separate control group; the patients acted as their own controls as they were assessed at baseline and were continued on same drugs and dosages as prior to induction into the study. These patients had not shown any clinical response on these drugs despite adequate dosages given for adequate period.

The results of this study show that patients as a group responded to ECT as the score on BPRS changed significantly from baseline to 4 ECTs and further at the end of 6 ECTs. The mean scores on PANSS also showed a significant change from baseline to 4 ECTs as well as at the end of 6 ECTs. The PANSS has integrated the items from BPRS and has most items from BPRS with additional items for measuring psychopathology. This explains the similarity on results of both the scales. The significant changes in scores on the GAS and the CGI further show that ECT is effective in TRS. The findings show that a short course of ECT can be sufficient as majority of the patients, more so patients with predominantly positive symptoms, showed significant response at the end of 4 ECTs. This further implies that ECT can be considered early in the treatment of schizophrenia. The mean BPRS score at the end of six ECT sessions was 36.2 which put the group in the improved category.

Two earlier studies have also shown significant improvement on BPRS scores in TRS after a course of ECT (Kumar et al., 2003; Tang & Ungvari., 2002). Another study on 15 patients of TRS showed change in BPRS score after ECT from baseline to the end of the study, though it was not statistically significant (p = 0.430) (Tang & Ungvari., 2003).

The mean duration of illness in our study was 9.7 ± 3.9 years (range 4-17 years) as compared to 7.6 years, 18 years and 19 years respectively in earlier studies (Kumar et al., 2003; Tang & Ungvari, 2002; Tang & Ungvari, 2003). The finding of one of the earlier studies with mean duration of illness of 19 years supports the role of ECT in chronic TRS (Tang & Ungvari, 2002). In all these studies, including ours, the patients were continued on the same antipsychotic medications, which they were taking at the time of entering into the study. Although the patients were resistant to these antipsychotics, it is possible that ECT might have potentiated the therapeutic effects of these drugs. In order to see the exclusive efficacy of ECT, antipsychotics need to be discontinued during the course of ECT. This can be studied in future research, though ethically it would be difficult for the clinicians to discontinue the drugs totally, as the majority of these patients have severe psychopathology and caregivers would be reluctant to discontinue medication even if there has been no response to these drugs.

ECT not only led to reduction in score on BPRS and PANSS, but there was a perceptible clinical improvement with ECT. This is supported by significant change in scores on Global Assessment of Functioning Scale as well as on Clinical Global Impression Scale. Similar improvement on these scales has been reported in earlier studies (Tang & Ungvari, 2002; Tang & Ungvari, 2003). The results indicate that the change in scores on various rating scales resulted in functional improvement in various domains of life.

Despite stringent methodology, the study still has certain limitations. It was an open, non-randomized, prospective trial. Even though all the patients were under regular follow-

up in the department of psychiatry and medical records supported resistance to at least two antipsychotics, the records were based on subjective reports of patients and their relatives without assessment of serum levels of prescribed drug for ensuring compliance. All the patients were continued on the same antipsychotic to which they were resistant and thus improvement cannot be attributed exclusively to ECT. The placebo effect of ECT might have contributed to the improvement. Another limitation of the study was that we did not carry out formal assessment of the side effects of ECT. However, no patients suffered any side effect that resulted in discontinuation of ECT. As per the clinical records of the patients, 7 patients reported mild headache after ECT that was relieved with usual analgesics. Another limitation was that we did not use any scale to assess the depressive symptoms. So, it could be argued that improvement was due to improvement in depressive symptoms. However both BPRS and PANSS have items relating to depressive symptoms and the patients showed improvement on positive as well as negative symptoms along with depressive symptoms as seen on the scales used in this study. Thus, we conclude that the improvement on psychotic symptoms was independent to improvement on depressive symptoms. The study reports short term improvement with ECT over a period of 4 weeks and it needs to be seen whether the improvement persists over a longer period of time.

In conclusion, a short course of ECT is effective in chronic patients with schizophrenia who fail to respond to multiple antipsychotics.

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