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LONG TERM FOLLOW-UP OF CLOZAPINE RESISTANT SCHIZOPHRENIA TREATED WITH A SHORT COURSE OF ELECTROCONVULSIVE THERAPY

Psychiatry

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ABSTRACT

Introduction: Open label, non-randomized, follow up study was done to assess 10 years naturalistic outcome of clozapine resistant schizophrenia treated with a short course of electroconvulsive therapy.

Material and methods: 11 consecutive clozapine resistant schizophrenia patients aged 18 – 65 years participated in the short term study in 2006-07. 6 sessions of bi-temporal modified electroconvulsive therapy were administered twice a week. Naturalistic follow up was done in 2016. Brief psychiatric rating scale, positive and negative syndrome scale for schizophrenia, clinical global impressions and global assessment of functioning were applied at baseline, after 4 sessions, after 6 sessions and after 10 years.

Results: Age of 11 participants was 30.64 ± 6.120 years. Brief psychiatric rating scale score improved significantly from baseline score of 55.91 ± 7.217 to 37.45 ± 16.312 after 6 ECT sessions ($p < .005$***). The score of positive and negative syndrome scale changed from 89.27 ± 18.488 at baseline to 67.73 ± 25.535 after 6 sessions ($p < .008$***). After 10 years, the score on brief psychiatric rating scale was 45.91 ± 9.163 and that of positive and negative syndrome scale was 60.29 ± 14.761. The socio occupational functioning of the patients was poor at follow up.

Conclusions: Electroconvulsive therapy is efficacious and safe in short term for patients with clozapine resistant schizophrenia. However, the improvement is lost once therapy is discontinued. Long term outcome of clozapine resistant schizophrenia remains poor.

KEYWORDS

clozapine, electroconvulsive therapy, resistant, schizophrenia

Introduction

Clozapine is the drug of choice for treatment resistant schizophrenia (TRS).[1,2] However, 40% to 70% patients are even resistant to clozapine.[1,3] Treatment strategies for clozapine resistant schizophrenia (CRS), including electroconvulsive therapy (ECT), are promising, but require further validation.[4] The use of ECT in schizophrenia has reduced over time owing to the introduction of antipsychotics which are equally effective, less stigmatizing and more socially acceptable.[2,5] ECT is recommended in schizophrenia for psychotic exacerbations of an abrupt onset, catatonia, schizophreniform disorder, schizoaffective disorder, when rapid improvement is desired and where patients show limited response to medication.[3,5,6]

The evidence for efficacy of ECT in CRS is not very robust because of lack of research evidence. The authors are not aware of any study reporting long term follow up of patients with CRS except a case report of a patient with refractory schizophrenia treated with clozapine and maintenance ECT who showed good response.[7] Few small open label studies and case reports have found the clozapine - ECT combination effective in short term.[3,5,8-13] However, in majority of these, clozapine was started along with ECT, added to ECT or discontinued much before patients were given ECT. So, clozapine resistance was not stringently reported in these studies.[1,3,10] A recent single blind comparison found that clozapine - ECT combination was more effective than clozapine monotherapy in short term.[2] The literature on this topic from India is almost nonexistent. The authors are aware of only 2 reports (total 4 patients) which found the combination to be safe and effective in short term.[14,15]

The present study is a long term naturalistic follow-up of 11 patients of CRS who were included in an earlier study to examine the efficacy of ECT in patients with TRS over a short period.[16] After the short term study, ECT was discontinued and naturalistic follow up was done after 10 years.

Material and Methods

Study design and settings: It was an open label, non-randomized, prospective study conducted at a general hospital psychiatry unit in north India.

Study duration: The short term study was conducted between February 2006 and September 2007. The long term follow up was conducted in December 2016.

Inclusion Criteria: Patients aged 18 – 65 years diagnosed as schizophrenia as per ICD 10 [17] and fulfilling criteria for TRS and CRS were included. For the purpose of study, TRS was defined according to modified Kane etal. Criteria.[16,18] To establish clozapine resistance, patients should have been resistant to adequate effective dosage of clozapine for at least 3 months as reported by the family members as well as supported by the clinical records of the patient. Patients were accompanied by a reliable informant who was primary caregiver and both patient and caregiver were willing to participate in the study.

Exclusion Criteria were 1) History of epilepsy, or any other neurological or systemic disorder which could make the patients unfit for general anesthesia 2) Co morbid substance dependence except nicotine 3) Patients who had received ECT in the past one-year 4) Patients who had received at least 4 ECT's in the past without any significant improvement 5) Intellectual disability 6) Schizoaffective or bipolar disorder.

Study Protocol: The details of the short term study are reported elsewhere.[16] It was a longitudinal study with five assessments, one at baseline, second after 4 ECT's, third after 6 ECT's, fourth at the end of the course of ECT's and fifth after 10 years in December 2016.

Out of the thirty patients included in the short term study, eleven fulfilled criteria for CRS and their clinical records were retrieved. Patients who were still following up in the department were called telephonically and given appointments for assessments. Patients who had been lost to follow-up were contacted telephonically. In case the telephone number had changed, letters were sent to their addresses informing them regarding the study and they were invited to participate in the long term follow-up. In case the patients did not report within 2 weeks, home visit was made to find out reason for the same. The record of different medications continued by the patients since the ECT course and their symptomatic course were obtained from the case record files and interviews with patient and family members. Written informed consent was obtained from all the

participants for the assessments.

Ethical Considerations: The defined guidelines of Central Ethics Committee for Biomedical Research on human subjects by Indian Council of Medical Research [20] were adhered to and the principles enunciated in the 'Declaration of Helsinki' [21] were followed. The study was approved by the ethics committee of the institution. The trial is registered with the clinical trial registry India vide registration number CTRI/2011/08/001960 on 24/08/2011.

ECT procedure: The details of the ECT procedure have been explained elsewhere.[16]

Antipsychotics used prior to inclusion in the study: Before inclusion into the study, seven patients had taken risperidone (mean dose 7.88 mg/day; mean duration 10.71 months), five had taken olanzapine (mean dose 22 mg/day; mean duration 11 months), three had taken haloperidol (mean dose 28.33 mg/day; mean duration 17.67 months). Two patients each were resistant to aripiprazole (mean dose 22.5 mg/day; mean duration 4 months), chlorpromazine (mean dose 600 mg/day; mean duration 4 months) and trifluperazine (mean dose 22.5 mg/day; mean duration 12 months). One patient each had taken injectable flupenthixol and ziprasidone.

Medications continued during the ECT course: During the ECT course, all the 11 patients were continued on the same dosage of clozapine that they were taking prior to inclusion. No other antipsychotics or psychotropic agents like mood stabilizers, antidepressants or benzodiazepines were permitted during the study. Over the counter analgesics for headaches or body aches emerging during the study were allowed.

Rating Scales: The details of the scales used in short term have been reported earlier.[16] At the long term follow up, Brief Psychiatric Rating Scale (BPRS),[19] Positive and Negative Syndrome Scale for schizophrenia (PANSS), [22] Clinical Global Impressions (CGI) [23] and Global Assessment of Functioning (GAF) [24] were used.

Statistical analysis

Analyses were conducted using IBM SPSS statistics version 22.0 (Armonk, NY: IBM Corp). All the relevant data collected was transferred on to the SPSS. Non-normal distributed variables were compared using Wilcoxon Signed Ranks Test (paired data) to analyze significant effect. The p-value ≤ 0.05 was taken as critical level of significance.

Results: Eleven patients were included in the short term study. Mean age of the participants was 30.64 ± 6.120 years (range 22 – 40 years). Majority of the patients were males (7, 63.6%), single (8, 72.7%), unemployed (8, 72.7%) and came from nuclear families from an urban locality (7, 63.6%). Six (54.5%) patients had less than 12 years of formal education.

The mean duration of illness was 102.55 ± 30.882 months (range 42 - 144). The mean dose of clozapine used prior to study was 331.82 ± 100.680 mg/day (200 - 500). The mean duration of clozapine intake was 10.27 ± 10.326 months (range 3 - 36).

Table 1: Change in scores on the Brief Psychiatric Rating Scale and Positive and Negative Syndrome Scale for Schizophrenia

Scale	Subscale	Baseline score mean (sd) (range; median)	Score after 4 ECT's mean (sd) (range; median)	Score after 6 ECT's mean (sd) (range; median)	Z score/ P value baseline to 4 ECT's	Z score/ P value baseline to 6 ECT's	Z score/ P value 4 ECT's to 6 ECT's
Brief Psychiatric Rating Scale		55.91 (7.217) (46-70; 56)	39.73 (14.772) (21-70; 36)	37.45 (16.312) (20-70; 36)	-2.810/ < .005**	-2.805/ < .005**	-2.207/ < .027*
Positive and Negative Syndrome Scale	Positive syndrome subscale	21.55 (3.174) (15-25; 22)	17.00 (5.099) (7-24; 16)	16.64 (5.124) (7-24; 16)	-2.666/ < .007**	-2.670/ < .008**	-1.633/ < .102
	Negative syndrome subscale	20.36 (9.266) (7-40; 21)	16.64 (9.320) (7-35; 15)	16.00 (9.187) (7-33; 14)	-2.524/ < .012*	-2.527/ < .012*	-2.070/ < .038*
	General psychopathology subscale	47.36 (11.111) (35-67; 44)	37.27 (13.154) (26-65; 34)	35.09 (13.845) (21-62; 29)	-2.670/ < .008**	-2.666/ < .008**	-2.384/ < .017*
	PANSS total	89.27 (18.488) (67-131; 86)	70.91 (24.627) (43-122; 64)	67.73 (25.535) (35-117; 64)	-2.666/ < .008**	-2.666/ < .008**	-2.371/ < .018*

Patients received 6.73 ± 1.421 (6 – 10) ECT sessions. Only 3 patients out of 11 (27.27%) received more than 6 ECT sessions. Hence, short term results are reported only up to 6 ECT sessions.

As can be seen from table 1, the scores on BPRS and PANSS and its subscales changed significantly from baseline to all the follow up assessment points except the positive syndrome subscale in which the change from 4 to 6 ECT sessions was not significant.The percentage improvement in eleven patients on the basis of total PANSS score till 6 ECT sessions was 61.96%, 55%, 32.89%, 29.35%, 27.14%, 19.77%, 16.88%, 14.92% and 10.69% for 9 patients. Two patients had no improvement at all till 6 ECT sessions. Thus, five patients showed more than 20% improvement on the total score of PANSS. In fact another patient with score of 19.77 % is very close to 20% improvement. However, the remaining 5 patients had not reached the level of response. The corresponding percentage improvements on the BPRS were 65.52%, 60%, 58.33%, 35.71%, 34.92%, 41.3%, 34.04%, 35.71% and 8.19% for 9 patients respectively. Thus, on BPRS, 8 patients showed more than 20% improvement after 6 ECT sessions. However, if response is considered as 40% or 50% improvement on BPRS, only 4 and 3 patients respectively achieved it.

The improvement on GAF and CGI was statistically significant (CGI baseline score 5.64 ± .674 (range = 5-7; median = 6) and score after 6 ECT sessions 4.27 ± 1.489 (range = 2-7; median = 4); Z score = -2.549; $p < 0.011^*$) and GAF baseline score 26.36 ± 6.742 (range = 20-40; median = 30) and score after 6 ECT sessions 45.91 ± 18.278 (range = 20-75; median = 40); Z score = -2.371; $p < 0.018^*$). On CGI, at baseline, five patients each were rated as 'markedly' and 'severely' ill and one patient was rated as 'among the most extremely ill'. At the end of 6 ECT sessions, one and two patients respectively were rated as 'among the most extremely ill' and 'severely ill'. Five patients were rated as 'moderately ill', two as 'mildly ill' and one as 'borderline mentally ill'. Global improvement on CGI was 2.73 ± 1.009 (range = 1-4; median = 3). After the ECT course, one patient was rated as 'very much improved', four as 'much improved', three as 'minimally improved' and three as 'no change'. Efficacy index was 7.82 ± 4.332 (range = 1-13; median = 9). Efficacy index is rated in terms of therapeutic effect and side effects. Three patients had an efficacy index of 6 which meant that they had some 'side effects that do not interfere with patients functioning'. 8 patients had no side effects at all.

Comparison of baseline variables to assess predictors of response: The baseline variables of five patients who showed more than 20% improvement on PANSS from baseline to 6 ECT sessions were compared to six patients who showed less than 20% improvement to see if any predictors of response could be identified (table 2). The two groups were not different at baseline from each other in terms of any sociodemographic variable except that patients who showed more than 20% improvement had a significantly longer duration of illness. Patients who showed less than 20% improvement had a greater mean score on the negative syndrome subscale of PANSS as compared to

patients who showed more than 20% improvement, though it did not reach statistical significance**Long term follow up:** Out of eleven

Table 2: Comparison at baseline between patients showing more than and less than 20% improvement

Variable		Patients who showed less than 20% improvement on PANSS (n = 6)	Patients who showed more than 20% improvement on PANSS (n = 5)	Z score/ P value
Age (years) mean (sd) (range; median)		30.17 (6.911) (22-40; 29.50)	31.20 (5.762) (24-38; 30)	-.365/ .715
Duration of illness (months) mean (sd) (range; median)		86 (29.557) (42-132; 87)	122.40 (19.718) (108-144; 108)	-2.216/ < .029*
Dose of clozapine (mg/day) mean (sd) (range; median)		341.67 (120.069) (200-500; 350)	320.00 (83.666) (200-400; 300)	-.383/ .702
Duration of clozapine use (months) mean (sd) (range; median)		7.00 (5.586) (3-18; 6)	14.20 (13.864) (2-36; 12)	-.466/ .641
Number of ECT sessions mean (sd) (range; median)		6.50 (1.225) (6-9; 6)	7.00 (1.732) (6-10;6)	-.813/ .416
Baseline BPRS score total mean (sd) (range; median)		55.83 (8.976) (46-70; 55.50)	56.00 (5.431) (48-63; 56)	-.367/ .714
Baseline PANSS score total mean (sd) (range; median)		92.00 (23.221) (67-131; 85)	86.00 (12.490) (70-100; 92)	-.183/ .855
Baseline positive syndrome subscale score mean (sd) (range; median)		21.17 (2.563) (18-24; 21)	22.00 (4.062) (15-25; 24)	-.843/ .399
Baseline negative syndrome subscale score mean (sd) (range; median)		23.83 (10.907) (7-40; 22.50)	16.20 (5.119) (10-22; 17)	-1.555/ .120
Baseline general psychopathology subscale score mean (sd) (range; median)		47.00 (12.977) (35-67; 41.50)	47.80 (9.884) (35-58; 51)	-.091/ .927
Gender	Males n (%age)	4 (66.7)	3 (60)	1.000
	Females n (%age)	2 (33.3)	2 (40)	
Education	< 12 years of formal education n (%age)	3 (50)	3 (60)	1.000
	> 12 years of formal education n (%age)	3 (50)	2 (40)	
Family type	Nuclear n (%age)	5 (83.3)	2 (40)	.242
	Joint n (%age)	1 (16.7)	3 (60)	
Marital status	Single n (%age)	4 (66.7)	4 (80)	1.000
	Married n (%age)	2 (33.3)	1 (20)	
Occupation	Unemployed n (%age)	4 (66.7)	4 (80)	.402
	Others n (%age)	2 (33.3)	1 (20)	
Locality	Urban n (%age)	2 (33.3)	2 (40)	1.000
	Rural n (%age)	4 (66.7)	3 (60)	

patients, two did not turn up after the ECT course and could not be traced. The mean follow up period for remaining nine patients was 93.44 ± 35.892 (range 35-130) months and the mean number of visits was 40.22 ± 26.931 (range 11-95). One patient out of nine died of complications of carcinoma stomach in April 2013 and another patient died in March 2014 and the reason of death is not known. Thus, seven patients were assessed at follow- up. The mean BPRS score of seven patients at follow up was 44.429 ± 3.823 (range 22-50). The mean scores on total PANSS scale, positive syndrome subscale, negative syndrome subscale and general psychopathology subscales were 60.29 ± 14.761 (range 45-90), 14.88 ± 6.644) (range 7-26), 14.71 ± 5.823 (range 7-21) and 31.88 ± 7.081 (range 25-45) respectively. On CGI, three patients were rated as 'severely ill' and 4 as 'markedly ill'. The mean score on CGI was 5.143 ± 0.934 (range 4-6). Out of the seven patients, the clinician rated socio occupational functioning was rated as poor for four patients. Two male patients were still unemployed, another housewife was almost non-productive at home. Another notable finding was that three female patients who were single at baseline were still single. The mean score on the GAF was 30.71 ± 3.934 (range 25-40).

Treatment received since ECT course: One patient has been receiving intermittent ECT sessions and another received a full course of 10 ECT sessions for a relapse in 2011. Four patients were prescribed risperidone to control acute symptoms emerging during follow up. One patient each was prescribed olanzapine, aripiprazole, quetiapine, chlorpromazine and amisulpride and two patients were prescribed haloperidol during follow up period.

Clozapine monitoring was regularly done for all the patients. It was unremarkable for all patients except one who was diagnosed as having diabetes mellitus. Six patients reported sedation during the course of treatment and two had significant obsessive compulsive symptoms while on clozapine. Clozapine had to be discontinued in four patients (due to diabetes mellitus in one and sedation in three). Three patients were still on clozapine at the time of follow up and the dosage was 466.67 (152.752) (300-600) mg/day. One patient was on quetiapine 1000 mg/day and another patient was on a combination of risperidone 6 mg/day and olanzapine 20 mg/day. Another patient was taking haloperidol 20 mg/day. One patient was non-compliant and not taking the medication prescribed.

Discussion

This is the first Indian study to report efficacy of ECT in CRS. The major strengths of the study are sound methodology, use of standardized rating scales and ensuring stringent clozapine resistance before administering ECT. It is a naturalistic follow up and the long term outcome cannot be ascribed to the short term ECT course, which should be kept in mind while interpreting the results.

The short term improvement on BPRS and PANSS with clozapine and ECT has been reported earlier.[2,8-10,14, 25,26] However, the improvement seen on negative symptoms in the present study is highly encouraging since these symptoms have traditionally been considered difficult to improve. Two recent studies using combination of clozapine and ECT have found improvement in negative symptoms. [26,27]

Though the change in score was statistically significant, nearly 50% and 30% patients showed less than 20% improvement on PANSS and BPRS respectively. Recently, it has been argued that response criteria with this combination should be at least 40% or 50% improvement on BPRS.[2] Using this criterion, only 4 and 3 patients would show 40 % or 50% response respectively. This implies that the statistically significant improvement seen on total scores was due to the significant improvement seen in a few patients and some patients did not improve much. Though we tried to look at the predictors of response by

comparing the baseline variables of patients who improved to those who did not improve, we did not find any. The authors reckon that a study with larger sample would be able to answer this question.

In the present study, the longer duration of illness observed among patients who showed more than 20% improvement refutes the long held belief that a long duration of illness portends poor response to ECT. Our study supports the recent finding by another group of researchers.[28]

To our knowledge, this is the first study to report long term outcome of patients with CRS who were treated with a short course of ECT. The authors did not control the medications that patients received after ECT course. So, this is more of a naturalistic report on what happens to these patients in long term. The findings of long term follow up in our study are not very encouraging. Three patients were still rated as 'severely ill' and four as 'markedly ill' on CGI, similar to baseline. The socio occupational functioning at follow up does not give an encouraging picture. One male patient changed his city of residence due to continuous positive psychotic symptoms, continues to have disabling positive psychotic symptoms and is not working. Two patients (one male and one female) are home bound, have prominent negative symptoms and need nursing care even for their daily chores. Another female patient has disabling positive symptoms and her family members have to lock her inside the house when they go out to work so that she might not run away from home. Two female patients have intermittent psychotic symptoms. Though they have been involved in supported employment in the department (one goes to half way home and another has been employed in Disability Assessment and Rehabilitation Triage services), they are irregular at work and have low productivity. Another male patient has his own shop, but he needs assistance to run the shop and continues to have positive psychotic symptoms. The illnesses of these patients had a profound influence on their families as well. Out of seven patients, three belong to upper middle class and their families are capable of arranging regular assistance for them. Remaining 4 patients belong to poor families and their families are finding it difficult to manage them at home and are looking for permanent hospitalization.

The patients in our study were the most severely ill and disabled as compared to cases seen in routine clinical practice. They were resistant even to clozapine which is the drug of choice for TRS. Treatment options for these patients are limited. Short term improvement in our study raises hope that maintenance ECT might lead to sustained improvement in these patients which has been found in a previous case report.[7] Though we did not administer maintenance ECT to our patients, it should be considered as a research option for future.

In the present study, only three patients had short lasting mild side effects which did not interfere with the functioning. Previous research has expressed concern that combination of ECT and clozapine may lead to side effects like delirium, memory problems, tachycardia, tardive seizures and lowering seizure threshold.[10] However, we did not find this in our study and other recent studies have also refuted these concerns.[2,3,10] However, long term side effects due to clozapine are a matter of concern. Four patients had to discontinue clozapine due to diabetes mellitus and sedation. This raises a very important question of how to manage the patients who are resistant to multiple antipsychotics and suffer side effects from the only medication that is effective.

Limitations: The present study had certain limitations like small sample size, non randomized, non blinded study. The gap between short term course and long term assessment was 10 years and maintenance ECT was not used. So, the long term outcome cannot be ascribed to short term ECT course. Hence, this is more of a naturalistic follow up of these patients. The side effects were rated using CGI and not a specific scale.

Conclusions: It can be concluded that short course of ECT leads to speedy improvement in positive as well as negative symptoms of schizophrenia in patients who were resistant to clozapine, though the improvement is not maintained after ECT is discontinued. The long term outcome of clozapine resistant schizophrenia remains poor. The combination is safe and effective in the short term among patients with long standing illness who are resistant to a number of antipsychotic drugs. Larger studies are required to assess the efficacy of the combination therapy in the long term using continuation and maintenance therapy.

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