ORIGINAL ARTICLE

ELECTROENCEPHALOGRAPHIC ABNORMALITY AND CLINICAL RESPONSE IN PATIENTS WITH FIRST-EPISODE SCHIZOPHRENIA TREATED WITH CLOZAPINE

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Abstract

Objective: **Clozapine is seen as a gold standard for treatment refractory schizophrenia; however, it is not recommended for the treatment of first-episode psychosis mainly due to concerns of severe side effects. An indicator for response holds tremendous clinical value to select patients who can benefit from clozapine, safely. EEG abnormality has been reported to be one such parameter, yet the definite conclusion of the nature of EEG changes and its predictive value remains undetermined. The present study was undertaken to examine electroencephalographic (EEG) abnormalities and clinical response subsequent to clozapine therapy in schizophrenia.** ***Methods:*** **A total of 80 first-episode patients were recruited for a 12 week study, from a tertiary care centre in Mumbai, India. First episode was defined as an illness of less than 2 years duration and first hospitalization since illness. EEG abnormalities, psychopathology, and positive and negative symptoms were examined at baseline and again after 12 weeks of clozapine treatment.** ***Results:*** **There were some types of EEG abnormalities found in pretreatment state in at least two-thirds of patients. The number of patients showing EEG abnormality at the end of the 12 weeks of treatment increased significantly, which included theta (θ) frequency, slow waves, and sharp waves. Symptomatically, significant improvement was seen in both positive as well as negative symptoms scores. However, there was no significant correlation between EEG changes and clinical outcome.** ***Conclusion*****: There was significant abnormality in the number of patients exhibiting EEG abnormalities. Baseline pretreatment EEG abnormalities were present in a considerable number of patients, and these EEG abnormalities did not significantly correlate with clinical improvement, except suggesting a trend towards such correlation.** ***ASEAN Journal of Psychiatry, Vol. 15 (1): January – June 2014: 30-38.***

Keywords: EEG, clozapine, Schizophrenia, Psychopathology

Introduction

Early intervention in psychosis has consistently been shown to result in good outcome in the management of schizophrenia, yet maintaining this outcome after initial response is a challenge. In particular, this lack of maintenance limits the benefits of early intervention programs. High rates of relapse, primarily after discontinuation of antipsychotics, side-effects, and poor adherence to medication, jeopardize the outcome of antipsychotic treatment. The search for safe and effective antipsychotic medications continues in the treatment of schizophrenia. Clozapine is seen as a gold standard for treatment of refractory schizophrenia[1]; however, its response rate is limited to 40-50% of patients, while 30-40% of patients develop serious and life-threatening side effects. The propensity of clozapine to cause these severe adverse effects such as agranulocytosis (1-2%), and an unusually high incidence of seizures[2,3] has limited its utilization in clinical practice in general, including its usage in treatment resistant patients in the early phase of schizophrenia.Consequently, far fewer patients are being prescribed clozapine in comparison to those who need it [4].Though clozapine causes significantly fewer extra-pyramidal symptoms [5] than any other antipsychotic, it remains a continuous deterrent for clinicians to select clozapine as a treatment option. An indicator for response as well as for side effects, holds tremendous clinical value to select patients who can benefit from clozapine, safely. There have been a number of predictors proposed for clinical response to clozapine, in order to properly select patients, and minimize the risk of side effects, but this has not been met with much success[6].EEG abnormality has been reported to be one such parameter, yet definitive conclusion of the nature of EEG changes and its predictive value remains undetermined.

EEG abnormalities due to clozapine range from 16% to 75%, with the most common abnormalities being slow wave background abnormality, epileptogenic activity, spikes, and sharp waves [7,8]. The difficulty has been that EEG abnormalities are also seen in a number of other conditions which has confounded the results of many studies, and makes it difficult to conclude that these EEG changes are exclusively arising due to clozapine. As such, evidence of EEG abnormality due to clozapine remains equivocal. A study by Pillay et al. [9] and another by Treves et al. [10] showed that there is no significant relationship between EEG and clinical response. On the other hand, a study by Khodayri-Rostambad et al. [11] showed that EEG abnormality was a significant predictive factor for clinical outcome. Furthermore, in some patients, clozapine can cause cerebral dysrhythmia; therefore, an argument can be made that those patients who develop dysrhythmia and have abnormal EEG pattern may be separate subgroups of patients. It is possible that these patients get a different clinical response Regardless of these inconclusive results, EEG abnormality in relation to clozapine needs to be further elucidated.

This study has been undertaken to examine the status of EEG abnormalities subsequent to clozapine treatment, in a relatively early phase of schizophrenia, which has become resistant to a number of antipsychotics. The objective is to determine a potential predictive role of EEG in clinical response.

Materials and Method

Subjects

This study was carried out in a non-governmental, psychiatric hospital in Mumbai, India. This was an open label, prospective cohort study with a 12-week follow-up period. Consenting patients from a cohort of first-episode psychosis (less than 2 years duration of the illness and first hospitalization since the illness) who met diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) were screened and recruited. Diagnosis was confirmed using Structured Clinical Interview for the DSM-IV (SCID). Patients were then selected as per clinical indication in a naturalistic clinical setting for outpatient and hospitalized treatment.132 patients with treatment-resistant schizophrenia were recruited, 80 (60%) of which completed the 12 week treatment with clozapine. During the 12-week treatment

period, 52 (40%) patients were discontinued because of side effects and worsening of symptoms. No side effects were seen in 32 (37.6%) patients.

Ethics permission was obtained from the Local Independent Ethics Committee of Mumbai. The inclusion criteria were: patients had to be between the ages of 18 and 45 years, and patients were considered treatment resistant as per Kane's criteria (those who have undergone a trial of adequate dose and duration of 3 antipsychotics from at least two different classes of antipsychotics)[12]. The exclusion criteria were: history of severe medical co-morbidity (i.e. obesity or hypercholesterimia), history of a previous trial of clozapine, obesity, diabetes, hypertension, neurological disorder, seizure disorder and hematological conditions, cardiac abnormality, and pregnancy. Clinical assessment and a conventional 12-Channel EEG recording, which are commonly used in psychiatry, were done at baseline and 12 weeks[13].

Procedure

Patients were investigated for haemogram, liver, kidney, lipids, sugar, and thyroid function along with electrocardiogram (ECG). Previous medication was gradually tapered off within a period of 3-5 days. Patients were switched to clozapine two days after previous medication was stopped. Benzodiazepines (clonazepam or lorazepam) were used for symptoms of anxiety and agitation, if any after stopping clozapine.. Clozapine was administered in a dose of 25 mg per day, with gradual escalation of 25 mg every fourth day. Therapeutic dose was determined by symptom remission and clinical judgment. No other drugs besides benzodiazepine, trihexyphenidyl, and valproic acid were used concurrently with clozapine. Complete blood count monitoring was done every week for the first month, and then subsequently every two weeks for the following two months. Serum clozapine level could not be measured due to a lack of facilities. Of the 132 patients recruited, 52 patients were excluded during the 12 weeks period.

Clinical Assessment

Positive and Negative Syndrome Scale (PANSS), and the Clinical Global Impression Scale (CGIS) were used to assess for psychopathology [14,15].

Electroencephalography (EEG) Measures

A conventional 12-Channel EEG was recorded in an awakened state with electrode placement as per international 10-20 system, in an eyes-closed state for 30 minutes prior to starting clozapine, as well as at the end of the study period. Three minutes of hyperventilation as well as photic stimulation in different frequencies were also obtained. EEG was visually interpreted by an expert and trained electroencephographist. The following parameters of EEG were studied: 1) an overall abnormal EEG as per visual impression of the electroencephographist, and 2) slow wave and epileptogenic activities.

Primary Outcome Criteria was: 1) change in EEG abnormality, and 2) level of clinical response as per CGIS and PANSS changes in EEG patterns. Two sets of criteria were used for identifying the presence of EEG abnormality. Criteria 1 were the presence of slow and theta, θ activity; Criteria 2 was the presence of epileptoform activity (slow waves, sharp waves, or spikes) at end point. The presence of greater than 50% per minute recording of slow wave activity was considered abnormal. This was decided by opinion of the electrophysiologist based upon his experience. A composite value was also worked out representing a number of patients showing both the abnormalities. Primary outcome and good recovery was based on CGIS and PANSS total score. A CGIS score of less than 2, total PANSS reduction by more than 30%, and statistically significant reduction in mean scores of PANSS total from baseline to endpoint were considered as good outcomes.

Secondary Outcome Criteria

A secondary outcome criteria for positive and negative symptoms was considered. A score of 14 or below on Positive and negative symptoms score at the endpoint was

considered as good outcome. EEG abnormality and clinical endpoint differences from baseline to the end of the 12 weeks was evaluated using McNemar's chi-square tests for dichotomous measures, and paired t-tests for continuous measures. Chi-square tests were used to examine the association between EEG abnormalities at baseline and clinical outcomes at the end of the study.

Results

Sample characteristics are given in Table 1. The majority of patients were male (83% male, 17% female) with a mean age of 33 years and a mean illness duration of 2.5 years. A number of patients were taking other medications prior to taking clozapine; 1.3% were taking trifluperazine, 42.5% risperidone, 52.5% olanzapine, 78.5% quetiapine, 35.0% aripiprazole, and 37.5% clopixole.

A significant number of patients (55%) had co-morbid axis I disorders, (16%) substance abuse, and 20% were never hospitalized. Overall, the subjects represented a severe form of the illness, and almost all patients were on more than one antipsychotic before switching to clozapine.

Table 1. Patient characteristics

N = 80	
Characteristic	**Frequency(%) Mean (SD)***
Gender	
Male	66 (82.5%)
Female	14 (17.5%)
Marriage – Married	33 (41.3%)
Clinical Diagnosis	
Disorganized	18 (22.5%)
Paranoid	16 (20.0%)
Schizoaffective	16 (20.0%)
Undifferentiated	18 (22.5%)
Residual	12 (15.0%)
Age (Years)	33.4 (7.1)*
Duration of Illness (Months)	30.8 (8.5)*
Age of Onset (Years)	30.7 (7.2)*
Previous Medication Use	
Trifluoperazine	1 (1.3%)
Risperidone	34(42.5%)
Olanzapine	42 (52.5%)
Quetiapine	63(78.5%)
Aripiprazole	28(35.0%)
Clopixole	30 (37.5%)

N = 80	
Hospitalizations	
Never	16 (20.3%)
Past - 1	29 (36.7%)
Past - 2	27 (34.2%)
Past - 3	7 (8.9%)
Substance Abuse	
No substance abuse	51 (63.8%)
Current	11 (13.8%)
Cannabis	7 (8.8%)
Alcohol	5 (6.3%)
Poly-substance	6 (7.5%)
Comorbidities	
Comorbidity – 3	
Comorbidity – Axis 1	44 (55.0%)
Comorbidity – Axis 2	13 (16.3%)

EEG Changes

At baseline, both types of EEG abnormality were observed; slow wave and theta frequency in 34 (42%) patients, and epileptoform activity in 31 (38.8%) patients (Table 2). Both types of abnormalities showed significant worsening at end point. Slow wave abnormality increased to 91.3% from 42% ($p < .001$), and epileptoform changes increased in 75% of patients from 38.8% ($p < 0.001$). The unusually high prevalence of slow wave abnormality seen in 91% of patients was potentially due to the physiological state during the EEG recording

(Table 2). Independently EEG abnormality as per both the criteria showed worsening from baseline to endpoint.

Table 2. EEG abnormalities at baseline and end point (McNemar's Chi-square test), N = 80

	EEG Frequency	Baseline	End of Study (Week 12)	*p*-value
(1)	Slow & θ* (≤7)	54 (67.5%)	77 (96.3%)	< 0. 001
(2)	Sharp Waves/Spikes	31 (38.8%)	60 (75.0%)	< 0.001
(3)	*Composite Abnormality* Slow (>50) or Sharp waves	12 (15.0%)	33 (41.3%)	< 0.001

*θ = Theta

However, EEG abnormality as per any of the two criteria did not show significant correlation with response to clozapine.

Table 3. Clinical parameters at baseline and end of study

	Baseline	Week 12	Difference	*p*-value
CGIS				
>2 (Abnormal)	80 (100.0%)	32 (40.0%)	49.9% reduction	< 0.001
PANSS Total				
Mean (sd) > 30% Reduction	102.4 (13.3)	51.3 (10.3) 6 (7.5%)	51.1 (18.8)	< 0. 001
Negative Symptoms			45.6% reduction	
Mean (sd) >14 (Abnormal) > 30% Reduction	26.5 (5.4) 77 (96.3%) 22 (27.5%)	12.1 (5.3) 21 (26.3%) 0 (0.0%)	14.4 (7.9) (70%)	< 0. 001
Positive Symptoms			54.7% reduction	
Mean (SD) >14 (Abnormal) > 30% Reduction	25.4 (3.9) 12 (15.0%)	11.6 (4.8) 22 (27.5%) 0 (0.0%)	13.9 (5.8)	< 0. 001

(CGIS = Clinical Global Impression Scale; PANSS = Positive and Negative Syndrome Scale; SD = Standard deviation)

Psychopathological Measures

Following the 12-week treatment with clozapine, 48 (60%) patients showed significant improvement on CGIS (score less than or equal to 2, $p < .001$). There was a significant reduction from baseline to endpoint seen on the CGIS (5.1 vs. 1.5, $p < .001$), mean PANSS total score (102.4 vs. 51.3, $p < .001$), negative symptoms (26.5 vs. 12.1, $p < .001$), and positive symptoms (25.4 vs. 11.6, $p < .001$; Table 3). At end point, 74 (92.5%) patients showed improvement on PANSS scores ,45.6% in negative symptoms, and 54.7% in positive symptoms, as per reduction of more than 30% in scores. A reduction of greater than 50% in total mean scores indicating clozapine was equally effective for treating both positive and negative symptoms.

Dosage

The mean clozapine dosage was 265 mg/day. The mean clozapine dose was not significantly correlated with the percent of slow wave activity at baseline ($r = -.10$, $p = .44$), but dose was positively correlated with the percent of slow wave activity at endpoint ($r = .27$, $p = .04$). Higher clozapine dose predicted a greater percentage of slow wave activity ($p < .001$) only after the 12 weeks of treatment (Table 4).

Table 4. Change in EEG abnormality between baseline and week 12 in relation to clinical parameters

	Baseline slow wave, θ		
	≤7 (Abnormal)	>7 (Normal)	*p*-value
CGIS≤2	34 (63.0%)	14 (53.9%)	0.436
NS≤14	43 (79.6%)	16 (61.5%)	0.085
PS≤14	39 (72.2%)	19 (73.1%)	0.936
	Epileptogenic Abnormality		
	Normal	**Abnormal**	
CGIS≤2	13 (52.0%)	35 (63.6%)	0.325*
NS≤14	15 (60.0%)	44 (80.0%)	0.060*
PS≤14	18 (72.0%)	40 (72.7%)	0.946*
	Composite Criteria 1		
	Normal	**Abnormal**	
CGIS≤2	38 (55.9%)	10 (83.3%)	0.110*
NS≤14	49 (72.1%)	10 (83.3%)	0.502*
PS≤14	49 (72.1%)	9 (75.0%)	0.999*

(Abnormality criteria: Slow Waves – theta,θ > 50 per minue recording activity, sharp waves/spikes, epileptogenic activity = abundant. (*Fisher's Exact); NS = negative symptoms ; PS = positive symptoms.)

Discussion

The present study shows three main findings: firstly, the response rate of clozapine in treatment resistant schizophrenia is good compared to what has been generally reported. The investigators observed improvement (60%) on CGIS which appears consistent with previous Indian studies. Also, we have found that clozapine was equally effective in reducing both positive and negative symptoms. Secondly, EEG abnormalities were seen in a significantly high number of patients in both pre-treatment and post treatment phases of clozapine therapy. Lastly, none of the EEG changes found were correlated with clinical outcome parameters. However, there was a trend of significant correlation between a higher dosage of clozapine and a greater percentage of slow wave activity only after 12 weeks of treatment.

A previous study by Srivastava et al.,[16] evaluated the effectiveness of clozapine at a 3 year follow-up and reported a significant reduction in 85% of patients. Another study by Riswin et al.,[17] reported the usefulness of clozapine in 68 non-bipolar subjects. Three-fourths of them showed good clinical response following treatment. Similarly, Dutt et al.[18], evaluated the short term and long term effectiveness of clozapine in 51 subjects, predominantly those diagnosed with schizophrenia, and concluded that during the inpatient stay (mean duration 63 days), there was a 34.7% reduction in total PANSS rating after starting clozapine at a mean dose of 298.97 mg/day. A recent Cochrane (2009) meta-analytical review of 52 clinical trials involving 4,746 patients determined that improvement was seen more frequently and relapse was less frequent amongst those taking clozapine[19].In addition, the study showed that a quarter of patients remain with persisting symptoms, which is similar to this study's findings. Therefore, whatever short term benefits clozapine may have, these must outweigh the severity of adverse effects and much research is still needed regarding the efficacy of clozapine in increasing social and global functioning. Response to clozapine in general remains limited to 30-40% in subjects, despite adequate dose and duration of treatment. In this study, response to clozapine after 12 weeks appeared somewhat better as per CGIS and PANSS scores. This outcome is likely to be due to less chronic sample of patients, shorter mean duration of illness (30 months), and with a lesser incidence of cannabis use (9%), alcohol use (7%), less number of hospitalizations (>50% has 1 or less and 20% without hospitalization), and a later mean age of onset of psychosis (30.7 years) [20,21]. Consistent with previous research, EEG abnormalities were seen in patients who had a shorter duration of the illness and those who had a better response to clozapine, although these were not statistically significant. Although EEG changes seem to occur during therapeutic intervention with

clozapine, these changes do not necessarily lead to seizure activity or convulsions and could be dependent on dosage and duration. In a cross sectional study of 87 patients, Goyal et al.,[22] concluded that EEG abnormalities were observed in 63.2% of patients. Both slow wave and epileptiform activities were noted in 41.4% of patients. However, these EEG abnormalities were not associated with dose or duration of clozapine exposure. In another study, 37 patients demonstrated that pretreatment EEG can predict clozapine response [23]. It is undetermined why the presence of EEG abnormality was in such a high number of patients before starting clozapine (39% to 68%). The present study found that EEG abnormality increased in about 26% of patients between baseline and the 12 weeks of treatment. The presence of slow wave, theta activity and epileptogenic activity was present in 15% of patients at pre-treatment, and in 41.3% of patients at the end point, indicating a statistically significant increase. Post-treatment EEG abnormalities may not have been due to clozapine alone. It could be argued that such changes may also appear because of a combination of factors existing prior to introduction of clozapine. Such factors include pre-clozapine antipsychotics, particularly atypical antipsychotics[22], the presence of EEG abnormalities before the start of any antipsychotic, total antipsychotic exposure during pre-clozapine stage, EEG abnormality that did not normalize with antipsychotic treatment, or any other causes such as co-morbid substance abuse[24].There is a significant presence of EEG abnormality in individuals with schizophrenia in general[25],which makes these individuals highly vulnerable to seizure which is particularly prevalent in Indian subjects (up to 16-18%) [26].

Though independently all EEG parameters showed worsening after 12 weeks, none of these have been found to be significant in predicting a response to clozapine on clinical parameters. Research examining EEG as a predictor for clinical response has been an interesting area of research, but so far it has remained inconclusive. It is a sparsely studied area, particularly with conventional EEG measures. A dose –response and EEG relationship shows that a mean dose was not correlated with slow wave changes at baseline, but it was positively correlated at the endpoint. Higher dose of clozapine was positively correlated with slow wave changes following 12 weeks of treatment.

The study shows that EEG abnormality is not correlated with current level of clozapine response. There is, however, a possibility of response with longer duration of treatment. EEG changes due to clozapine used for more than 12 weeks and their correlation with long term outcome of more than 12 weeks remains a matter of future research. A lack of association between EEG changes and clinical response might be attributed to less sophisticated power of conventional EEG, and uncertainty of actual EEG worsening at the end point due to high rates of pre-treatment EEG abnormality.

Conclusion

This study shows that clozapine is clinically effective in treatment resistant patients of first-episode schizophrenia following 12 weeks of treatment, with a response rate of 60% based on CGIS scores. The investigators found that 40% of patients had EEG abnormality before starting clozapine and EEG abnormality at the endpoint was seen in 75% of patients. None of the baseline or post-treatment EEG abnormalities predicted clinical response to clozapine, yet patients taking a higher dosage of clozapine did exhibit slow wave changes at endpoint.

Limitations

There are certain limitations in this study which prevent straight forward conclusions. This study was an open study and no comparative parameter is available. Secondly, the use of conventional EEG lacks the electrophysiological sophistication of newer EEG measures. A well-designed, prospective double blind study is required to ascertain the role of EEG abnormalities in predicting a clinical response.

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