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EFFECT OF CLOZAPINE ON DRUG RESISTANT SCHIZOHRENIA

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Summary :

Fifteen cases of Schizphrenia (nine male and six female) who were resistant to conventional anti psychotic therapy attended psychiatric out patient department of Psychiatry, Bangabandhu Sheikh Mujib Medical University Hospital were included in this study to evaluate prospectively the effectiveness of Clozapine therapy during the period of September, 1998 to January, 1999. Their mean age was 27.33 (±22.21) years. Schizophrenia was diagnosed clinically according to DCR of ICD-10. All the patients were interviewed before starting Clozapine as well as 6 weeks and 12 weeks after initiation of treatment with Clozapine. Initially the patients were interviewed using a semi-structured questionnaire followed by thorough psychiatric assessment. Then Brief Psychiatric Rating Scale (BPRS) was used to find out the quantum of Schizophrenia. The average score on BPRS was 28.33 (±8.31) before starting clozapine therapy. Then it was 13.87 (±6.22) and 9.2 (+5.79) a 6 weeks and 12 weeks of starting treatment with Clozapine respectively which was statistically significant at 5% level in terms of remission of symptoms for each duration of treatment overall the outcome of clozapine therapy between the starting point and after 3 months was highly significant (P<0.001) that coincides with the results of similar respresentatives studies. The finding indicate the effectiveness of clopzapine in resistant cases of Schizophrenia and it is very much applicable in our context when baseline monitoring could be done.

Introduction :

After introduction of chlopromazine a number of different antipsychotic drugs have been discovered to treat Schizophrenic patients, which varied in respect of side effects induced by their use but no difference in respect of efficacy (Donaldson et al 1983)[1]. Drug treatment showed most effect on the positive symptoms of schizophrenia such as hallucination, delusions, least effect on the negative symptoms. In other studies it was found up to 20% of the patients

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derive little benefit and present major management problems, both with respect to positive symptoms such as hallucinations and hostility and negative symptoms such as slowness and social withdrawal (Davis et al 1980; Davis & Andriukaitis 1986; Kane 1997)[2-4].

Clozapine was developed in 1960s and entered in market in 1972. It showed well established therapeutic efficacy and minimum extra pyramidal symptoms (EPS), but due to a cluster of report of agranulocytosis in Finland it lost its popularity[5]. Overall it was noted having very good efficacy in improving 30-60% of treatment refractory schizophrenic patients[6].

In 1988, a definitive study found clear efficacy of Clozapine over Chlorpromazine in treating at least a third of the treatment resistant schizophrenics[6]. Another subsequent study showed unprecedented effects on previously treatment resistant positive symptoms, some negative symptoms, improved cognitive functions as with semantic memory, improved quality of life : extrapyramidal function remained unimpaired and terdive dyskinesia improved[7]. Readmission in Hospital (relapse) and family burden were markedly reduced which achieved significant reduction in the final cost of treatment. Patients were able to improve social relationship and functioning, could live independently and even re-employed.

Clozapine has been introduced in Bangladesh since 1998, usually used in schizophrenic patients with proved lack of responsiveness to typical antipsychotic therapy. The present study was undertaken to evalute the effectiveness of clozapine therapy among schizophrenic cases who were resistant to conventional antipsychotic therapy.

Materials & Methods :

A total of 20 men and women between the ages of 15 and 45 years who attended the psychiatric out patients department (OPD) of Bangabandhu Sheikh Mujib Medical University (BSMMU) and met the DCR of ICD-10 criteria of schizophrenia8 as well as diagnosed to be treatment-resistant were initially included into this uncontrolled prospective study. Five patients out of 20 were dropped out within 2 weeks of starting clozapine therapy due to either lack of sufficient motivation for the new drug or financial inability to purchase medicine and other costs involved in monitoring.

"Treatment-resistance" was defined as a failure to respond to at least 3 anti-psychotics prescribed for at least 2 months duration and in sufficiet dose. Initially all the selected patients and their guardians were thoroughly explained about the probable outcome of treatment as well as the possibility of adverse effects including agranulocytosis. Informed consent was taken from the patients' guardian before commencement of the study.

A base line routine blood count was done to exclude any patients from the study having a total WBC count of less than 5 x 109/L or neutrophil count of less than 2.5 x 109/L or who had a history of drug induced blood dyscrasia.

Before starting Clozapine therapy, all the patients were on conventional anti-psychotics and as such the patients entered a maximum four week ' wash out' period before commencement of the new drug in which the existing antipsychotics were gradually withdrawn. The clozapine was

started according to dosing regimen of Maudsley prescribing guideline. The therapeutic dose range was 300 mg to 500 mg each day.

The patients were evaluate before treatment and at 6 weeks and 12 weeks after starting treatment. Initially the patients were interviewed using a semi-structured questionnaire followed by thorough psychiatric assessment. Then Brief Psychiatric Rating Scale (BPRS) was used to quantify schizophrenia9. BPRS was designed as an efficient and clinically valid measure of assessing efficacy in psychopharmacological research and has been used most widely among patients with psychotic disorders it consists of 18 separate symptoms constructs, each of which rates on 7 point scale of severity. Individual score was recorded before starting treatment and at 6 weeks at 12 weeks of clozapine therapy. The patients were advised to contact the researchers at any time during the study period at the event of any undesired side effect(s). All adverse events were recorded as reported by the patients, their relatives or nurse, with degree of symptoms from mild to severe. Blood was taken and haematological measurements including total count and differential count of WBC and hemoglobin were made at entry to the study and later on every weekly throughout the study.

Results :

Of the 20 patients enrolled into the study, 5 were dropped out within 2 weeks of starting clozapine therapy either due to lack of sufficient motivation for the new drug of financial inability of purchase medicine. Among the rest 15 evaluable patients who completed the study were analyzed. Their sociodemographic characteristics are shown in Table-I. Majority were male (60%), nearly

Table-I

Sociodemographic Characteristics of patients

Characteristics	Number (n=15)	%	Characteristics	Number (n=15)	%
Sex :			Educational Status :		
Male	10	60.00	Illiterate	0	0.00
Female	5	40.00	Primary	2	13.33
M/F ratio	1:0.67		Secondary & Higher	11	73.34
Age (In yrs) :			Secondary Graduate	2	13.33
15-25	5	33.39			
26-35	9	60.00	Occupational Status :		
36-45	1	6.66	Employed	4	26.67
			Unemployed	11	73.33
Area of Residence :			Marital Status :		
Rural	6	40.00	Single	13	86.67
Urban	9	60.00	Married	2	13.33
Economic Status					
Higher	0	0.00			
MIddle	12	80.00			
Lowest	3	20.00			

three quarter (73.34%) had education upto higher secondary level, 80% of them from middle-class socio-economic group. Most of them (73.33%) were currently unemployed, from urban area (60%) and only 13.33%) of them were married. Regarding types of Schizophrenia, majority (46.67%) of the patients suffered from Residual Schizophrenia, 4 (26.67%) were characterized as Hebephrenic, 2 (13.33%) Undifferentiated and one (6.67%) described for both Paranoid and Simple Schizophrenia. Table-II shows premorbid personality of the patients. Seven (64.67%) patients had schizoid personality also another 7 had adequate premorbid personality while only 1 patient was categorized as dependent type.

The severity and chronicity of illness of the studied patients is indicated by the mean duration of illness of 7.8 years. The mean age of patients at entry was 27.33 (22.21) years and the mean age at first onset of illness was 19.7 years. Table-III shows duration of treatment with conventional anti-psychotics were upto 5 years (60%, n=9), 5 to 10 years (6.6%, n = 1) and 10 to 15 years (33.33%, n = 5).

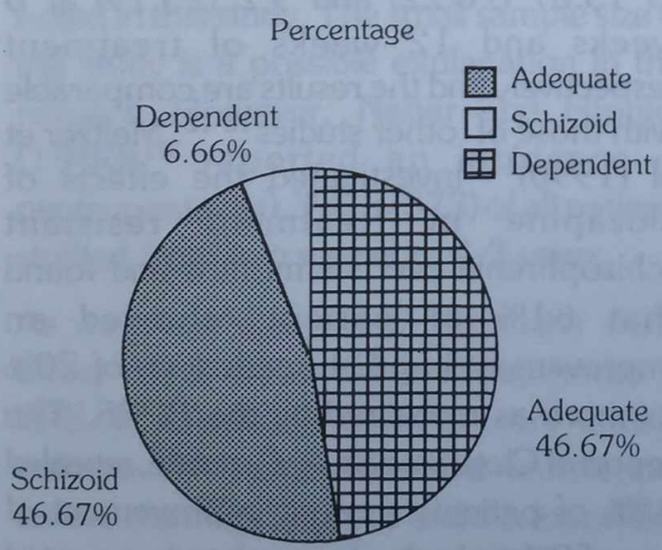

Fig-1 : *Distribution of patients by their pre-morbid personality.*

The distribution of BPRS score of patient is shown in Table - IV. The average score on BPRS was 28.33 (±8.31) before starting clozapine therapy. Improvement of patients in terms of remission of both positive and negative symptoms is indicated by the fact that the mean BPRS score dropped to 13.87 (±6.22) and 9.2 (±5.79) after 6 weeks and 12 weeks of starting treatment with clozapine respectively which is found statistically significant at 5% level.

Of the adverse events noted, hypersalivation was most frequent as reported by 7 (46.67%) patients, but dry mouth was also reported by 13.33% (n=2) patients. Drowsiness and sedation were also reported by a number of patients during initial first and second week of treatment. However, with continuation of treatment, all these adverse effects graudally ceased. Other adverse effects reported were constipation, neusea, headache, hypertension and tachycardia. No demonstrable relationship was seen between clozapine and these adverse events. Seizure was not reported by any patients as well as neutropenia and agranulocytosis was not found in this study.

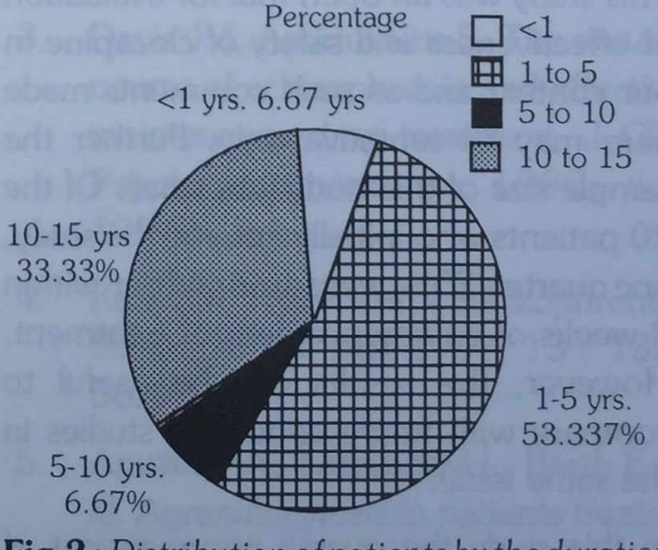

Fig-2 : *Distribution of patients by the duration of treatment with conventional anti-psychotic (before starting clozapine therapy).*

Table-IV

BPRS score of patients

Case No.	BPRS score of patient		
	Before starting clozapine	After 6 wks of treatment	After 12 weeks of Treatment
1	37	13	16
2	33	20	18
3	29	23	18
4	25	05	03
5	18	09	09
6	31	15	11
7	46	17	15
8	19	10	06
9	33	16	04
10	17	12	06
11	18	02	01
12	32	22	05
13	33	20	09
14	33	08	03
15	22	16	14
Mean	28.33 (±8.31)	13.87 (±6.22)	9.2 (±5.79)

Discussion :

This study was an open trial for evaluation of effectiveness and safety of clozapine in our context and as such comments made here may be tentative only. Further the sample size of this study was small. Of the 20 patients who initially entered the study, one quarter (25%) were dropped out within 2 weeks of commencement of treatment. However, the results can be useful to compare with future controlled studies in the same issue.

In this study the overall improvement of symptoms is satisfactory as revealed by the drop of average BPRS score from 28.33 (±8.31) before commencement of treatment to 13.87 (±6.22) and 9.2 (±5.79) at 6 weeks and 12 weeks of treatment respectively and the results are comparable with those of other studies[10-12]. Meltzer et al (1990)[11] investigated the effects of clozapine in treatment resistant schizophrenia over six months and found that 61% of patients showed an improvement in psychopathology of 20% or more as measured by the BPRS. The report of Clozapine Study Group[13], revealed 42% of patients showed improvement of over 59% in both observed and reported psychopathology measured by the Comprehensive Psychopathological Rating

Scale (CPRS). The most marked improvement was over the first 6 weeks of clozapine therapy. The most satisfying result of this study was improvement of both positive and negative symptoms of the patients, as we know that the negative symptoms of Schizophrenia are often difficult to treat with the conventional neuroleptics. The results are consistent with the findings of other studies[6,11,12].

Early termination of treatment due to adverse reactions of the drug was not noted in this study, However, in other short-term studies, early termination on account of adverse reactions have been reported to be 6% and 7% respectively (Kane et al, 1988 and Naber & Hippius, 1990)[6,10]. The most frequently reported side effect was hypersalivation affecting nearly 47% patients. This figure is much higher than that described by Kane et al (1988)6 (13%) and Naber & Hippius (199)() (7%)[10]. It is possible that the figure may be exaggerated due to specific request to the patients for reporting any occurrence of salivation during the course of treatment. Not a single report of neutropenia or agranulocytosis have been noted in this study. The small sample size of the study is a possible explanation in this respect. However, Naber and Hippius (1990)[10] reported an incidence of neutropenia of 0.3% (2/573) of all patients studied from two weeks to 4.3 years.

As we know that one of the major side - effect of conventional anti-psychotics is EPS. In this study patients were initially withdrawn from conventional neuroleptics before starting clozapine and it is found that there was reduction in their EPS over the course of treatment with clozapine. The findings are consistent with other documented literature. Lieberman et al (1991) found that approximately 43% of patients with dystonic feature were improved with clozapine.

Conclusion :

The results of the present study indicate the effectiveness of clozapine in resistant cases of schizophrenia and it is very much applicable in our context even as out patients basis when baseline monitoring could be done.

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