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Research Article

Clinical and economic outcomes of risperidone versus clozapine in the treatment of chronic schizophrenia

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ABSTRACT

Background: The purpose of this study was to examine clinical outcomes and direct cost associated with risperidone and clozapine for the treatment of chronic schizophrenia.
Methods: In a prospective observational study on 100 patients with schizophrenia in a tertiary care setting clinical outcome was measured using positive and negative syndrome scale (PANSS) and costs by direct medical cost.
Results: Both risperidone and clozapine significantly reduced the severity of psychotic symptoms (scores on the PANSS) from baseline, with no significant between group differences. The clinical improvement was more in the case of clozapine compared to risperidone group (p=0.479). In both groups, extrapyramidal symptoms and other adverse events were few, and their severity was generally mild. A statistical significance was noted in the total direct cost which was higher in patients receiving clozapine when compared to risperidone.
Conclusions: Risperidone was well tolerated and as effective as clozapine in patients with chronic schizophrenia and more economical than clozapine.

Keywords: Atypical antipsychotics, Pharmacoeconomics, Adverse drug reactions

INTRODUCTION

Schizophrenia, a clinical syndrome with a profound influence on public health, has been called "arguably the worst disease affecting mankind, even AIDS not excepted."[1] According to World Mental Health Report 2008 the incidence of schizophrenia is 0.8/1000 population. It is, therefore, essential that any intervention must be appropriate, cost-effective and efficacious.

Atypical antipsychotics specifically have been found to control both positive and negative symptoms with a lower incidence of adverse effects. Treatment of schizophrenia involves significant cost because of the high prevalence, early onset, chronicity, debilitating effects on quality of life and frequent need for rehospitalization associated with this disease. So far, there had been a general consensus that atypical antipsychotics are effective and reliable in the treatment of schizophrenia, and similar in their efficacy,[2,3]

although clozapine appears to be more effective than other atypicals.[4]

Risperidone and clozapine share some pharmacologic similarities, such as a higher affinity for serotonin 5-HT2 receptors than dopamine D2 receptors, but they differ in other pharmacologic properties and side effects.[5-7] Clozapine produces no extrapyramidal symptoms (EPS) and has been shown to be effective in the management of positive and negative symptoms.

There are very few studies in Indian setting which have compared the cost and outcome of atypical antipsychotics in the treatment of chronic schizophrenia. Pharmacoeconomic evaluation is required to be done in a real setting so that it becomes a guide for better patient care.

The present study was a prospective observational study on 100 patients with chronic schizophrenia in a tertiary care setting to examine the clinical outcome and costs of treating chronic schizophrenia with either risperidone or clozapine. Risperidone and clozapine were the two drugs available in the setting during the study period and were prescribed for the patients having chronic schizophrenia.

METHODS

The study participants were 100 men and women from inpatient and outpatient departments (OPD). As required by the inclusion criteria, patients above 15 years who met Diagnostic and Statistical Manual of Mental Disorders - Text Revision criteria for chronic schizophrenia and who received treatment with atypical antipsychotics risperidone and clozapine were included. Patients with schizoaffective disorder, mental retardation, or other cognitive disorders were excluded.

The study was conducted according to the principles of the Helsinki. Each patient's legal guardian gave written informed consent to participate in the study. Approval for the study was obtained from Institutional Ethics Committees.

Data were collected using a questionnaire. In the case of inpatients, all information relevant to the study was entered by interviewing the patient and bystander during ward rounds as well as from their case records. Change in therapy, add-on therapy, and clinical improvement until the patient was discharged from the hospital to a maximum of 14 days, whichever was earlier was noted from case records. Follow-up for inpatients was conducted after 8 weeks in the OPD. In the case of outpatients, the information relevant to the study was entered by interviewing the patient and bystander and follow-up was also conducted after 8 weeks.

Clinical outcome was measured using score positive and negative syndrome scale (PANSS) for schizophrenia. More than 30% improvement in PANSS score was considered as a clinical improvement. The economic outcome was measured using direct cost incurred by the patient during his/her stay in the hospital in case of inpatients until the follow-up is over after 8 weeks. In outpatients, the direct cost was estimated from the time of participation in study until the follow-up is over after 8 weeks.

The direct cost involved in the treatment process during the study period was calculated in Indian rupees. The direct costs included the direct medical cost and direct non-medical cost. The direct medical costs included the cost for the drugs, laboratory investigations, and the cost for treatment of adverse drug reaction (ADR) if any. The direct non-medical cost included the cost for transportation, food, lodging for both patients, and bystanders. The cost of the drugs was calculated based on the average wholesale price given in current index of medical specialties (CIIMS). The laboratory investigation costs were as per the costs in the manual of the laboratory of the hospital. Any other relevant investigations done outside in private laboratory was also considered. The ADRs were recorded in an ADR reporting form.

The data obtained were analyzed using SPSS version 16. To examine the associations and comparison between different variables Chi-square test and independent t-test were used for demographic profile. Clinical outcome was analyzed by Wilcoxon signed ranks and Mann–Whitney U-test. Economic outcome were analyzed using independent t-test and ADRs by Chi-square test.

RESULTS

This prospective observational study was conducted for 6 months. A total of 100 patients enrolled: 50 patients received risperidone and 50 patients received clozapine. There were 19 inpatients and 31 outpatients in the risperidone group and 13 inpatients and 37 outpatients in clozapine group. Dose of the two study medications at initial level (risperidone 3.9 mg and clozapine 160 mg) were maintained throughout the study. The mean age of risperidone group was 39.58 years and that of clozapine 36.92 years. Male predominance was observed in both the groups. The difference in mean monthly income of the family receiving clozapine (391 rupees) and that of risperidone (328 rupees) were not statistically significant.

The majority of patients in both the groups were from a rural area (98%), recently married, belonged to BPL (below poverty line) category and educational status was up to high school level. 51.7% was diagnosed as schizophrenia paranoid in clozapine group and 48.3% in risperidone group. There was no difference between the groups with reference to chronicity of the disease. The majority had no co-morbid disease except diabetes mellitus (4%), hypertension (2%) and bronchial asthma (2%), in the risperidone group. 50%

of the patients in clozapine groups, and 44% in risperidone group had a family history of psychiatric illnesses.

Clinical outcome

At initiation of the study, the difference in mean rank of PANSS score between both groups was not statistically significant. Hence, the two groups appear to be identical in clinical profile of the disease at the time of enrolment to the study. 8 weeks after treatment, difference was not found to be statistically significant. The mean rank of difference between PANSS total after 8 weeks and PANSS total at initiation of the study in both the groups was highly significant (p=0.000). This indicates that there was significant improvement in PANSS score after 8 weeks in both the groups. The clinical improvement was more in the case of clozapine compared to risperidone group (p=0.479). Percentage improvement in PANSS score was not significant (Table 1).

Economic outcome

The mean total direct medical cost was less with risperidone group and difference was statistically significant (p=0.002). Total direct non-medical cost was observed to be higher in clozapine group (p=0.122). Finally, the mean total direct cost was 1612.1 rupees in the risperidone group and 2419.0 rupees in clozapine group (p=0.006) (Table 2).

Drug safety profile

ADRs were more in clozapine group (92%) which was not statistically significant. Majority had central nervous system related adverse effects in both the groups. The ADR related to cardiovascular system (CVS) was more in clozapine group. The difference was found to be statistically significant (p=0.042) (Table 3).

The majority of the study subjects (84%) on risperidone had EPS compared to clozapine group. In clozapine group, 10% had tachycardia. The difference in ADR events between two groups was found to be statistically significant (p=0.000). 41 (82%) patients in risperidone group had past history of ADRs and 49 (98%) in clozapine group had past history of ADR. The difference was found to be statistically significant (p=0.008). 82% of subjects in the risperidone group and 50% in clozapine group received ADR treatment the difference were found to be statistically significant (p=0.001).

Table 1: Clinical outcome in risperidone and clozapine group (original).

PANSS	Mean rank (n=50)		p value
	Risperidone	Clozapine	
PANSS total at initiation of the study	53.57	47.43	0.290
PANSS total after 8 weeks	54.13	46.87	0.210
PANSS total after 8 weeks minus PANSS total at initiation of the study	25.50	25.50	0.000
Difference in PANSS score (PANSS total after 8 weeks minus PANSS total at initiation of the study)	52.55	48.45	0.479
Percentage improvement in PANSS score	49.29	51.71	0.676

PANSS: Positive and negative syndrome scale

Table 2: Economic outcome between risperidone and clozapine (original).

Cost	Risperidone (n=50)			Clozapine (n=50)			p value
	Mean	SD	SEM	Mean	SD	SEM	
Drug cost	232.24	106.276	15.030	576.78	342.721	48.468	0.000
Adjuvant drug cost	417.79	427.80345	60.50054	554.00	768.32086	108.65698	0.276
Lab investigation cost	183.2	382.369	54.075	312.5	271.245	38.360	0.05
Cost due to ADR	118.345	95.8384	13.5536	71.282	129.2606	18.2802	0.041
Total direct medical cost	951.57	655.25105	92.66649	1516.4	1103.67510	156.08323	0.002
Food cost	240.18	337.474	47.726	304.02	393.267	55.616	0.386
Cost of transport	406.58	359.881	50.895	598.52	578.879	81.866	0.049
Cost of lodging	9.80	37.715	5.334	0.00	0.000	0.000	0.069
Other costs	4.00	13.702	1.938	0.00	0.000	0.000	0.042
Total direct non-medical cost	660.56	643.693	91.032	902.54	887.726	125.543	0.122
Total direct cost (total direct medical cost total direct non-medical cost)	1612.1	1129.42765	159.72519	2419.0	1691.81817	239.25922	0.006

ADR: Adverse drug reaction, SD: Standard deviation, SEM: Standard error of mean

Table 3: ADR profile of risperidone and clozapine (original).

ADRs events	Risperidone (%)	Clozapine (%)
No ADR	8 (16)	4 (8)
EPS	42 (84)	8 (16)
Tremor	0 (0)	21 (42)
Tachycardia	0 (0)	5 (10)
Sialorrhea	0 (0)	10 (20)
Sedation	0 (0)	1 (2)
Dystonia	0 (0)	1 (2)
Total	50 (100)	50 (100)

ADR: Adverse drug reaction, EPS: Extrapyramidal symptoms

DISCUSSION

The results of this 8 weeks prospective observational study indicate that risperidone was well tolerated and as effective as clozapine but more economical in terms of total direct cost.

In general, the incidence of chronic schizophrenia is the same across sexes, although women tend to have a later age of onset than men.[8] In the present study, male predominance was observed in both groups and is comparable to a study by Bondolfi et al.[9] The other socio-demographic variables of the two groups were compared, and the differences were not statistically significant. The distribution of schizophrenia subtype in risperidone group was 42 paranoid, 6 undifferentiated, 2 hebephrenic. In clozapine group, it was 45 paranoid, 3 undifferentiated, 2 hebephrenic. This helped to compare the clinical and economic outcomes between the groups without much bias. In the study by Bondolfi et al.,[9] similar distributions in subtype were observed.

In both the groups, majority were from rural area (98%). This might be due to the fact that in the study locality, the rural-urban distribution was 66:44 (census data 2001). Hence, they had to spend much on travelling and lodging. Both rural and urban families' experienced equal burden and also perceived equal social support system as observed in a study by Ali and Bhatti.[10]

Regarding the socioeconomic status of the study subjects, in both groups majority belonged to BPL category. The difference in mean monthly income of the family in risperidone group (328 rupees) and in clozapine group (391 rupees) was not found to be statistically significant. However, still the financial burden on the family was much higher compared with western figures.[11]

The difference in employment status of risperidone group (40%) and clozapine group (44%) was not statistically significant. In the study conducted by Grover et al.,[11] employment status had significant influence on the costs of care. The total as well as direct costs were significantly higher among unemployed group. There was a strong correlation between the PANSS scores with total cost as well as various other components of costs in that study.

Diabetes mellitus was the comorbid illnesses common in the groups, hypertension and bronchial asthma were seen in the risperidone group. 94% subjects in clozapine group had no comorbid illness. In a study by Carney et al.,[12] subjects with schizophrenia were significantly more likely to have one or more chronic conditions when compared with controls. This might increase the cost of treatment of the disease both in terms of direct cost and indirect cost.

At the time of initiation of the study, the risperidone and clozapine group did not differ significantly in their mean PANSS score when analyzed by Mann–Whitney U-test. Hence, the two groups appeared to be identical in their clinical profile at the time of enrolment to the study. The results were comparable to the study conducted by Bondolfi et al.[9]

After 8 weeks of treatment, the mean rank of risperidone had increased to 54.13 which meant a slight deterioration in PANSS score from the time of initiation of the study and the score of clozapine decreased to 46.87 indicating improvement in the clinical outcome, and this difference was found to be statistically insignificant. But in the study by Bondolfi et al.,[9] there was significant improvement in both the groups after 8 weeks.

The difference in mean between PANSS total after 8 weeks and PANSS total at the time of initiation of the study in each group when analyzed by Wilcoxon signed ranks, was 25.5 in each group and the p=0.000 which showed that, in both the groups there was significant improvement in PANSS score, after 8 weeks. This was similar to that observed in the study by Bondolfi et al.[9]

The comparisons of difference in PANSS score (PANSS score after 8 weeks minus PANSS score at the time of initiation of the study) between risperidone group and clozapine group showed that there was no statistically significant change (p=0.479). In percentage improvement of PANSS, there was definitely improvement in both groups (mean rank >30% which means there is improvement). The clinical improvement was more in the case of clozapine compared to risperidone, but the difference was not found to be statistically significant (p=0.676). It was comparable to the results observed in the study by Bondolfi et al.[9] Other studies by Rosenheck et al.,[13] Rosenheck et al.,[14] Lewis et al.,[15] McEvoy et al.,[16] concluded that clozapine was better in chronic schizophrenia. An open clinical trial conducted by Krishnan et al.,[17] supported the evidence that risperidone is well tolerated in patients with chronic schizophrenia.

There were a very few studies which have evaluated the cost of mental illness in India.[11] The mean drug cost was 232.24 rupees in the risperidone group and 576.78 rupees in clozapine group for a period of 2-month. Hence, the greater

cost of treatment for clozapine patients when compared to the risperidone (p=0.000) was especially notable. The reason was risperidone was cheaper than clozapine. Many patients required adjuvant medication mainly to control the acute symptoms. The adjuvant drug cost was higher in subjects receiving clozapine when compared to the risperidone. However, the difference was found to be statistically not significant between the two groups (p=0.276). Thus, the direct non-medical costs associated with a treatment made clozapine more expensive. The lab investigation costs were higher in subjects given clozapine when compared to the risperidone. The difference was found to be statistically significant (p=0.05). This was because clozapine required more frequent blood count monitoring as agranulocytosis is an adverse effect which can occur with clozapine. However, the ADR cost was a higher in subjects receiving risperidone when compared to the clozapine (p=0.041) because patients taking ADR treatment was more in risperidone group when compared to clozapine group.

The total direct medical cost was higher in subjects receiving clozapine when compared to the risperidone (p=0.002). The total direct non-medical cost was 660.56 rupees in the risperidone group and 902.54 rupees in clozapine group (p=0.122).

The mean total direct cost (total direct medical cost plus total direct non-medical cost) as analyzed by independent t-test was 1612.1 rupees in the risperidone group and 2419.0 rupees in clozapine group (p=0.006). Thus, there was higher cost in the clozapine group, and the cost difference was statistically significant.

In this study, the direct cost of treatment was calculated for clozapine and risperidone for only 2 months. It was more for clozapine as the drug cost of clozapine was high and more lab investigations were needed for clozapine group. Factors associated with differences in cost are age, gender, ethnicity, marital status, education, relapse status and family support. The study on the economic outcome would increase awareness of the costs incurred by patient's families and treating agencies.[18]

The incidence of EPS was more in risperidone group despite the dose of 6 mg/day. In clozapine group around 10% had ADR related to CVS (p=0.042). This finding had implication while calculating the direct cost of these medicines. The lower incidence of EPS associated with clozapine was consistent with previous data.[19]

In Western and Indian studies, there are differences of opinion regarding the effectiveness of risperidone and clozapine in chronic schizophrenia. Many studies supported that clozapine was the best, some opined risperidone was well tolerated and yet there are other studies which supported that both were effective in chronic schizophrenia. It might be due to pharmacogenetic variation in drug response.

Limitations of the study

This study was conducted with a follow-up period of only 8-week. Clozapine generally takes more than 8 weeks to bring about the full effect.,[9] this indicates that 8-week may be too short a period to evaluate the overall effectiveness of clozapine and risperidone. The majority of study subjects were mainly those who were off drugs for more than 1 week. Another limitation of the study was that the scoring was done by different psychiatrists at the time of initiation of the study and also after 8 weeks. There was no weighing machine available in the study setting during the study period. Hence, exact measure in weight gain could not be assessed objectively, but subjectively there was weight gain in four patients on clozapine.

CONCLUSION

In this study, risperidone was found to be well tolerated and as effective as clozapine but more economical in terms of total direct cost.

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