ORIGINAL RESEARCH PAPER

Volume-7 | Issue-3 | March-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

EFFECT OF RISPERIDONE AND CLOZAPINE ON EXECUTIVE FUNCTIONS IN FIRST EPISODE SCHIZOPHRENIA

Psychiatry

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ABSTRACT

Aims: To compare the effect of risperidone and cloazpine on executive functioning in treatment naïve first episode schizophrenia.
Methods: A total of 55 treatment naïve first episode patients of schizophrenia as per ICD-10 criteria, were enrolled for the study. Baseline assessment for executive functioning was carried out with TMT- A & B. Clozapine and risperidone were used in the range of 200-600mg/ day and 4-8 mg/day respectively for 6 months.
Results: There was significant improvement in executive functioning in both the groups and the results were statistically significant for clozapine on TMT-B.
Conclusion: The findings of current study show that both risperidone and clozapine lead to improvement in executive functioning in first episode of schizophrenia and clozapine fared better than risperidone.

KEYWORDS

clozapine, risperidone, treatment naïve, first episode schizophrenia

INTRODUCTION

It is well established that cognitive deficits are core feature of schizophrenia[1]and that individuals with schizophrenia have clear deficits in most aspects of cognitive functioning .Furthermore, it has been demonstrated that people experiencing their first episode of schizophrenia are already exhibiting cognitive deficits.[2,3,4] In several studies, first-episode (FE) patients showed cognitive impairment equivalent to the impairment of those who had been ill for several years, particularly in the area of memory.[2,5,6,7] This impairment did not appear to be an effect of medication, as the deficits were also observed in FE subjects who were treatment naïve.[8]

Executive functions cover a wide range of cognitive processes that ultimately result in purposeful and goal-directed behavior. It has been found that many patients with schizophrenia have difficulties with most of these components of executive functions on formal neuropsychological tools. Schizophrenia patients might have difficulty in forming a conceptual framework to understand ambiguous stimuli.[9] These patients have trouble adapting to changes in the environment that require different behavioral responses even after understanding the concept.[10,11] Another important component of planning is often found to be impaired in schizophrenia.[12,13] Self-care, social, interpersonal, community, and occupational functions are all associated with executive functioning in schizophrenia [14] and hence, executive functioning tasks are consistently among the best predictors of functional performance. Importantly, executive functions are also associated with treatment success. Impairments in this domain are associated with less engagement in therapy [15], medication compliance [16] and longer hospital stays.[17]

Typical antipsychotics adversely effects the working memory, processing speed, motor skills, and other higher order cognitive abilities in patients with schizophrenia.[18,19,20,21]

Review of the literature suggests that compared to typical antipsychotics, atypical antipsychotic drugs (APD) produce a slight improvement in the global cognitive index, and several cognitive domains show a slight improvement in the neuropsychological performance of patients.[22,23] This suggests that initiation of treatment in schizophrenia should begin with an atypical antipsychotic early on, so that maximum beneficial improvement can be achieved. .

The atypical APD clozapine is well recognized for its superior efficacy in treatment-resistant schizophrenia and there has been interest in whether clozapine is also superior for the treatment of FES[24,25,26,27] (first episode schizophrenia).

However, there is no Indian study comparing the effect of risperidone and clozapine on executive functions in treatment naïve FES.

MATERIAL AND METHODS

It was a comparative, open-label, randomized, prospective study with intent to treat analysis. Patients of ICD 10 diagnosis of schizophrenia[28] were inducted from outpatient and inpatients setting of Department of Psychiatry, Government Medical College and Hospital (GMCH), Chandigarh, a tertiary care teaching hospital of north India. Patients who gave informed consent, and fulfilled inclusion and exclusion criteria were enrolled in the study. Fifty five consecutive patients of first-episode, treatment-naive schizophrenia in the age range of 18 and 40 years were included in the study. The patients were allocated to either risperidone group or clozapine group on the basis of computer-generated random table number. The dosages of the risperidone and clozapine were kept in therapeutic range of 4-8 mg/day and 200-600 mg/day respectively.

Patients having history of seizure disorder, heart conduction defects, history of agranulocytosis or total leucocyte counts (TLC) <3500/mm3 and diabetes mellitus, neurological disorders, head injury, movement disorder, lactating or pregnant women, patients with comorbid substance dependence except nicotine and patients with subnormal intelligence were excluded from the study.

Both the drugs were dispensed from the hospital dispensary free of cost. Each patient's socio-demographic and clinical variables were recorded on prescribed Performa designed for the study.

TLC/DLC/Platelet Count/absolute neutrophil counts were carried out on weekly basis for initial 18 weeks for patients receiving clozapine and thereafter these were done on monthly basis. Cognitive functions assessment was done using Trail Making Tests A & B (TMT-A & B) [29] at baseline, 1 month, 2 months, 4 months and at 6 month.

Trail Making Test (TMT)[30] consists of two parts; TMT-A requires an individual to draw lines sequentially connecting encircled numbers distributed on a sheet of paper. Task requirements are similar for TMT-B except that the person must alternate between numbers and letters (e.g., 1, A, 2, B, 3, C, etc.). The score on each part represents the amount of time required to complete the task. TMT gives information on scanning, visual search, mental flexibility, speed of processing, and executive functions.

Data was analyzed using SPSS 16.0 version. Significance level was $p < .05$

Results:

Table 1 shows comparison on socio-demographic characteristics of patients in clozapine and risperidone group. The two groups were comparable on mean age, gender, locality, education, occupation, income, family type and marital status.

Table 1. Comparison On Socio-Demographic Characteristics

Variable	Clozapine (n=28)	Risperidone (n=27)	Significance	
Age (Mean,SD)	30.89 (7.74)	29.03 (7.96)	0.392	
Sex	Male	15 (53.57%)	14 (51.8%)	0.896
	Female	13 (46.42%)	13 (48.14%)	
Area	Chandigarh	13 (46.42%)	11 (40.74%)	0.7916
	Punjab	8 (28.57%)	6 (22.22%)	
	Haryana	7 (25%)	10 (37.03%)	
Education	Below primary	7 (25%)	8 (28.57%)	0.9497
	Matric	13 (46.42%)	14 (51.85%)	
	Matric & Above	8 (28.57%)	5 (18.51%)	
Occupation	Working	9(32.14%)	14 (51.85%)	0.4551
	Non Working	17(60.71%)	10 (37.03%)	
	Student	2(7.14%)	3(11.11%)	
Family Income	< 5000	6(21.43%)	12 (44.44%)	0.191
	5001- 10000	12 (42.86%)	8 (29.60%)	
	>10000	10 (35.71%)	7 (25.93%)	
Family Type	Nuclear	14 (50%)	15 (55.56%)	0.573
	Joint	14 (50%)	12 (44.44%)	
Marital Status	Single	22(78.57%)	15 (55.56%)	.0429
	Ever-Married	6 (21.43%)	12 (44.44%)	

There was no significant differences between two groups on various dimension of psychopathology assessed on positive symptoms, negative symptoms, general psychopathology, and PANSS total scores.

Table 2.Comparison on executive functioning on Trail Making Tests at baseline assessment

Variable	Clozapine (n=28) Mean (SD)	Risperidone (n=27) Mean (SD)	Significance
Trail Making Test A Time	90.39 (48.72)	92.7 (42.43)	.8549
Trail Making Test A Error	3.607 (5.492)	3.148 (5.5156)	.7627
Trail Making Test B Time	178.82 (66.65)	191.44 (81.89)	.5402
Trail Making Test B Error	13.5 (8.99)	13.07 (9.4865)	.8660

As depicted in the table 2, there were no statistically significant difference between the two groups on trail making tests at the baseline.

Table 3.Comparison on executive functioning (trail making tests) between two groups across assessments on TMT Variable A

Variable (TMT A time taken)	**Clozapine Group Mean (SD)**	**Risperidone Group Mean (SD)**	**Significance P value**
1st assessment (at one month)	56.57(29.60)	70.48(27.39)	0.0417*
2nd assessment (at two months)	51.42(28.17)	57.22(17.78)	0.3766
3rd assessment (at four months)	52.14(12.81)	49.07(10.02)	0.3365
4th assessment (at six months)	48.53(17.43)	49.22(21.63)	0.8985
Variable (TMT A Total errors)	**Clozapine Group Mean (SD)**	**Risperidone Group Mean (SD)**	**Significance P value**
1st assessment (at one month)	1.75(3.44)	1.92(4.93)	0.8981
2nd assessment (at two months)	1.357(2.06)	1.40(3.86)	0.5184
3rd assessment (at four months)	1.17(3.09)	1.37(2.91)	0.8093
4th assessment (at six months)	1.12(3.17)	1.37(3.37)	0.9558

Table 4.Comparison on executive functioning (trail making tests) between two groups across assessments on TMT Variable B

Variable (TMT A time taken)	**Clozapine Group Mean (SD)**	**Risperidone Group Mean (SD)**	**Significance P value**
1st assessment (at one month)	115.46 (42.10)	174.40 (62.16)	0.0002*
2nd assessment (at two months)	104.78 (40.14)	153.25 (46.34)	0.0002*
3rd assessment (at four months)	95.63(28.96)	139.40 (30.48)	0.0003*
4th assessment (at six months)	90.23(25.63)	125.30 (29.63)	0.0025*
Variable (TMT A Total errors)	**Clozapine Group Mean (SD)**	**Risperidone Group Mean (SD)**	**Significance P value**
1st assessment (at one month)	5.57(7.38)	11.96(8.48)	0.0050*
2nd assessment (at two months)	4.64(5.67)	10.44(7.007)	0.0016*
3rd assessment (at four months)	3.71(5.53)	5.77(6.61)	0.2230
4th assessment (at six months)	2.53(5.23)	5.11(6.14)	0.1049

* Significant

Table 3 & 4 shows that both the molecules led to improvement in executive functioning in schizophrenia patients by reducing the time required to complete the task and reduction in numbers of errors occurred in completing the task. The effects of clozapine in reduction of errors on TMT-B were significant for clozapine as compared to risperidone.

Effects of Clozapine across Four Assessments

The four assessments were compared using repeated measures ANOVA in each of the group on all the variables.

Table 5. Change in Executive Functioning (Trail Making Test) with Clozapine

Variables	1 v/s 2 P	1 v/s 4 P	1 v/s 6 P	2 v/s 4 P	2 v/s 6 P	4 v/s 6 P
TMT-A Time taken	.508	.04707*	.0130*	.009032*	.00411*	.0005*
TMT-A Number of errors	.245	.005166*	.0088*	.0036*	.0418*	.0008*
Variables	1 v/s 2 P	1 v/s 4 P	1 v/s 6 P	2 v/s 4 P	2 v/s 6 P	4 v/s 6 P
TMT-B Time taken	.335	.0022*	.0145*	.0367*	.00013*	.0179*
TMT-B Number of errors	.5997	.02915*	.00814*	.005379*	.01542*	.041655*

*significant

Table 5 shows the comparison of executive functions within clozapine group at 1,2,4 and 6th month of intervention and found that there was statistically significant difference for executive functioning on TMT-A & B across different assessments.

Effects of Risperidone across Four Assessments

The four assessments were compared using repeated measures ANOVA in each of the group on all the variables.

Table 6. Change in Executive Functioning (Trail Making Test) with Risperidone

Variables	1 v/s 2 P	1 v/s 4 P	1 v/s 6 P	2 v/s 4 P	2 v/s 6 P	4 v/s 6 P
TMT-A Time taken	.0697	.36	.0321*	.430	.0678	.0945
TMT-A Number of errors	.6992	.6166	.06313	.968	.9702	.07369

Variables	1 v/s 2 P	1 v/s 4 P	1 v/s 6 P	2 v/s 4 P	2 v/s 6 P	4 v/s 6 P
TMT-B Time taken	.1623	.075	.00612*	.08549	.08213	.0369*
TMT-B Number of errors	.4763	.0926	.0765	.849	.105	.3830

*significant

Table 6 shows the comparison of executive functions within risperidone group at 1,2,4 and 6th month on TMT A & B and results revealed statistical difference only for time taken on TMT A & B and that too for first and sixth month assessment only and there was significant difference for errors.

DISCUSSION

The present study was carried out to compare the effect of clozapine and risperidone on executive functioning in treatment naive first episode schizophrenia by using Trail Making Test.

The executive functions were assessed using trail making test A & B and the findings showed that the time taken to complete the task in Test A & B was more than the average population, however, we do not have norms for the Indian population.[29,30] This can be interpreted that executive functions were already compromised in the treatment naïve first episode schizophrenia patients and the same has been reported in other studies too.[9-13] In our study, patients receiving clozapine consistently performed better on TMT A & B and also the number of errors reduced gradually with every assessment and these changes were statistically significant. Hence, it is cleared from the findings of current study that starting clozapine in the treatment naïve schizophrenic population leads to improvement in executive functioning whereas typical antipsychotics adversely effects the cognitive abilities in patients with schizophrenia.[18,19,20,21]

A review of studies assessed the effect of clozapine on cognitive functioning in schizophrenia showed that psychomotor speed, verbal fluency, verbal learning and memory might be improved by treatment with clozapine. The improvement in cognitive functions with use of clozapine may offer an advantage to patients with schizophrenia by improving their vocational functioning and quality of life.[31]

The present study found that risperidone also improved the executive functioning by reducing the time taken in the trail tests but it was not statistically significant and the reduction in number of errors was also not significant.

Our study reported that both clozapine and risperidone led to improvement in executive functioning, however, the difference was significant for clozapine including both time taken to complete the task as well as the number of errors made. In literature[31] it has been found consistently that clozapine led to improvement in cognition in all the domains but not necessarily in the same population sample and going with this explanation, it could be said that in our study population, clozapine led to greater recovery on trail making test B than risperidone. Earlier studies[32,33] have raised doubt on efficacies of these drugs on grounds that the patients on whom they were studied had received neuroleptics in past and these effects or improvement in cognition could have been the long term effect of those neuroleptics. However, our study population was exclusively treatment naïve, hence, such confounding factor could be ruled out in our results. The findings also indicate that clozapine should be considered early rather than waiting for the patient to become treatment resistant.

Conclusion

The findings of current study shows that both risperidone and clozapine lead to improvement in executive functioning in first episode treatment naïve patients of schizophrenia, however, clozapine was more effective in improving the cognitive functions than risperidone.

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