Memantine add-on to Atypical Antipsychotics for Treatment of Negative Symptoms in Schizophrenia

Pavan Kumar Pardal[1], Abhilasha Gupta[2]

ABSTRACT

Introduction: Studies on the role of adjunctive memantine to atypical antipsychotics in treatment of negative symptoms of schizophrenia have shown conflicting results. In view of the above, the present study was carried out to find the efficacy of memantine as add-on to ongoing atypical antipsychotics in treatment of negative symptoms in schizophrenia patients.

Material and Methods: The number of patients of schizophrenia selected were 40, based on specified inclusion criteria. They were divided into 2 groups of 20 each. Group 1 was the study group which received memantine in addition to their on going antipsychotics while, group 2 was the control group and received placebo and their on going atypical antipsychotics. PANSS was administered at baseline and after 8 weeks results were analyzed statistically.

Results: Both the groups were matched as far as various socio-demographic variables, duration of illness and PANSS scores at baseline were concerned. After 8 weeks, there was no significant difference in the PANSS negative syndrome scale scores between the 2 groups.

Conclusion - The main cause of disability in schizophrenia patients are the negative and cognitive symptoms. They are generally resistant to the current pharmacological treatments, including atypical antipsychotics. From current study we can say that Memantine add-on to atypical antipsychotics had no advantage over placebo.

Keywords: Memantine, Negative Symptoms, Schizophrenia

INTRODUCTION

The main cause of disability in schizophrenia patients are the negative and cognitive symptoms. They are generally resistant to the current pharmacological treatments, including atypical antipsychotics. Various medications have been tried as add-on therapies to atypical antipsychotics with no consistent benefit.

The glutamatergic system is currently being implicated in the etiology of schizophrenia. It has been suggested that the glutamatergic system, specifically the NMDA receptors are hypofunctional in schizophrenia.[1] In addition, hypofunctioning NMDA receptors could lead to a compensatory excessive glutamate release. NMDA receptor hypofunctioning would lead to decrease stimulation of GABA neurons in the cortex resulting in excess release of glutamate in the synapses causing neuronal cell death (excitotoxicity).[2] Such excitotoxic neuronal damage is suggested to have a role in causing the negative and cognitive symptom in schizophrenia. It has been suggested that glutamatergic antagonists could not only provide symptom relief but also be disease-modifying.[1,3]

Memantine is a drug currently licensed for use in people with moderate to severe Alzheimer's dementia. It is an uncompetitive antagonist of NMDA receptors and prevents a toxic influx of Ca^{++} and the resultant cell death.[4] It has been suggested that it could have benefit effects on the negative and cognitive symptoms of schizophrenia.[5]

Previous studies on the role of adjunctive memantine to atypical antipsychotics in treatment of negative symptoms of schizophrenia have shown conflicting results. While some studies have shown benefit,[6-10] other report no significant effect.[1,5,11] In some the data is inconclusive.[12,13]

In view of the above, the present study was carried out to find the efficacy of memantine as add-on to ongoing atypical antipsychotics in treatment of negative symptoms in schizophrenia patients.

MATERIAL AND METHODS

The study was carried out in a large tertiary care teaching hospital from May 2016 to March 2017. Necessary ethical clearance was taken.

The number of patients selected were 40, by purposive sampling, based on the following criteria-

1. Patients fulfilling the ICD-10 (DCR) criteria for schizophrenia
2. More than 2 years of illness.
3. Patients having predominant negative symptoms.
4. Age group of 18-60 years.
5. Patients on a stable close of atypical antipsychotics for at least 8 weeks.
6. No history of any major physical/neurological illness.
7. Patients/guardians had given informed consent.
8. No contraindications to memantine.

The patients were divided into 2 groups (group 1 and 2) of 20 each by simple randomization.

All patients were interviewed separately. Detail socio-demographic data, medical and psychiatric history was taken. Detail physical and psychiatric examination was also done in each case.

Patients were then administered the Positive and Negative Syndrome Scale (PANSS).[14] Group 1 patients (study group) were started on memantine 5mg/day in addition to their existing atypical antipsychotics. The dose of memantine was titrated to 20mg/day in 3 weeks. Group 2 patients (control group) were given placebo tablets in addition to the existing atypical antipsychotics. Compliance was monitored by pill counting and

[1]Professor, [2]Junior Resident, Department of Psychiatry, SRMS Institute of Medical Sciences, Bareilly, India

Corresponding author: DR. Abhilasha Gupta, Junior Resident Psychiatry, SRMS Institute of Medical Sciences, Bareilly-243202, India

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patients/caregivers reports. PANSS was again administered in each patient after 8 weeks.

STATISTICAL ANALYSIS

Statistical analysis was done with the help of Statistical Package for Social Sciences-16 (SPSS-16). In both the groups, socio-demographic and clinical variables (both continious and categorical) were summarized with the help of frequency, percentages, mean and standard deviation, as per the applicability. Comparison of socio-demographic variables across both the groups was done with Chi square or Student-t test, as applicable. The significance level was fixed at $P<0.05$.

RESULTS

Tables 1 and 2 show that both the study group (Group 1) and control group (Group 2) were matched as for as the various socio-demographic variables, including duration of illness, was concerned.

Table 3 shows the various PANSS scores at base-line viz. PANSS positive syndrome scale (PANSS-P), negative syndrome scale (PANSS-N), general psychopathology scale (PANSS-G), and total score (PANSS-T). There was no statistically significant difference in the different scores between the 2 groups.

Table 4 shows the PANSS scores after 8 weeks. There was no significant difference in the negative syndrome scale scores (PANSS-N) between the 2 groups. However, patients receiving memantine (Group 1) showed statistically significant difference in the PANSS-P, PANSS-G and PANSS- T scores as compared to the patients receiving placebo (Group2).

It would be pertinent to mention that no patient in both the groups complained of any significant adverse effects warranting withdrawal from the study.

DISCUSSION

Schizophrenia is the most devastating of the mental illnesses. The discovery of typical antipsychotics in the 1950s revolutionized the treatment of schizophrenia. They brought the positive symptoms under control within a matter of days. However, they were not found to be very effective against the negative symptoms. Atypical antipsychotics, discovered subsequently,

Variables		Group 1 N=20		Group 2 N=20		X^2	df	P
		N	%	n	%			
Sex	Male	17	85	19	95	1.111	1	0.605*
	Female	3	15	1	5			
Marital status	Unmarried	5	25	8	40	1.026	1	0.501*
	Married	15	75	12	60			
Religion	Hindu	15	75	17	85	0.625	1	0.695*
	Others	5	25	3	15			
Education	Below matric	8	40	11	55	0.401	1	0.527*
	Above matric	12	60	9	45			
Occupation	Employed	12	60	9	45	0.401	1	0.527*
	Unemployed	8	40	11	55			
Economic status	Lower	19	95	19	95	0.000	1	1.000*
	Middle	1	5	1	5			
Domicile	Rural	16	80	18	90	0.196	1	0.661*
	Urban	4	20	2	10			
* Not significant								

Table-1: Socio demographic characteristics of the 2 groups (categorical variables).

Variables	Group 1 (Study group) Mean±SD N=20	Group2 (Controlgroup) Mean±SD N=20	t	df	P
Age (years)	32.75±7.31	28.60±6.8	1.853	38	0.072*
Duration of illness (years)	8.20±6.69	6.50±5.30	0.890	38	0.379*
*Not significant					

Table-2: Socio demographic characteristics of the 2 groups (continuous variables).

	Group 1 (Study group) Mean±SD N=20	Group 2 (Control-group) Mean±SD N=20	t	df	P
PANSS-P	13.20±4.20	16.20±5.19	-2.010	38	0.052*
PANSS-N	29.45±5.20	29.90±4.16	-0.302	38	0.764*
PANSS-G	43.05±6.55	46.65±5.86	-1.831	38	0.075*
PANSS-T	85.20±10.93	91.75±11.42	-1.852	38	0.072*
*Not significant					

Table-3: PANSS scores at baseline.

	Group 1 (study group)	Group 2 (controlgroup)	t	df	P
PANSS-P	7.65±1.08	9.45±2.94	-2.562	38	0.014*
PANSS-N	17.30±4.36	19.65±3.52	-1.872	38	0.069**
PANSS-G	26.05±3.96	28.90±3.86	-2.301	38	0.027*
PANSS-T	51.00±7.96	58.00±7.63	-2.837	38	0.007*
*Significant, ** Not significant					

Table-4: PANSS scores after 8 weeks.

were initially claimed to be more effective against the negative symptoms. However, subsequent experience has brought out their limitations against the negative symptoms. In view of the above, various dugs as add-on to atypical antipsychotics have been tried.

The glutamatergic system is now being widely implicated in the pathogenesis of schizophrenia. With this in view, memantine add-on to atypical antipsychotics has been tried for the treatment of negative symptoms.

Our study shows that memantine add-on to atypical antipsychotics had no statistically significant advantage over placebo, after 8 weeks on the negative symptoms, as assessed by PANSS. Similar conclusions have been made by earlier studies.[1,5,11] However, some studies have shown benefits.[6-10] Though, not part of our present study, the memantine group had statistically significant advantage over placebo on the positive scale, general psychopathology and total scores of PANSS after 8 weeks. Memantine add-on to atypical antipsychotics was well tolerated as no patient had to be withdrawn from the study because of adverse effects.

Limitations of the study

1. Short period of study of 8 weeks, out of which it took 3 weeks for memantine to be titrated to its full dose.
2. Small sample size.
3. The variety of atypical antipsychotics used in the study were no sufficiently powered to detect their individual effects with add-on memantine.

CONCLUSION

Memantine add-on to atypical antipsychotics had no advantage over placebo after 8 weeks, as assessed by PANSS negative syndrome scale scores. However, a longer period of study with a larger sample size is warranted.

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