Effect of Adjunctive Sodium Valproate in Patients of Acute Schizophrenia

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ABSTRACT

Introduction: Sodium valproate is an anticonvulsant widely prescribed as a mood stabilizer for treating bipolar disorders. It's role in treating schizoaffective disorders is well documented. There are controversies regarding sodium valproate efficacy in schizophrenia. Although, some studies have reported that it is effective in the management of positive symptoms in acute psychosis, others have not found such an association. Study aimed at assessment the effect of adjunctive sodium valproate in acute stage of schizophrenia.

Material and Methods: A total of 60 schizophrenic patients (age 18-45 years) were taken. They were randomly allocated into two groups, A and B. Patients in group A received atypical antipsychotic with placebo and in group B atypical antipsychotic with adjunctive sodium valproate. Olanzapine was taken as atypical antipsychotic in both groups.

A diagnosis of schizophrenia was established based on ICD-10 DCR criteria. All patients were assessed by PANSS and CGI-S at baseline and at 6 weeks. The collected data were analyzed by Student and Paired t-tests through SPSS.

Results: Comparison of mean PANSS scores showed statistically significant improvement in positive symptoms ($p<0.014$), general psychopathology ($p<0.036$) and total score ($p<0.018$) in group B patients as compared to group A. CGI-S scores were also statistically significantly less in ($p<0.011$) group B patients as compared to group A after 6 weeks.

Conclusion: Our study shows that if used as an adjunctive to antipsychotic in the management of acute psychosis, sodium valproate will speed up the recovery of positive symptoms.

Key words: Olanzapine, Schizophrenia, Sodium Valproate

INTRODUCTION

Despite the introduction of antipsychotics in the 1950s, there is still a sizeable minority (at least 30% of people with schizophrenia and related conditions), who do not achieve remission of symptoms. For the past 40 years, a variety of adjunctive treatments have been used to treat schizophrenia.[1] Using mood stabilizers is one such approach. Sodium valproate, a mood stabilizer used to treat bipolar disorders, is not an approved medication for schizophrenia. However, it has become the most frequently prescribed mood stabilizer for patients with schizophrenia, with lithium lagging far behind.[2,3]

One possibility, the so-called "GABAergic origin hypothesis," is that N-methyl-D-aspartate receptor (NMDAR) hypofunction at GABAergic interneurons, in particular, is sufficient for schizophrenia-like effects.[4] Sodium valproate acts on GABA receptors and prevents the downstream hyperactivity of mesolimbic dopamine neurons which is associated with positive symptoms of schizophrenia. Studies found that it may help to reduce aggressiveness and hostility in schizophrenia as an "off-label" use.[5,6] Tseng et al. showed significantly better treatment effect with valproate augmentation therapy in patients with schizophrenia or schizoaffective disorder.[7] Omranifard et al. found that sodium valproate speeds up the recovery of positive symptoms of schizophrenia.[8]

Only one case study in India reported beneficial effect of adjunctive sodium valproate in functional hallucinations in schizophrenia.[9]

However, there are studies which show that sodium valproate is not effective in the management of patients with schizophrenia.[10-12]

Despite studies showing beneficial effects, the controversies regarding the role of sodium valproate as an adjunctive drug in the treatment of schizophrenia still persist. The present study aimed at assessing the effect of adjunctive sodium valproate in patients of acute schizophrenia, using more comprehensive tools and more sample size.

MATERIAL AND METHODS

This is a prospective, hospital based interventional study conducted at a tertiary care teaching hospital. Approval from institutional ethical committee was taken. The period of study was from Jan 2018 to Dec 2018. All the patients were enrolled in the study only after explaining the study to a significant family member and subsequently obtaining written informed consent from him/her.

All participants underwent detailed evaluation by qualified psychiatrists. Inclusion criteria included age between 18-45 years and a diagnosis of schizophrenia as per ICD-10 DCR.[13] Participants were excluded if they had co-morbid Psychiatric disorders, substance use disorder (except nicotine), personality disorder and mental retardation. Pregnant and breast feeding mothers were also excluded.

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A total 60 patients having acute schizophrenia were taken as per inclusion and exclusion criteria. They were divided in 2 groups, A and B of 30 each by random sampling (draw of lots). Patients in group A received atypical antipsychotic with placebo and in group B atypical antipsychotic with adjunctive sodium valproate. Olanzapine was taken as atypical antipsychotic in both groups.

Semi structured socio-demographic data sheet was used and groups were matched as nearly as possible for age, sex, religion, education, occupation, marital status, family income, family type, residence, previous consultation, family history of psychiatric illness and duration of illness.

The following scales were applied at baseline (first visit) and after six weeks.

(a) Positive and Negative Syndrome Scale for Schizophrenia (PANSS)[14] – It is a 30-item, 7-point rating instrument that has adapted 18 items from the Brief Psychiatric Rating Scale (BPRS) and 12 items from the Psychopathology Rating Schedule (PRS). Of the 30 psychiatric parameters assessed on the PANSS, seven were chosen a priori to constitute a Positive Scale (PANSS-P), seven a Negative Scale (PANSS-N), and the remaining 16 a General Psychopathology Scale (PANSS-G). Items were scored on a likert type scale with 1 to 7 score. 1 represents absence of psychopathology and 7 represents extreme of psychopathology. PANSS is having good reliability and validity and has been used in many previous studies of schizophrenia assessing psychopathology and improvement in psychopathology.

(b) Clinical global impression scale (CGI)[15] - The CGI was developed for use in NIMH-sponsored clinical trials to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication. The CGI measures: (a) severity of psychopathology (CGI-S) from 1 to 7 and (b) change from the initiation of treatment on a similar seven-point scale. Subsequent to a clinical evaluation, the CGI form can be completed in less than a minute by a rater. CGI can track clinical progress across time and has been shown to correlate with longer, more tedious and time consuming rating instruments across a wide range of psychiatric diagnoses. Only the CGI-S scores were assessed in our study.

If any patient developed significant side effects, he/she was terminated from the study. Any patient not coming for follow up was considered as drop out and new patients were enrolled again.

STATISTICAL ANALYSIS

The statistical analysis was done with the help of statistical package for social sciences – 20 (SPSS-20). In both the groups, the socio demographic and clinical (both continuous and categorical data) were summarized with the help of frequency, percentages and mean and standard deviation as per the applicability.

Descriptive statistics were used to define the sample characteristics. Comparison of socio-demographic variables across the study groups was done using Chi square test. Student t-Test was applied for the comparison of continuous variables. Significance level was taken as $P<0.05$.

RESULTS

The study sample consisted of 60 patients. The mean age of patients was 25.77 $\pm$ 6.68 years in group A (Olanzapine with placebo) and 26.77$\pm$ 7.15 years in group B (Olanzapine with sodium valproate). There was no significant difference between the two groups with regard to sociodemorgaphic profile. (Table 1a and 1 b).

Variables		Olanzapine + placebo N=30		Olanzapine + sodium valproate N=30		value $\chi 2$	df	P* Value
		N	%	n	%			
Sex	Male	21	70	19	63	0.3	1	0.584
	Female	9	30	11	37			
Religion	Hindu	25	83	25	83	0.13	1	0.71
	Others	5	17	5	17			
Education	Primary	20	67	24	80	1.36	1	0.243
	Secondary	10	33	6	20			
Occupation	Employed	7	23	10	33	0.739	1	0.39
	Unemployed	23	77	20	67			
Maritial status	Single	18	60	13	43	1.669	1	0.196
	Married	12	40	17	47			
Family income (per month)	<10000	12	40	14	46	0.519	1	0.602
	>10000	18	60	16	53			
Family	Nuclear	11	37	16	53	1.684	1	0.194
	Joint	19	63	14	46			
Previous consultation	Nil	10	33	9	30	0.077	1	0.781
	≥ One	20	67	21	70			
Family history of psychiatric illness	Absent	25	83	26	87	0.131	1	0.718
	Schizophrenia	5	17	4	13			
P<0.05* (level of significance)								

Table-1(a): Comparison of sociodemographic characteristics between two groups (categorical variables)

Variables	Olanzapine with placebo mean ± sd N=30	Olanzapine with sodium valproate mean ± sd N=30	t	df	P* (Value)
Age (years)	25.77 ± 6.68	26.77 ± 7.15	-0.56	58	0.578
Duration of untreated illness(months)	1.80 ± 1.186	1.86 ± 0.899	-0.245	58	0.807
P<0.05* (level of significance)					

Table-1(b): Comparison of sociodemographic characteristics between two groups (continious variables)

	Olanzapine with placebo mean ± SD N=30	Olanzapine with sodium valproate MEAN ± SD N=30	t	df	P*
PANSS –P	38.53 ± 4.56	36.76 ± 5.23	-1.392	58	0.169
PANSS-N	22.53 ± 7.70	26.10 ± 8.77	-1.673	58	0.1
PANSS-G	38.10 ± 7.55	39.43 ± 11.17	-0.542	58	0.59
PANSS –T	99.16 ± 19.81	102.29 ± 25.17	-0.685	58	0.494
P<0.05* (level of significance)					

Table-2: Comparison of scores of PANSS at baseline (0 week) between olanzapine with placebo and olanzapine with sodium valproate groups.

	Olanzapine with placebo Mean ± SD N=30	olanzapine with sodium valproate Mean ± SD N=30	t	df	P*
PANSS –P	14.56 ± 6.21	11.30 ± 3.38	2.529	58	0.014*
PANSS-N	15.13 ± 6.26	15.50 ± 6.26	-0.227	58	0.821
PANSS-G	28.70 ± 7.97	24.60 ± 6.77	2.145	58	0.036*
PANSS –T	58.39 ± 20.44	51.40 ±16.41	2.432	58	0.018*
P<0.05* (level of significance)					

Table-3: Comparison of scores of PANSS at 6 weeks between olanzapine with placebo and olanzapine with sodium valproate groups.

	Olanzapine with placebo Mean ± SD N=30	Olanzapine with sodium valproate Mean ± SD N=30	t	df	P*
CGI-S(0 week)	5.43 ± 0.50	5.50 ± 0.57	-0.479	58	0.634
CGI-S(6 weeks)	3.96 ± 0.55	3.56 ± 0.62	2.616	58	0.011*
P<0.05*(level of significance)					

Table-4: Comparison of scores of CGI-S at baseline (0 week) and after six weeks between olanzapine with placebo and olanzapine with sodium valproate groups.

At baseline (0 week), the PANSS scores of group A were as follows - PANSS total score (PANSS-T) (99.16 ± 19.81), positive syndrome score (38.53 ± 4.56), negative syndrome score (22.53 ± 7.70) and general psychopathology scores (38.10 ± 7.55) and the scores in group B were as follows - PANSS total score (102.29 ± 25.17), positive syndrome score (36.76 ± 5.23), negative syndrome score (26.10 ± 8.77) and general psychopathology scores (39.43 ± 11.17). (Table 2). There was no statistically significant difference between the two groups at baseline.

PANSS was again applied at 6 weeks and showed the following scores for group A - PANSS total score (58.39 ± 20.44), positive syndrome score (14.56 ± 6.21), negative syndrome score (15.13 ± 6.26) and general psychopathology scores (28.70 ± 7.97) and the score for group B after 6 weeks were - PANSS total score (51.40 ± 16.41), positive syndrome score (11.30 ± 3.38), negative syndrome score (15.50 ± 6.26) and general psychopathology scores (24.60 ± 6.77). (Table 3). PANSS-P, PANSS-G and PANSS-T scores were statistically significantly less in group B patients as compared to group A.

The CGI –S score at baseline (0 weeks) in group A was 5.43 ± 0.50 and in group B was 5.50 ± 0.57. There was no statistically significant difference in CGI-S scores in both the groups. CGI-S score after 6 weeks in group A was 3.96 ± 0.55 and in group B was 3.56 ± 0.62. (Table 4). CGI-S scores are statistically significantly less in group B patients as compared to group A.

DISCUSSION

Treatment of schizophrenia is complex and still needs better understanding of the pathophysiology of the disorder, which may provide further insight into the mechanism of action of antipsychotics and other psychotropics for the better management and relapse of symptoms.

Present study was a modest attempt for comparing the combined effectiveness of one of the most commonly used atypical antipsychotic, olanzapine and sodium valproate.

In our study, comparison of PANSS score between two groups ie A and B, showed that in group B (olanzapine with sodium valproate) there was a statistically significant improvement in positive symptoms ($p<0.014$), general psychopathology ($p<0.036$) and total score ($p<0.018$) compared to group A (olanzapine and placebo). These findings were consistent

with those of Horowitz E et al.[5] and Ananthavarathan[6] who showed that sodium valproate helps to reduce aggressiveness and hostility in schizophrenia. Tseng et al.[7] also found effectiveness of adjunctive sodium valproate in patients of schizophrenia.

Our findings were also in conformity with Omranifard et al.[8] who showed the positive effect of sodium valproate on the speed of recovery of positive symptoms.

The comparison between two groups also suggested that the CGI-S scores were statistically significantly decreased ($p<0.011$) in group B as compared to group A after 6 weeks.

Limitations of our study

1. The number of our subjects was low due to rigid inclusion criteria and time constraint.
2. The study sample consisted of mainly male subjects with female subjects being less in number.
3. We were also unable to find the optimum and effective dose of sodium valproate in improving the psychotic symptoms.
4. The increased chance of adverse effects and drug interactions in such a combination has not been investigated.
5. Only combination of one antipsychotic, that is olanzapine with sodium valproate was studied.
6. The period of study was only 6 weeks.

CONCLUSION

The study shows that adding sodium valproate to olanzapine had beneficial effects on symptoms of acute schizophrenia after 6 weeks.

Further studies with larger sample sizes. A longer period of study to find out whether the advantage of antipsychotic and sodium valproate combination versus antipsychotic monotherapy is sustained over time. Combination of different antipsychotics with valproate should also be studied to find out whether combination of valproate with any particular antipsychotic is more beneficial.

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