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Original Research Article

Comparative evaluation of levetiracetam and valproic acid as monotherapy on cognitive impairment in patients of epilepsy

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ABSTRACT

Background: Cognitive decline with AEDs (Anti-epileptic drugs) is associated with learning and memory deficits especially in the younger age group. The data regarding the impact of levetiracetam and valproic acid as monotherapy on cognition in epileptic patients is scarce. The present study was done for evaluation of cognitive decline associated with the use of AEDs.

Methods: Present study was a prospective study on 60 patients on AEDs for a period of 12 weeks. Patients were enrolled from the Department of Neurology, Swami Rama Himalayan University, Dehradun, Uttarakhand, India and divided into group A (levetiracetam) and group B (valproic acid) with 30 patients in each group. Permission from the institutional ethics committee and written informed consent was taken from all the patients. They were analyzed for cognitive impairment using MMSE and MoCA scales at baseline and 12 weeks.

Results: The mean duration of disease was 2.13±1.1 years and 2.08±1.1 years and mean age of the patients was 14.67±1.9 years in group A and 16.20±1.6 years in group B. GTCS was present in 31 patients (52%) followed by partial seizures in 29 patients (48%). The mean change in the MMSE scores from baseline to 12 weeks was significant in group A 1.30±1.1 (p value <0.05) and change group B was -0.20±1.4 not statistically significant. The mean change was observed in MoCA scores from baseline to 12 weeks was significant in both groups A and B by 1.17±1.1 and -0.70±1.1 respectively (P value <0.05).

Conclusions: Patients on levetiracetam showed cognitive improvement, whereas patients on valproic acid showed a decline in the MMSE and MoCA scores.

Keywords: Cognitive impairment, Epilepsy, MMSE, MoCA

INTRODUCTION

Epilepsy is one of the most common causes of neurological diseases. According to WHO 50 million people are suffering from epilepsy.[1] Patients of epilepsy usually undergo long-term treatment for years with antiepileptic drugs (AEDs).[2] Anti-epileptic drugs (AEDs) are known to impact the cognitive abilities in the patient of epilepsy. The major cognitive adverse effects associated with AEDs are impaired attention, vigilance, slowing of mental and psychomotor speed. Cognitive impairment as an entity itself puts a depressing impact on the self-confidence of the patient.[3] Long-term consequences of AED in term of cognitive impairment are obvious in the early ages of life.[4] Despite the large number of newer agents, most neuropsychological studies have compared newer drugs to older AEDs with high risk cognitive impairment or against newer drugs at dosages that do not reflect current prescribing pattern making, the comparative effect of newer agents unclear.[5] Comparative Data are lacking on

their effects on cognition, hence this study is planned for a better understanding of comparative evaluation of levetiracetam and valproic acid as mono-therapy on cognitive impairment in patients of epilepsy.

METHODS

Present study was observational and follows up study with two parallel groups conducted in newly diagnosed patients of epilepsy as per the ILAE classification.[6] A minimum of 60 patients were required with 30 patients in each group based on a previous study. The study was approved by the institutional ethical committee.

Participants

Eligible participants were male and females in the age group of 12-18 years newly diagnosed with epilepsy as per the ILAE classification. The patients were recruited from the outpatient unit of the Department of Neurology, Swami Rama Himalayan University, Dehradun, Uttarakhand, India, after obtaining a prior written informed consent. Follow up time for the patients were 12 weeks. Patients with any progressive CNS disease, serious cardiac abnormality, underlying malignancy, hypersensitivity to any of the study drugs, uncontrolled severe concurrent illness, abnormal liver and kidney functions, pregnant and lactating females, history of seizures due to drugs, alcohol, acute medical illness, psychiatric disorders and patients leaving the study due to any reasons will be excluded from final analysis. Demographic profile and detailed history were obtained from each recruited patient, this included family history, educational status, age of onset of epilepsy, duration of disease, personal habits. A general physical examination was performed, and blood pressure was recorded EEG and CT heads was done. Blood test (haematological and biochemistry were done before starting of the treatment. Study subjects included in the study were divided into two groups of 30 each. The drugs were given to subjects on the basis of physician's discretion.

The dose ranges of the two drugs at the start of the study were as follows for levetiracetam (LEV) 500-2000 mg/day and for valproic acid (VPA) 300-1000 mg/day. After recruitment patients were assessed for the cognitive impairment based on the MMSE and MoCA questionnaires. Patients were evaluated at 0, 6 and 12 weeks or earlier as the need arose. For efficacy and safety, they were assessed on each visit with the help of patient-maintained seizure diary and self-reporting of adverse drug reaction.

Study measurements

Patient reported outcomes were assessed by well validated measures. The MMSE and MoCA questionnaires were used to describe cognitive impairment in patients. The patients were asked to fill both the questionnaire scales. Scores for MMSE and MoCA scales range from a minimum of 0 to a maximum of 30. Lower the score worse is the cognitive outcome. A cut-off score of less than 24 on the MMSE scale and less than 26 on the MoCA scale was used as an indicator of cognitive impairment. These cut off scores were chosen based on a previous study assessing cognitive performance.[7]

Data regarding these outcomes were collected at baseline and 12 weeks to assess cognitive impairment with the use of anti-epileptic drugs (AEDs).

End points

Primary parameters

- Change in the MMSE score,
- Change in montreal cognitive assessment scale (MoCA).

Secondary parameters

- Freedom from seizure: this will refer to number of seizure episodes till the last follow up using seizure diary,
- Adverse drug reaction as per check list along with spontaneous (ADRs) will be recorded.

In assessment of safety, a checklist of adverse drug reactions was prepared according to the most common adverse events due to study drugs. Adverse drug reactions were recorded at every visit of the patient to the OPD. Seizure diary was used by the patient to self-record his/her experiences every week and to observe the improvement or deterioration in frequency of seizures, duration of episodes, duration of post-ictal confusion and any seizure related injury.

Data management

Data management and analysis was done using Microsoft Excel 2007 and IBM SPSS version 20.0. Demographic data was presented as either frequency or Mean±SD. Intra-group comparison was done using paired sample student t-test and inter-group analysis was done using unpaired student t-test. Adverse events were interpreted and analyzed using descriptive statistics and chi-square test.

RESULTS

Patient characteristics

From January 2017 to December 2017, 120 patients were screened from which sixty patients who fulfilled the eligibility criteria (42 male, 18 female) were enrolled in this study (Table 1). The patients were newly diagnosed epileptic patients on monotherapy on either valproic acid or levetiracetam based on physician's discretion. Patients were followed up for a period of 12 weeks after enrolment for cognitive impairment due to AEDs.

Table 1: Demographic profile and baseline characteristics of patients of epilepsy in both the groups.

Demographic profile		Group A (LEV)(n=30)	Group B (VPA) (n=30)
Total no. of patients		30	30
Age in years (mean±SD)		14.67±1.882	16.20±1.648
Sex (male/female)		18/12	24/6
Smoker/non-smoker		4/26	7/23
Alcoholic/non-alcoholic		8/22	5/25
Residence (urban/rural)		13/17	20/10
Religion (Hindu/Muslim/Christian/ Sikh)		25/4/1/0	26/3/0/1
Education (above 10/less than 10)		6/24	12/18
Parameters	Type of seizures — GTCS	6	25
	Type of seizures — Partial	24	5
	Family history — Present	5	7
	Family history — Absent	25	23
Duration of disease (years)		2.13±1.080	2.08±1.089
Frequency of seizures		1.93±0.907	2.63±1.326

Table 2: Comparison of the change from baseline to 12 weeks in the mean MMSE score in group A (LEV) and group B (VPA).

MMSE parameters	Group A (LEV) (n=30)			Group B (VPA) (n=30)		
	Baseline	12 weeks	Mean change	Baseline	12 weeks	Mean change
Orientation	9.37±0.72	9.87±0.35*	0.50±0.57*	9.40±0.77	9.43±0.82	0.03±0.67#
Registration	2.93±0.25	2.93±0.25	±0.00	2.87±0.35	2.90±0.35	0.03±0.32
Attention and calculation	4.10±0.71	4.47±0.68*	0.37±0.56*	4.23±0.68	4.17±0.79	-0.07±0.64 #
Recall	2.40±0.68	2.47±0.63	0.07±0.52	2.63±0.49	2.57±0.57	-0.07±0.58
Language	7.07±0.74	7.57±0.57*	0.50±0.73*	7.17±0.65	7.03±0.76	-0.17±0.53#
Total MMSE	25.80±1.5	27.10±1.3*#	1.30±1.02*	26.33±1.71	26.10±1.8	-0.20±1.40 #

Values expressed as mean (±SD), *Student t-test p <0.05 was considered statistically significant intra-group, #Student t- test p <0.05 was considered statistically significant inter-group.

Table 3: Comparison of change in mean MOCA scores in group A (LEV) and group B (VPA) from baseline to 12 weeks.

MOCA parameters	Group A (LEV) (n=30)			Group B (VPA) (n=30)		
	Baseline	12 weeks	Mean change	Baseline	12 weeks	Mean change
Visuo-spatial	4.50±0.572	4.47±0.776	-0.03±0.809	4.57±0.626	4.37±0.718	-0.13±0.629
Naming	2.87±0.346	2.97±0.183	0.10±0.403	2.90±0.305	2.90±0.305	-0.07±0.365
Attention	5.00±0.910	5.60±0.675*	0.60±0.894*	5.43±0.935	5.33±0.758	-0.07±1.015
Language	2.10±0.305	2.13±0.346	0.03±0.414	2.30±0.466	2.37±0.490	0.10±0.548
Abstraction	0.93±0.365	1.20±0.407*	0.27±0.450*	1.27±0.450	1.10±0.305	-0.20±0.484
Delayed recall	3.37±0.765	3.43±0.504	0.07±0.907	3.57±0.728	3.23±0.430*	-0.27±0.691
Orientation	5.87±0.346	5.93±0.254	0.07±0.365	5.83±0.379	5.83±0.461	-0.03±0.183
Total MOCA	24.93±1.112	26.10±1.296*	1.17±1.147*	26.23±1.591	25.53±1.655*	-0.70±1.119

Values expressed as mean (±SD), Student t-test *p <0.05 significant.

No statistically significant differences in between the groups were observed based on the basis of their baseline characteristics. The two groups differed only on the base of their personal history (alcoholism and smoking) (Table 1).

Significant improvements in MMSE sub scores were seen in all the parameters in the LEV group from baseline to 12 weeks except registration and recall parameter.

In the VPA group, improvement in the orientation and registration parameters was seen which were not statistically significant, the total score deteriorated from 26.33±1.709 at baseline to 26.10±1.77 at the end of 12 weeks but the change was not statistically significant (Table 2). Intra group comparison in groups A and B for total MOCA scores showed difference that was statistically significant from baseline to the end of the study at 12

weeks. Significant Improvements in the scores were seen in attention and abstraction parameters in the LEV group (p <0.05). In the VPA group, all the parameters showed deterioration in the scores except the language parameter which showed improvement, but the change was not significant and only significant difference in the scores was seen in the delayed recall parameter (p <0.05). Total score significant improvement was seen from 24.93±1.112 to 26.10±1.296 in the LEV group (p <0.05), in the VPA group the total score deteriorated from 26.23±1.591 to 25.53±1.655 which was also statistically significant (p<0.05) (Table 3).

On comparing MMSE score changes in both the groups in patients with partial seizures, there was improvement in the MMSE scores in patients of group A (LEV) when compared to MMSE scores in patients of group B (VPA) in all the parameters except recall which showed improvement, but which was not statistically significant (Table 3).

Table 4: Comparison of mean change in MMSE and MOCA scores between group A (LEV) and group B (VPA) based on the seizure type from baseline to 12 weeks.

Parameters	Partial		GTCS	
MMSE parameters	**Group A (LEV)**	**Group B (VPA)**	**Group A (LEV)**	**Group B (VPA)**
Orientation	0.54±0.58	0.00±0.00	0.33±0.516	0.04±0.735
Registration	0.00±0.00	0.00±0.707	0.00±0.00	0.04±0.200
Attention and calculation	0.38±0.576	0.20±0.447	0.33±0.516	-0.12±0.66
Recall	0.17±0.381	0.40±0.548	-0.33±0.816*	-0.16±0.554
Language	0.38±0.647	0.00±0.00	1.00±0.894	-0.20±0.557
Total MMSE	1.42±1.060	0.40±1.817	0.83±0.753	-0.32±1.314
MOCA parameters	**Group A (LEV)**	**Group B (VPA)**	**Group A (LEV)**	**Group B (VPA)**
Visuo-spatial	-0.08±0.830	0.00±0.00	0.17±0.753	-0.16±0.688
Naming	0.08±0.408	-0.20±0.447	0.17±0.408	-0.04±0.351
Attention	0.63±0.928	0.00±0.00	0.50±0.837	-0.08±1.115
Language	-0.04±0.359	0.20±0.447	0.33±0.516	0.08±0.572
Abstraction	0.29±0.464	-0.20±0.447	0.17±0.408	-0.20±0.500
Delayed recall	0.21±0.884	-0.40±1.140	-0.50±0.837	-0.24±0.592
Orientation	0.08±0.282	0.00±0.00	0.00±0.632	-0.04±0.200
Total	1.13±1.11	-0.20±1.304	1.33±1.366	-0.80±1.080

Values expressed as mean (±SD), Student t-test *p <0.05 significant.

Table 5: Adverse events during the study period in Group A (LEV) and Group B (VPA).

Adverse Effects	Group A (LEV) (n=30)	Percentage (%)	Group B (VPA) (n=30)	Percentage (%)
Anorexia	-	-	1	3
Decreased sleep	-	-	1	3
Hair fall	-	-	3	10
Headache	2	7	7	23
Increased sleep	-	-	5	17
Irritability	4	13	2	7
Tiredness	1	3	1	3
Weight gain	-	-	2	7
Total	7	23	22 *	73

Adverse events presented as frequency, *p <0.05 statistically significant (chi-square).

On comparing MMSE score changes in both the groups in patients with GTCS, there was deterioration in the MMSE scores in patients of group B (VPA) when compared to MMSE scores in patients of group A (LEV) except in the registration parameter which showed improvement, but which was not statistically significant. On comparing MOCA score, changes in both the groups in patients of partial seizures, there was deterioration in the scores in patients of group B (VPA) when compared to MOCA scores in patients of group A (LEV) except visuospatial and language parameters which showed improvements in scores, but which were not statistically significant (p<0.05). On comparing MOCA score, changes in both the groups in patients with GTCS, there was deterioration in

all the scores from baseline to 12 weeks in patients of group B (VPA) when compared to MOCA scores in patients of group A (LEV) (Table 4). Adverse events in group A (LEV) and group B (VPA) were well recorded. Adverse events recorded were 7 and 22 in group A and B respectively. This was found to be statistically significant (p= 0.00, chi square= 15.017).

In the group A (LEV), adverse effects were noted in 23% of the patients. Most common adverse effects in the group A (LEV) was irritability (13%) followed by headache (7%) and tiredness (3%).

In the group B (VPA), adverse effects were noted in 73% of the patients. Most common adverse effects in the group B (VPA) was headache (23%) followed by somnolence (17%), hair fall (10%), irritability (7%), anorexia (3%), decreased sleep (3%) and tiredness (3%) (Table 5).

Seizure freedom was seen at 6 and 12 weeks in both the groups. It was seen that patients achieved a better seizure control in the levetiracetam group than valproic acid group at 6 weeks (Figure 1).
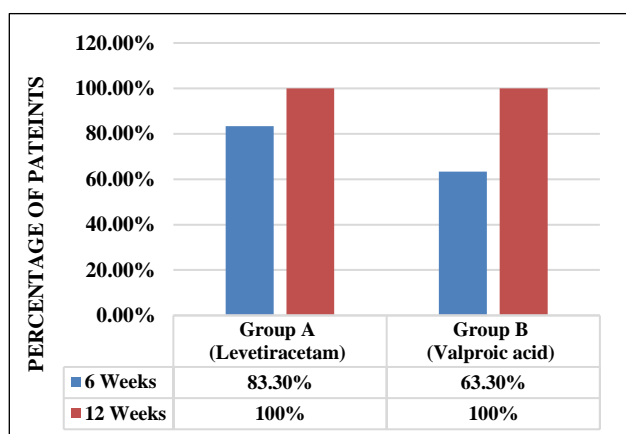

	Group A (Levetiracetam)	Group B (Valproic acid)
6 Weeks	83.30%	63.30%
12 Weeks	100%	100%

Figure 1: Seizure freedom at 6 and 12 weeks in group A (LEV) and group B (VPA).

DISCUSSION

The purpose of treatment of patients with epilepsy is freedom from seizures, normalizing his/her daily activities which are otherwise hindered and reducing the anticipation anxiety due to seizures due to epilepsy. Cognitive impairment due to disease as well as the AEDs used in the treatment add to the already existing problems in patients of epilepsy, reducing the patient's self-confidence and may impair the day to day activities.

General baseline demographic characteristics included in this study were age, gender and place of residence. Mean age of the study population in the present study was 14.67±1.882 in the levetiracetam group and 16.20±1.648 in the valproic acid group (Table 1) which was similar to the mean age (15.4 years) observed in a study on cognitive impairment by Sulheim D et al.[8] The adolescent and young

adult population forms a vulnerable group where the cognitive impairment due to AEDs can lead to adverse consequences. The patients in the age group 12-18 years were selected in this study as a very limited data is available for the cognitive impairment aspect of the AEDs in this age group.

In the present study, the male to female ratio was 70:30 which was higher compared to another study by Piña-Garza JE et al, where the male to female ratio was 53:47 with higher number of male patients (Table 1).[9]

Baseline total MMSE (mean) scores from baseline to 12 weeks changed by 1.30±1.022 in the group A (LEV), which were in accordance to a study by Lippa CF et al, at 3 months, the participants who remained on levetiracetam showed excellent cognitive tolerability.[10]

Whereas in group B (VPA), the total MMSE scores deteriorated from the baseline with a mean change of -0.20±1.40. The change in both the groups was not statistically significant. Similar results were observed by Fleisher AS et al, in the study (Table 2) and also concluded that valproic acid treatment was associated with accelerated brain volume loss over 1 year using MRI and perhaps with greater cognitive impairment.[11]

Baseline mean total MOCA scores from baseline to 12 weeks changed by 1.17±1.147 in the group A (LEV) whereas in group B (VPA), the total MoCA scores deteriorated from the baseline with a mean change of -0.70±1.119 (Table 3). The change in both the scores from baseline were statistically significant (p <0.05). These results were not in accordance with a study by Gordon K et al, where valproic acid had a cognitive enhancing effect, probably by reducing epileptiform discharges.[12] The decrease in the MoCA with the use of valproic acid was similar to a study conducted on the IQ of patients of epilepsy on valproic acid by Khusainova I et al.[13]

Mean baseline total MMSE score in patients with GTCS in group A (LEV) (Table 4) improved significantly by 0.83±0.753 from baseline after 12 weeks (p <0.05). Results were similar to the study by Lippa CF et al, where an improvement in cognition was seen with the use of levetiracetam for 3 months by approximately 2.2 points on MMSE scale in patients with seizures.[12] Whereas in group B (VPA), the scores deteriorated by -0.32±1.314 (Table 4) similar to the study conducted by Li GH et al, on cognitive impairment.[14]

In patients with partial seizures, mean baseline total MMSE score in group A (LEV) improved significantly by 1.42±1.060 from baseline to 12 weeks (p <0.05). Similar results were seen in another study.[15] Whereas in of patients in group B (VPA) changed by 0.40±1.817 similar results were observed in a study by Li GH et al, where an increase in cognition scores were noticed in patients taking valproic acid (Table 4).[14] Irrespective of the type of epilepsy levetiracetam showed favourable effects of over valproic

acid on cognitive profile. Mean total MOCA score in patients with GTCS in group A (LEV) improved by from baseline 1.33±1.366 to the end of 12 weeks significantly (p <0.05). Similar findings were reported by Wu HL in epileptic patients.[16] Whereas, in group B (VPA), the total scores deteriorated significantly by -0.80±1.080 similar to the findings in a study by Jiang Y et al, where there was a decrease in the MOCA scores in epileptic patients with the use of valproic acid (Table 4).[15]

In patients of partial seizures, the mean total MOCA scores in patients in group A (LEV) showed significant improvement by 1.13±1.11 from the beginning of the study to the end of 12 weeks (p <0.05) (Table 4). Findings were similar to another study in the same regard.[16] In group B (VPA), there was deterioration in the mean total MoCA scores by -0.20±1.304 (Table 4). Similar results were also shown by Zhao J et al.[17]

Various studies have pointed towards the widespread positive effects on cognitive profile in patients of epilepsy with the use of levetiracetam, which may be advantageous specifically in cases associated with the use of pre-existing cognitive deficits.

In this study, cognitive impairment was reported with the use of valproic in many of the MMSE and MoCA parameters that were analyzed. Whereas, improvements in cognition was seen with the levetiracetam on the same parameters.

Seizure frequency at baseline is an important parameter for evaluating the response to treatment in terms of seizure reduction. Seizure frequency at baseline (per month) in group A (LEV) was 1.93 and in group B (VPA) was 2.63 (Table 1). Similar seizure frequencies were seen in a study conducted in Brazil by Li LM et al.[18]

Freedom from seizures (Figure 1) is an important factor for measurement of the efficacy of treatment in epilepsy patients, which was measured by means of a self-reported seizure diary. Mean seizure frequency per month at the beginning of the treatment was 2.63±1.326 in VPA group and 1.93±0.907 in LEV group (Table 1) similar to the baseline seizure frequency of 1.7±3.4 and 2.5±2.8 in the VPA and LEV respectively reported by Guilfoyle SM et al.[19]

The patients reporting total seizure freedom at 6 weeks were 83.3% and 63.3% in the levetiracetam and valproic acid groups respectively, whereas by 12th week both the groups had achieved complete seizure freedom (Figure 1), which is in accordance with another study by Lowenstein DH et al, where seizure freedom did not vary between newer and older anti-epileptic drugs.[20]

Although, there was a reduction in the seizure frequency in both the groups at 12 weeks from baseline but there was also a significant improvement in cognitive scores with the use of levetiracetam as compared to valproic acid.

Irritability (13%) and somnolence (7%) in 4 and 2 patients respectively were the most commonly reported adverse drug reactions in the LEV group followed by tiredness in 1 patient (Table 5). These observed adverse effects were similar to the adverse events observed in another study by Folstein ME et al.[7]

Whereas, in the VPA group headache (23%), increased sleep (17%), hair fall (10%) irritability (7%) and weight gain (7%) were the most commonly reported adverse effects (Table 5).

As treatment with valproic acid has been associated with a tendency to cause a cognitive decline, regular monitoring for any signs of cognitive impairment is warranted especially in the adolescent and young adult age group where even a slight decline can prove to be harmful.

The data analysing the impact of AEDs on various sub-domains of the MMSE and MoCA tests remains limited, due to which the impact of drugs on specific parameters remain ambiguous, therefore the subgroup analysis of various sub-domains of the MoCA and MMSE tests have been done for both the study drugs in this study.

CONCLUSION

This observational analytical study was done to compare the effect of levetiracetam and valproic acid as monotherapy on cognition in newly diagnosed patients of epilepsy on MMSE and MoCA cognitive assessment tests for a period of 12 weeks.

LEV had a better cognitive profile compared to VPA in all the parameters of MOCA and MMSE. Patients on LEV showed significant improvement compared to VPA in terms of cognitive function. Safety profile of LEV was also better compared to VPA. Irritability and headache were the most common adverse effects in the LEV VPA groups respectively.

LEV, a member of newer anti-epileptic drugs was found to be comparable in efficacy to VPA but with a lesser frequency of adverse effects and had a positive influence on cognition when used as a monotherapy in both the generalized tonic-clonic seizures and partial seizures and maybe considered as an alternative drug to other older AEDs in the treatment of epilepsy.

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