e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(7); 978-984

Original Research Article

Comparative Study of Levetiracetam and Valproic Acid as Monotherapy on Cognitive Impairment in Epileptic Patients of Kerala

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Received: 01-04-2026 / Revised: 15-05-2026 / Accepted: 21-06-2026
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Conflict of interest: Nil

Abstract

Background: Antiseizure medications affect cognition by reducing neuron excitability or enhancing inhibitory neurotransmission. The cognitive side effects caused by antiepileptic medications are a major concern for patients with epilepsy taking medications. Hence, a drug that affects few or no cognitive disorders is an ideal drug for antiepilepsy.

Method: 86 epileptic patients aged between 12 and 18 years were studied. Of the 86 patients, 43 were treated with levetiracetam and 43 with valproic acid for 12 weeks; the pros and cons of both drugs were recorded.

Results: In the comparative study in both groups, group A (levtr) and group B, orientation, attention and calculation, language, and MMSE total score had a significant p-value in group A (levtr). In comparison of both groups of MOCA scores, attention, abstraction, and total MOCA score had significant p values ($p<0.001$) in group A, and delayed recall had a significant p value ($p<0.001$) in group B.

Conclusion: Patients treated with levetiracetam showed significant cognitive improvement, whereas patients treated with valproic acid showed a poor response in MMSE and MOCA scores.

Keywords: MMSE, MOCA, levetiracetam, valproic acid, cognitive impairment.

DOI: 10.25258/ijcpr.18.7.149

Introduction

Epilepsy is the most common neurological disease. According to the WHO (World Health Organization), about 50 million people are suffering from epilepsy globally [1]. Anticonvulsant medications are the backbone of epilepsy management for patients of all ages.

The target of treating epileptic patients is to control seizures completely without causing unwanted side effects.

Antiseizure medications are known to affect cognitive abilities in epileptic patients. Slowing of mental function and decreased concentration, awareness, and psychomotor speed are the main adverse cognitive events related to antiseizure medications [2].

Antiseizure medications affect cognition by reducing neuron excitability or enhancing inhibitory neurotransmission. The presence of cognitive side effects caused by antiepileptic medications is a major concern for patients with epilepsy taking medication.

Levetiracetam is one of the most prescribed anti-seizure medications and is widely used in many forms of treatment for epilepsy. It is used in the treatment of focal-onset, myoclonic, and generalised tonic-clonic seizures as monotherapy and add-on therapy [3]. Sodium valproate acid (VPA) is also a broad-spectrum antiepileptic medication used not only for epilepsy but also for other neuropsychiatric disorders, such as bipolar disorder and migraine [4]. Hence, an attempt is made to compare the efficacy and tolerability of both antiepileptic medications used as monotherapy.

Materials and Method

86 (eighty-six) patients aged 12-18 years, newly diagnosed with epilepsy as per the ILAE (International League Against Epilepsy) classification, who regularly visited the Department of Neurology, Dr. Moopen's Medical College, Wayanad, Kerala-673577, were studied.

Inclusion Criteria: Newly diagnosed epileptic patients aged between 12-18 years. Those who gave written consent for a 12-week follow-up were selected for the study.

Exclusion Criteria: Severe cardiac disease, underlying malignancy, abnormal liver and kidney disease, pregnant and lactating mothers, history of seizures due to drugs, patients already on anti-epileptic treatment, and anti-psychiatric treatment were excluded.

Method: Out of 86 epileptic patients, group A (levetiracetam) 43 patients and group B (valproic acid) 43 patients were classified by a lottery system. The dosage of drugs – levetiracetam (levetr) 500-2000 mg/day and group B Valproic acid (VPA) 300-100mg/day, after assessment for cognitive impairment based on MMSE (Mini-Mental State Examination) and MOCA (Montreal Cognitive Assessment) questionnaires. Every patient was evaluated at 0.6 and 12 weeks or earlier as the need arose. For efficacy and safety, every patient was assessed at each visit with the help of patients maintaining seizure diaries and self-reporting of adverse reactions.

Study pattern: Patient-reported outcomes were assessed by well-validated measures. The MMSE and MOCA questionnaires were used to describe cognitive impairment in patients. Patients were asked to report both MMSE and MOCA scores and recorded accordingly. The scores range from a minimum of 0 to a maximum of 30; the lower the score, the worse the cognitive outcomes. A cut-off score of less than 24 on the MMSE scale and less than 26 on the MOCA scale was used as an indication of cognitive impairment. These cut-off scores were chosen based on a previous study assessing cognitive performance [5]. 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 MMSE scores

Change in MOCA

- Secondary parameters

Freedom from seizure:

This will refer to the number of seizure episodes till the last follow-up seizure daily

- Adverse drug reactions as per checklist along spontaneous (ADRS) will be recorded. Patients were followed up every week and observed for improvement or deterioration in frequency of seizures, duration of episode, duration of post-ictal confusion and any seizure-related injury.

The duration of the study was from March 2026 to June 2026.

Statistical Analysis: Comparison of MMSE score and MOCA scores in both groups was carried out by t-test, and significant values were recorded. The statistical analysis was carried out using SPSS software. The ratio of males and females was 2:1.

Observation and Results

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

- Smokers / Non-smokers: 6/37 in group A (Levtr), 10/33 in group B (VPA)
- Alcoholic / Non-Alcoholic: 11/32 in group A (Levtr), 7/36 in group B (VPA)
- Resident Urban/Rural: 19/24 in group A (Levtr), 29/14 in group B (VPA)

B) Parameters

- Types of seizures: GTCS – 9 in group A, 36 in group B.
- Partial: 34 in group A, 7 in group B.
- Family history: 7 present in group A, and 10 in group B
- Absent: 36 in group A, 33 in group B.
- Duration of disease: 2.15 (±1.2) in group A, 2.09 (±1.1) in group B
- Frequency of seizures: 1.94 (±0.8) in group A, 2.64 (±1.2) in group B.

Table 2: Comparison of change from baseline to 12 weeks in the mean MMSE score in both groups

- Orientation: 12 weeks and mean change in group A (levtr) has a significant p value ($p<0.001$).
- Attention and calculation: in group A 12 weeks and mean change has significant (in group A) p value ($p<0.001$).
- Language: 12 weeks and mean change has a significant p value ($p<0.001$ in group A (levetr)
- Total MMSE score: 12 weeks mean change in group A (levetr) has a significant p-value ($p<0.001$).

Table 3: Comparison of change in mean MOCA scores in group A (levetr) and group B (VPA) from baseline to 12-week study

- In attention: 12 weeks and mean change has a significant p-value ($p<0.001$) in group A (levetr).
- In abstraction: 12 weeks and mean change has a significant p value ($p<0.001$) in group A (levetr).
- In delayed recall: 12 weeks has a significant p value ($p<0.001$) in group B (VPA).
- Total MOCA score: 12 weeks scores and mean change of group A (levetr) and 12 weeks of group B (VPA) have a significant p value ($p<0.001$).

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

Demographical profile	Group A (Levetr.)	Group B (VPA)
A) Smoker / Non-smoker	6/37	10/33
Alcoholic / Non-Alcoholic	11/32	7/36
Resident Urban/Rural	19/24	29/14
B) Parameters Types of seizures GTCS	9	36
Partial	34	7
Family History present	7	10
Absent	36	33
Duration of disease (years)	2.15 (± 1.2)	2.09 (± 1.1)
Frequency of seizure episodes	1.94 (± 0.8)	2.64 (± 1.2)

GTCS = Generalised Tonic Clonic Seizure

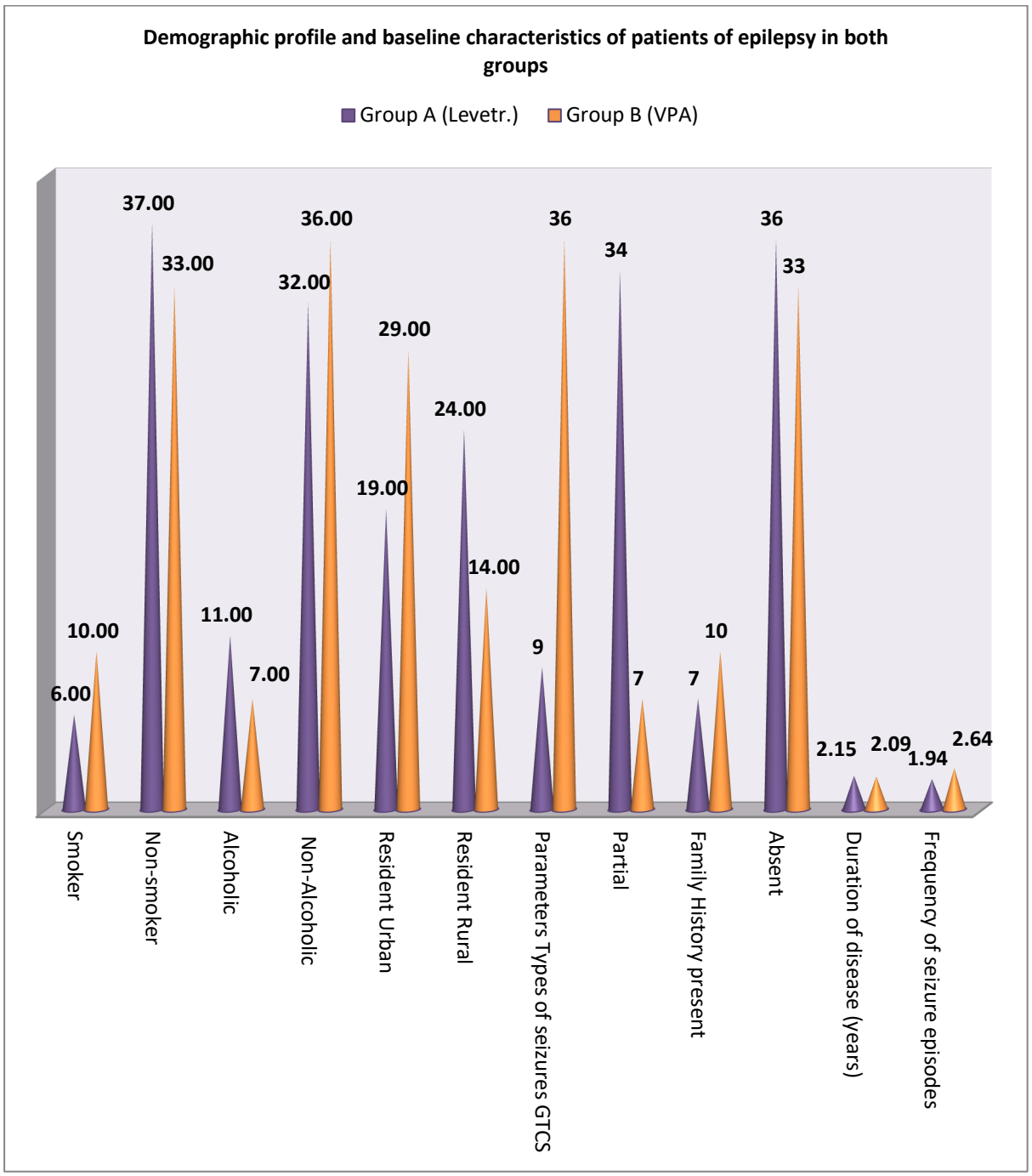

Figure 1: Demographic profile and baseline characteristics of patients of epilepsy in both groups

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

MMSE parameter	Group A (Levtr.)			Group B (VPA)		
	Baseline	12 weeks	Mean change	Baseline	12 weeks	Mean change
Orientation	9.39 (±0.70)	9.89 * (±0.36)	0.52 * (±0.55)	9.42 (±0.75)	9.42 (±0.80)	0.04 (±0.65)
Registration	2.95 (±0.23)	2.95 (±0.23)	0 (±0.0)	2.85 (±0.33)	2.89 (±0.32)	0.04 (±0.30)
Attention and calculation	4.12 (±0.68)	4.49 * (±0.66)	0.39 * (±0.55)	4.25 (±0.65)	4.19 (±0.77)	0.09 (±0.65)
Recall	2.42 (±0.66)	2.49 (±0.60)	0.09 (±0.52)	2.65 (±0.45)	0.59 (±0.55)	0.09 (±0.55)
Language	7.09 (±0.72)	7.59 * (±0.55)	0.52 * (±0.70)	7.19 (±0.63)	7.05 (±0.72)	0.19 (±0.50)
Total MMSE Score	25.82 (±1.3)	27.12 * (±1.2)	1.32 * (±1.03)	26.30 (±1.68)	26.12 (±1.68)	0.22 (±1.38)

*** = p<0.05 (p-value is significant). MMSE = Mini-Mental State Examination**

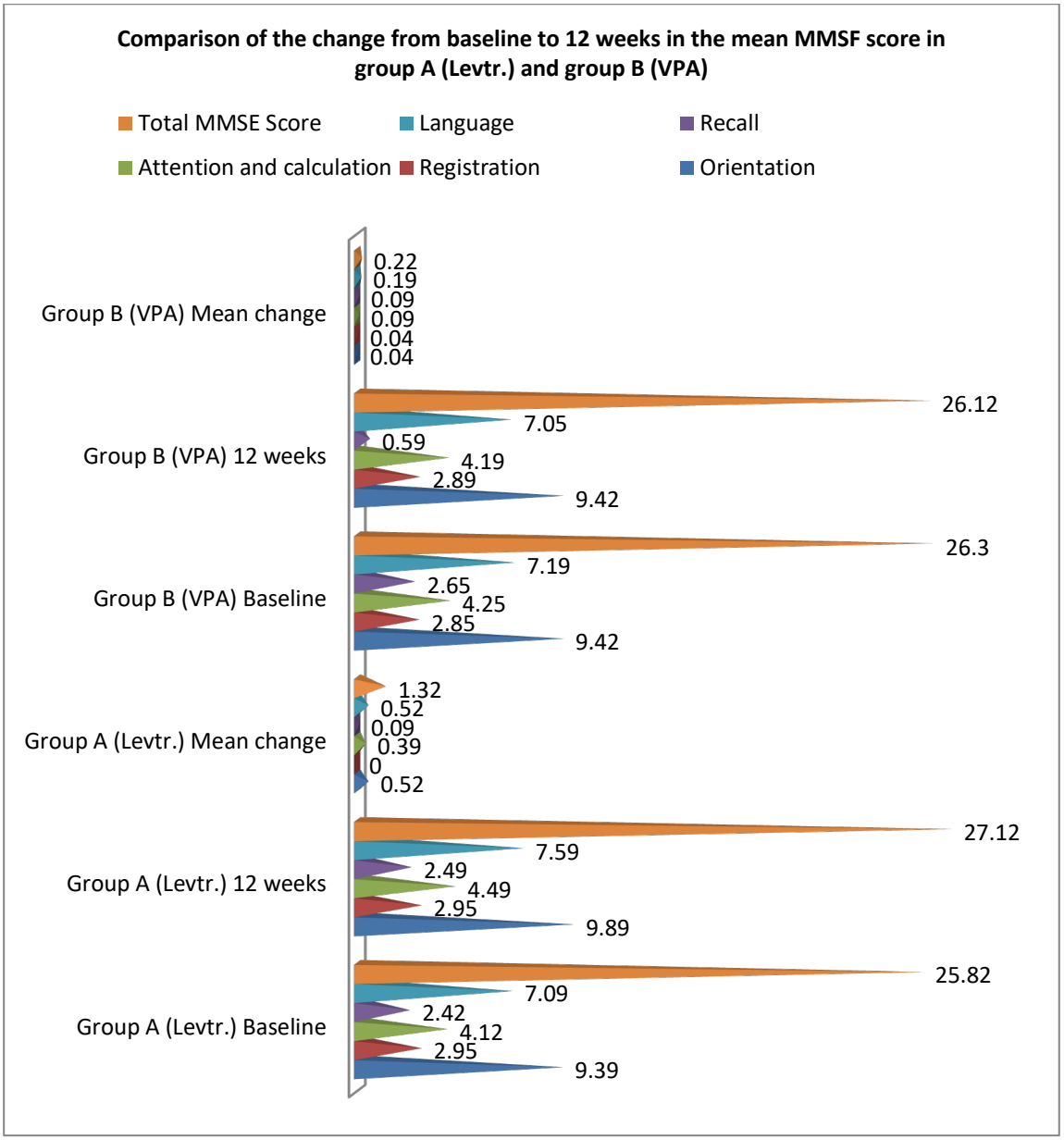

Figure 2: Comparison of the change from baseline to 12 weeks in the mean MMSF score in group A (Levtr.) and group B (VPA)

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

MOCA parameter	Group A (Levtr.)			Group B (VPA)		
	Baseline	12 weeks	Mean change	Baseline	12 weeks	Mean change
Visco-spatial	4.52 (±0.55)	4.49 (±0.75)	0.04 (±0.82)	4.59 (±0.60)	4.39 (±0.70)	0.14 (±0.60)
Naming	2.89 (±0.32)	2.95 (±0.16)	0.12 (±0.42)	2.92 (±0.32)	2.92 (±0.32)	0.09 (±0.38)
Attention	5.02 (±0.90)	5.62 * (±0.65)	0.62 * (±0.88)	5.42 (±0.92)	5.32 (±0.72)	0.09 (±1.02)
Language	2.12 (±0.28)	2.15 (±0.32)	0.05 (±0.40)	2.32 (±0.44)	2.35 (±0.47)	0.12 (±0.52)
Abstraction	0.94 (±0.34)	1.22 * (±0.42)	0.29 * (±0.44)	1.29 (±0.44)	1.12 (±0.28)	0.22 (±0.46)
Delayed recall	3.39 (±0.74)	3.45 (±0.48)	0.09 (±0.89)	3.59 (±0.70)	3.22 * (±0.42)	0.29 (±0.67)
Orientation	5.89 (±0.32)	5.95 (±0.23)	0.09 (±0.34)	5.82 (±0.35)	5.82 (±0.45)	0.04 (±0.16)
Total MOCA Score	24.92 (±1.10)	26.12 * (±1.27)	1.15 * (±0.12)	28.20 (±1.6)	26.52 (±1.4)	0.72 (±0.01)

MOCA = Montreal Cognitive Assessment. * = p<0.05; p values are significant

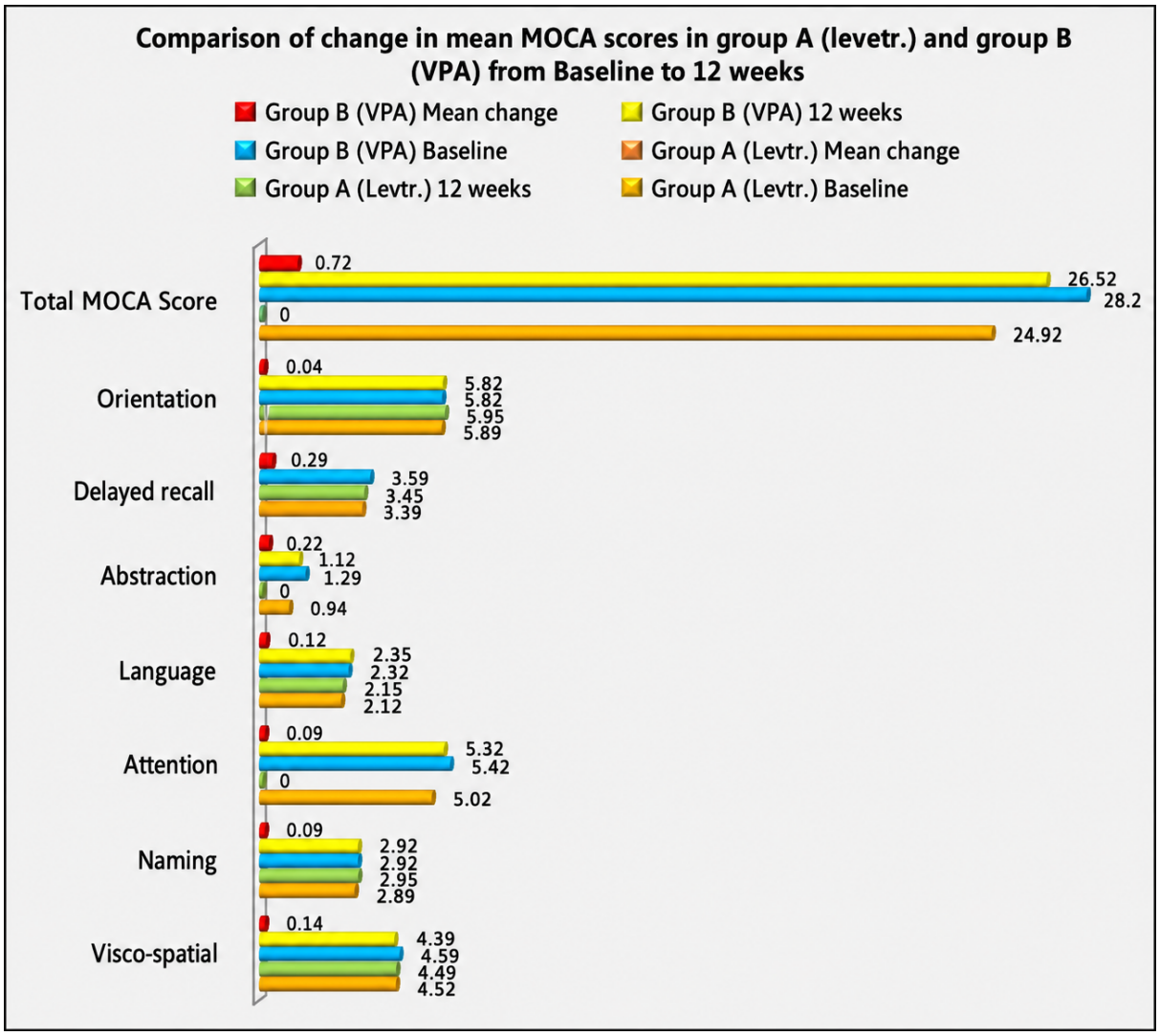

Figure 3: Comparison of change in mean MOCA scores in group A (levetr.) and group B (VPA) from Baseline to 12 weeks

Discussion

Present a comparative study of levetiracetam and valproic acid as monotherapy for cognitive impairment in patients of Kerala. The smokers are 6 in group A and 10 in group B; 11 alcoholics in group A, 7 alcoholics in group B; 9 have GTCS, and 34 have partial seizures in group A, and 36 have GTCS, and 7 have partial seizures in group B; 7 have a family history in group A, and 10 have a family history. Duration of disease was 2.15 (±1.2) in group A and 2.09 (±1.1) in group B. Frequency of seizure episodes was 1.94 (±0.8) in group A and 2.64 (±1.2) in group B (Table 1). In a comparative study, MMSE parameters had a significant p-value in group A (levtr) (Table 2). Similarly, the MOCA score was compared in both groups and was highly significant in group A (levtr) (Table 3). These findings are more or less in agreement with previous studies [6,7,8].

In the 1960s, there were increased efforts to develop sedatives that were supposed to act via the inhibitory effect of the GABAergic system. For this purpose, several pyrrolidone derivatives were synthesised with the rationale to design a cyclic analogue of γ-aminobutyric acid [9]. It binds to synaptic vesicle protein 2A (SV2A), controls vesicle fusion and exocytosis, and reduces current through T-type Ca++ channels.

Levetiracetam is rapidly and almost completely absorbed after oral administration. Peak plasma concentration is reached 1 hour after administration to fasting subjects. The half-life of oral levetiracetam is 7 ± 1 hour. Twice-daily dosing was established in an early pharmacodynamic and phase-III controlled study. Levetiracetam is less than 10% protein-bound. Steady-state plasma levels are achieved after 2 days of twice-daily dosing [10]. Valproic acid (VPA) is an endogenous fatty acid synthesised as an organic solvent. VPA may antagonise epileptic activity. Its pharmacological effects involve increased GABAergic transmission, reduced release and/or blockade of voltage-gated sodium channels, and modulation of dopaminergic and serotonergic transmission. This drug may regulate the expression of neuroprotective genes and protect against excitotoxicity. It is about 90% bound to plasma proteins, and the degree of binding decreases with drug concentration within the clinically occurring range [11].

Lev. has minimal protein binding, lacks hepatic metabolism, and has no significant drug interactions. The most common adverse effects in the lev. The group was drowsy, and in the VPA group were anorexia and drowsiness. The majority portion of lev. is eliminated renally; hence, it is not hepatotoxic, but elderly patients with renal impairment require a decreased dosage of levt. Levt. has no drug interactions with other AEDs, phenytoin, valproic acid, carbamazepine, phenobarbital, primidone, digoxin, or warfarin. Its metabolism rate and clearance may be increased by other AED levt. is effective in the treatment of generalised epilepsy and monotherapy in juvenile myoclonic epilepsy (JME) and generalised tonic-clonic seizures (GTCS) [12].

Summary and Conclusion

In the comparative study of levtr. And VPA as monotherapy on cognitive impairment in epileptic patients. The aim of antiepileptic drug (AED) pharmacotherapy for epilepsy is to sustain seizure-free periods with minimal adverse effects. Levetiracetam probably has a neuroprotective benefit over phenobarbital, unlike older AEDs. It has no significant effect on metabolism. The safety and tolerability of levtr. are more apparent than VPA. Adjunctive levt. is extremely beneficial in the treatment of refractory or drug-resistant epilepsy with higher or comparable seizure cessation. The present study demands further genetic, environmental, nutritional, and pharmacological studies because the exact mechanism and mode of action of both AEDs are still unclear.

Limitation of study: Owing to the remote location of the research centre, a small number of patients, and a lack of the latest techniques, we have limited findings and results.

This research work was approved by the ethical committee of Dr. Moopen's Medical College Hospital, Wayanad, and Kerala-673577.

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