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ASSESSMENT OF CLINICAL EFFICACY AND NEUROPSYCHOLOGICAL EFFECT OF LEVETIRACETAM IN STROKE PATIENTS

***S. Anandkumar, Juliya G. John, S. Harini and Grace N. Raju**

Dept. of Pharmacy Practice, Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode, Namakkal (Dt), India.

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***Corresponding Author**
S. Anandkumar
Dept. of Pharmacy Practice, Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode, Namakkal (Dt), India.

ABSTRACT

Aim: The study aimed to determine the clinical efficacy of Levetiracetam in preventing the occurrence of seizure and to assess its neuropsychological effect in stroke patients. **Methods:** The prospective observational comparative study was conducted in tertiary care teaching hospital. Clinical efficacy of Levetiracetam was assessed by comparing the occurrence of late onset post stroke seizure in group of patients on Levetiracetam treatment (500 mg BD) with group of patient without Levetiracetam treatment. The neuropsychological effect of the drug was assessed by Modified Mini-Mental State Examination. **Results:** Patients not on Levetiracetam treatment reported 16% occurrence of post stroke seizure, while 97% patients on Levetiracetam remained seizure free at the daily dose of 500 mg BD and 1 patient was responsive to dose of 1500mg/day. There was an increased percentage (57.1%) of patients on Levetiracetam treatment with significant cognition after 3 months. The final follow up, mean 3MS score for patients on Levetiracetam was 25.8 ± 2.06 and patient not on Levetiracetam was 16.04 ± 2.57. **Conclusion:** The present comparative study suggested that the antiepileptic drug, LEV had significant effect on preventing the post stroke seizure. The improvement in the cognitive status of LEV group by the third month revealed the neuropsychological effect of the drug. As per the study result, LEV monotherapy was the better treatment option for preventing post stroke seizure and improving cognitive status.

KEYWORDS: Levetiracetam, Post stroke seizure, Neuropsychological effect, Cognition.

1. INTRODUCTION

Levetiracetam (LEV) having a crucial role in regulation of epileptogenesis and neuroprotection. LEV binds with synaptic vesicle protein 2A which interacts with the presynaptic protein synaptotagmin, the primary calcium sensor for regulating calcium-dependent exocytosis of synaptic vesicle, thus indirectly regulates neurotransmitter release.[1] LEV's neuroprotective properties was tested in the rat middle cerebral artery occlusion model and found that the use of LEV reduced the infarct volume without altering body temperature, with better results than those obtained by application of non-competitive N-methyl-D-asparticacid antagonist.[2]

This article on clinical efficacy and neuropsychological effect of LEV was based on extent of LEV-mediated neurological protection and potential for easing epileptogenesis by executing it as single drug candidate for treating post cognitive impairment and preventing post stroke seizure in stroke population.

2. METHODS

The study was conducted at Neurology and General Medicine Department of 300 bedded multispecialty tertiary care teaching hospital. Out of 82 patients screened, 66 patients were included in the study population based on following inclusion and exclusion criteria after obtaining informed consent. Patients diagnosed with stroke with age group of 45 and above are included in the study. Patient with past medical history of mental impairment, preexisting epilepsy and no other concomitant conditions potentially responsible of epilepsy (alcohol abuse; dementia; electrolyte disturbance), psychoactive treatment and Glassgow Coma Scale score less than 6 were excluded. A specially designed data entry form was used to collect demographic details. Clinical efficacy of LEV was assessed by comparing the occurrence of late onset post stroke seizure in group of patients on LEV treatment (500 mg BD) with group of patient not on LEV treatment. The latter group received treatment with either Citicoline or Nurokind LC. Modified Mini mental state examination (3MS) scale was used to assess the neuropsychological effect of LEV. The test was conducted on the first to fourth day of hospital stay and during the follow up periods of first 3 months.

2.1 STATISTICAL ANALYSIS

Student t- test was used to analyze the statistical difference between two groups. It was done using Microsoft Excel. The clinical efficacy and neuropsychological effect with and without

LEV treatment was expressed as Percentage and Mean ± SD. P<0.05 with a confidence interval of 95% was considered as statistically significant.

3. RESULTS

From the Neurology and General medicine department, as per the study criteria 66 stroke patients were enrolled in the study, of which 60 patients completed the study. Six patients withdrew from the study: 3 discontinued treatment during the second month of follow-up, 2 missed during the neuropsychological follow-up and 1 decided to continue the treatment in a different hospital. Thus the dropout rate was 9.09%.The study population consisted of both ischemic and haemorrhagic patients documented through CT/MRI. 48.3% patients diagnosed with ischemic stroke and 51.6% with haemorrhagic stroke.

3.1 PATIENT DEMOGRAPHICS

Among 60 stroke patients screened, 35% of patients were in the age group of 65-74 years, 33.3% of patients were in the age group of 75 -84 years and 8.3% of patients were in age group of ≥85 years. Gender wise distribution data indicated a predominant male population (61.6%) and 38.3% female population. The study populations were grouped into two, one group was given with LEV 500 mg BD and other without LEV treatment. Both group received proper stroke treatment.

3.2 CLINICAL EFFICACY OF LEV

Clinical efficacy of LEV was assessed by detecting the occurrence of seizure in group of patients not on LEV V/s patient on LEV treatment. The potential of LEV preventing in post stroke seizure in terms of efficacy and safety was determined.

Assessment of post stroke seizure occurrence in patients without LEV

Out of 25 patients in without LEV group, 4 patients (16%) reported seizure episodes. Episodes consisted of complex partial seizure (3 patients) and secondary generalised seizure (1 patient).Overall result suggested that patient had haemorrhagic stroke develop seizure more likely than ischemic stroke. (Table: 1).

Table: 1 Percentage of Post Stroke Seizure Occurrences in Patients without LEV

Sl.No.	Types of Stroke	Total No. of Patients	No. of Patients Developed Post stroke seizure	Percentage (%)
1	Haemorrhagic stroke	10	3	30
2.	Ischemic stroke	15	1	6.7

Assessment of Post Stroke Seizure Occurrence in Patients on LEV

The daily dose of LEV was fixed at 500mg twice daily. Out of 35 patients, 34 patients (97%) on LEV treatment did not report the onset of seizure episode up to the follow up period of 3 months. In one patient, the dose of LEV was increased up to 500 mg thrice daily as the patient had a episode of late onset tonic clonic seizure during the course of treatment and the further follow up data revealed that patient was seizure free up to two months. In patients with LEV treatment, 6 patients (17%) reported mild side effects like headache, somnolence, anxiety and agitation.

3.3 NEUROPSYCHOLOGICAL EFFECT OF LEVETIRACETAM

Neuropsychological effect of LEV was assessed by the changes in cognition after stroke in two groups. Initial data collection was performed as soon as possible after stroke, with formal follow-up to 4 days of hospital admission and first to three months after diagnosis of first stroke. Assessment was done using the modified version of MMSE questionnaire.

3.3.1 Neuropsychological assessment of patients not on LEV

As per the 3MS score interpretation patients were categorised based on the degree of impairment into significant cognition, mild impairment, moderate impairment and severe impairment during each follow up. Significant changes in cognition were determined.

Grading of cognitive status based on 3MS score

Neuropsychological assessment during 1st follow up based on 3MS score, 92% patients were categorised to moderate degree of impairment and 8% on severe cognitive impairment whom required 24-hours supervision and assistance with activities of daily living**.** At the time of second follow up, 96% on moderate cognitive impairment and 4% on severe cognitive impairment. During the third follow up, 4 patients were at mild cognitive impairment (16%) and 21 patients at moderate impairment (84%).There were no patients on severe cognitive impairment and those with significant cognition**.**

Monitoring of cognitive changes within the group

Assessment of cognitive changes during the days of hospital admission and follow up period were done. Baseline data was collected on the first day. The result revealed even after 3rd month the patients had deteriorated cognition **(Table: 2).**

Table 2: Cognitive Changes in Patients not on LEV based on 3MS Score.

Sl.No.	Cognitive Assessment	3MS Score Mean ± SD
1	Baseline	1.32 ± 1.24
2	Second Day	3.84 ± 1.46**
3	Third Day	6.88 ± 2.02**
4	Fourth Day	9.96 ± 1.79**
5	First follow up	12.68 ± 1.86**
6	Second follow up	14.16 ± 2.28*
7	Third follow up	16.04 ± 2.57*

3MS-Modified mini mental state examination
SD-Standard Deviation LEV-Levetiracetam
*P Value <0.05 was considered to be significant.
**P Value < 0.0001 was considered to be extremely significant

3.3.2 Neuropsychological assessment of patients on LEV

Categorisation based on the degree of impairment in patients on LEV and assessment of significant changes in cognition was done.

Grading cognitive status based on 3MS score

Neuropsychological assessment during the first follow up, categorised 31.42% patients on mild cognitive impairment and 68.57% on moderate cognitive impairment. At the time of second follow up, 8.57% patients had the significant cognition, 82.85% patient on mild cognitive impairment and the balance 8.57% were on moderate cognitive impairment. During the period of 3rd follow up, a drastic improvement of 57.1% of patients with questionably significant cognition. 40% patients were on mild cognitive impairment and moderate cognitive impairment for 2.85% patients.

Monitoring of Cognitive Changes within the Group

Comparison of the mean 3MS scores of patients on LEV treatment on the days of hospital stay and follow up periods for the determination of mean improvement of cognition were done. The mean 3MS score of patient on the third follow up was 25.8± 2.03, a questionably significant cognition **(Table: 3).**

Table: 3 Cognitive Changes in Patients on LEV Based on 3MS Score.

Sl.No.	Cognitive Assessment	3MS Score Mean ± SD
1	Baseline	2.14 ± 1.26
2	Second Day	6.17 ± 2.92**
3	Third Day	11.25 ± 3.21**
4	Fourth Day	14.8 ± 3.21**
5	First follow up	19.28 ± 2.78**
6	Second follow up	22.71 ± 2.24**
7	Third follow up	25.8 ± 2.03**

3MS-Modified mini mental state examination, SD-Standard Deviation, LEV-Levetiracetam
**P Value < 0.0001 was considered to be extremely significant

3.4 Comparison of Domains score in 3MS b/w patients on LEV and those not on LEV

The 8 variables/domains score in the 3MS were assessed separately to determine the neuropsychology of stroke patients. Neuropsychological evaluation monitored the following domains after a stroke: orientation to time, orientation to place, attention, recall, language, repetition and complex commands through the 3MS score. Changes in the score of each domain within the group and between the groups were compared. Baseline data was taken from the 4th day of hospital stay and the endpoint data was taken from assessment data on the final follow up **(Table: 4).**

Table: 4 Comparisons of 3MS Domains Score b/w Study Groups.

Domains		3MS score Mean ± SD	
		Base line	Endpoint
Orientation to Time	LEV	1.68 ± 0.96#	4.08±0.78**##
	NOT LEV	0.96±0.53	2.28±0.84**
Orientation to Place	LEV	2.45 ± 0.81##	4.51±0.61**##
	NOT LEV	1.48±0.58	2.52±0.65**
Registration	LEV	1.05 ± 0.63#	2.4±0.69**##
	NOT LEV	0.6±0.7	1.12±0.88*
Attention	LEV	2.02 ± 1.22#	4.34±0.80**##
	NOT ON LEV	1.28±1.13	2.16±1.21*
Recall	LEV	0.48 ± 0.65#	1.68±0.52**##
	NOT ON LEV	0.2±0.5	0.48±0.65*
Language	LEV	1.91 ± 0.28	2±0*
	NOT LEV	1.8±0.57	1.92±0.27
Repetition	LEV	0.85 ± 0.35	1±0*
	NOT LEV	0.76±0.43	1±0*
Complex commands	LEV	4.11 ± 1.13	5.8±0.42**##
	NOT LEV	3.68±1.06	4.8±0.83**

3MS-Modified mini mental state examination, SD-Standard Deviation, LEV-Levetiracetam
*P Value <0.05 was considered to be significant (within the group).

**P Value < 0.0001 was considered to be extremely significant (within the group).
#P Value <0.05 was considered to be significant (b/w the group).
##P Value < 0.0001 was considered to be extremely significant (b/w the group).

3.5 Comparison of cognitive status b/w two groups based on 3MS total score

The neuropsychological effect of LEV can be determined through the 3MS score mean comparison b/w two study groups at the time of hospital stay and follow up. The results showed a significant change between two groups **(Table: 5).**

Table: 5 Comparative Assessment of Cognition b/w Study Groups.

Sl.No.	Cognitive Assessment	3MS SCORE (Mean ± SD)	
		LEV	Not on LEV
1	Baseline	2.14 ± 1.26*	1.32 ± 1.24
2	Second Day	6.17 ± 2.92**	3.84 ± 1.46
3	Third Day	11.25 ± 3.21**	6.88 ± 2.02
4	Fourth Day	14.8 ± 3.12*	9.96 ± 1.79
5	First follow up	19.28 ± 2.82**	12.68 ± 1.86
6	Second follow up	22.71 ± 2.28**	14.16 ± 2.28
7	Third follow up	25.8 ± 2.06**	16.04 ± 2.57

3MS-Modified mini mental state examination, SD-Standard Deviation
*P Value <0.05 was considered to be significant.
**P Value < 0.0001 was considered to be extremely significant.

4. DISCUSSION

Post stroke seizure, the common causes of hospital admissions require appropriate management and support in long term.[3] Prophylaxis for seizures is the standard of care for individuals with moderate to severe injuries at risk for developing seizures. The novel drug LEV is capable of improving the cognitive areas and also it differentiated from conventional AED by its anti-epileptogenic effect other than the property of controlling seizures.[4]

We assessed the clinical efficacy and neuropsychological effect of LEV by comparing study group, one given with LEV 500mg BD (58.3%) and other not on LEV treatment(41.6%). The study showed that the patients not on LEV treatment had an increased incidence of late onset seizure after stroke. But 97% of patients on LEV treatment remained seizure free during the study period. The results of LEV's prophylactic antiepileptic efficacy derived from the present investigation are consistent with study carried out by Karamchandani RR[5], Zafar SN[6] and Taylor S[7] et al. They reported that the prophylactic use of LEV can recommended as it was safe and significantly reduces the incidence of seizure.

In present study, 30% patients diagnosed with haemorrhagic stroke and 6.7% with ischemic stroke developed post stroke seizure revealed that there was a greater incidence for seizure in patients diagnosed with haemorrhagic stroke.Similar result was demonstrated in the studies conducted by Md Abu Naser Siddique[8] and Burn J[9] et al. On the total of 35 patients on LEV treatment 6 patients were reported of the mild side effects like agitation, headache, somnolence and anxiety. The side effects observed in this study was found to be similar with the prospective observational study conducted by Vincenzo Belcastro et al., in elderly population.[10]

Comparison of cognitive status b/w two groups based on 3MS score days indicated a significant improvement during hospital and extremely significant improvement in follow up periods in patients on LEV treatment. The final 3MS score mean in the LEV group was 25.8 ± 2.06 and not on LEV group was 16.04 ± 2.57. The present study simultaneously discusses the positive effects of LEV on cognitive functions, seizure frequency in the post stroke patients. The findings correlated with the Lippa CF et al., study reported that LEV was the effective antiepileptic drug in elderly individuals with cognitive impairment and at third month, participants who remained on LEV showed excellent cognitive tolerability.[11] Anne Sophie Ciesielski et al., suggested that add-on LEV has a favorable neuropsychological and psychiatric impact.[12]

The 8 variables/domains score in the 3MS for determining the neuropsychology of stroke patients were compared among the two groups during the follow up periods.3MS scores for the variables of orientation to time, orientation to place, registration, attention, recall and complex commands were found to be extremely significant indicated the effect of drug in stroke patients on LEV treatment. The variables of language and repetition, patients had better scoring on both the groups. TonyWu et al., study stated that LEV contributes to improvements in neuropsychological functions such as recall, language, interpersonal sensitivity, and paranoid ideation in seizure patients.[13] The significant improvements in the domains of neuropsychological tests : verbal and visual attention, psychomotor speed, mental flexibility, executive function, verbal fluency and word generation by LEV was seen in the study of Koo DL et al., in newly diagnosed epileptic patient.[14] Julio Cesar Magalhaes et al., displayed the neuropsychological improvement in attention, working memory, planning and decision making after LEV treatment in healthy individual.[15] The current study results agreed with those of previous investigations describing an improvement in cognitive areas.

5. CONCLUSION

The present study suggested that the antiepileptic drug LEV had significant effect on preventing the post stroke seizure. The improvement in the cognitive status of LEV group by the third month revealed the neuropsychological effect of the drug. The elderly population had the greater risk for both post stroke seizure and post stroke cognitive impairment. LEV has better tolerability and didn't cause any drug interactions in the study population. The efficacy of LEV demonstrated it as the best-choice drug against post stroke seizures in elderly. As per study result LEV monotherapy was the better treatment option for preventing post stroke seizure and improving cognitive status.

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