IJPSR (2023), Volume 14, Issue 11 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 07 September 2023; received in revised form, 12 October 2023; accepted 25 October 2023; published 01 November 2023

LACOSAMIDE AS AN ADD-ON THERAPY FOR DRUG-RESISTANT EPILEPSY: A PROSPECTIVE OBSERVATIONAL STUDY AT A TERTIARY CARE HOSPITAL IN SOUTH INDIA

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Keywords:

Lacosamide, Drug-resistant Epilepsy, Seizures, Refractory epilepsy

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ABSTRACT: Background: Epilepsy is a common and chronic neurological disorder. The prevalence of drug-resistant epilepsy (DRE) is reported as 25-30% among epileptic patients. So, there is a need of drugs for resistant epilepsy. **Objective:** To assess the effectiveness and tolerability of Lacosamide (LCM) as an add-on therapy in patients with Drug-Resistant Epilepsy in our patient population. **Methods and Material:** A total of 43 patients with Drug Resistant Epilepsy were screened, and 32 were included in the study based on inclusion and exclusion criteria and Lacosamide was added as an add-on therapy, and the patients were prospectively followed up for a minimum 3 months. Out of 32 patients, 25 had focal and the remaining 7 were having generalized epilepsy. The Lacosamide dosage used was between 4 - 12mg/kg/day. Seizure frequency, adverse effects, and tolerability were noted in the study participants. **Results:** Two patients lost follow-up. Hence 30 patients were taken for intension to treat analysis. Out of 30 patients with DRE, 11(36.6%), 25(83.3%) had seizure reduction of more than 90%, 50% respectively. None of the patients developed significant adverse effects so as to warrant discontinuation of the drug. **Conclusion:** Lacosamide was found to have been better tolerated and was effective in reducing seizure frequency of more than 50% in patients with Drug-Resistant Epilepsy of both focal and generalized epilepsy in our patient population.

INTRODUCTION: Epilepsy is one of the most common and chronic neurological disorders. The prevalence of epilepsy in India is estimated to be approximately 8–10 per 1000 [1]. It is estimated that 20 to 30% of epilepsy patients are refractory to medical treatment [2]. Hence, the development of new therapeutic options and various drug combinations are strongly warranted.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(11).5541-54

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.14(11).5541-54

Drug-resistant epilepsy (DRE) is defined as failure of response to two tolerated, appropriately chosen, and used antiepileptic drug schedules to achieve sustained seizure freedom, which could be either 3 times the prior inter-seizure interval or 1 year, whichever is longer [3].

Lacosamide acts by selectively enhancing the slow inactivation of voltage-gated sodium channels. Lacosamide was approved in 2008 in the European Union and the USA as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adults and adolescents with epilepsy [2]. Lacosamide was found to be safe and effective in primary generalized tonic-clonic seizures too [4].

Currently, it is used in patients aged more than 4 years in US and in the European Union [5]. Lacosamide has a predictable pharmacokinetic profile with a high oral bioavailability and a low potential for clinically relevant pharmacokinetic drug-drug interactions [6]. Hence, it is preferable when multiple antiepileptic drugs are used.

Objectives: The primary objective of the study was to assess the effectiveness of Lacosamide in reducing seizure frequency. A secondary objective is to find out the tolerability of Lacosamide as an add-on therapy in patients with drug-resistant epilepsy (DRE).

MATERIALS AND METHODOLOGY:

Study Design: It was a prospective interventional study conducted at the neurology department, Chengalpattu Medical College Institute, between October 2021 to September 2022.

Inclusion Criteria: Epileptic patients age more than 4 years who fulfill the criteria for drug-resistant epilepsy (DRE) and give informed consent were included in the study.

Exclusion Criteria:

- Epileptic patients with multiple seizure/ myoclonic type.
- Patients with known cardiac disease.
- Patients with poor drug compliance.
- Patients with Intellectual Disability.
- Patients who were pregnant or planning to become pregnant were excluded from the study.

Methodology: After ethics committee approval (No. IEC-CMC/Approval/19/2021 Dated 15.11.2021) and getting informed written consent, we enrolled patients in the study. Lacosamide was given as an add-on drug in Drug-Resistant Epilepsy patients in the dose range of 4 to 12 mg/kg/day in two divided doses. The starting dose was 4mg/kg/day. The treating neuro-physician did subsequent titration of Lacosamide. Pre-Lacosamide baseline details were collected. Patients were followed up every month or whenever they got a breakthrough seizure. Patients were followed up in this manner till 3 months after starting lacosamide. All patients were asked to maintain a seizure diary. Drug compliance was noted. Pre- lacosamide and post- lacosamide seizure frequency and seizure free interval were compared. Side effects experienced by the patients are noted.

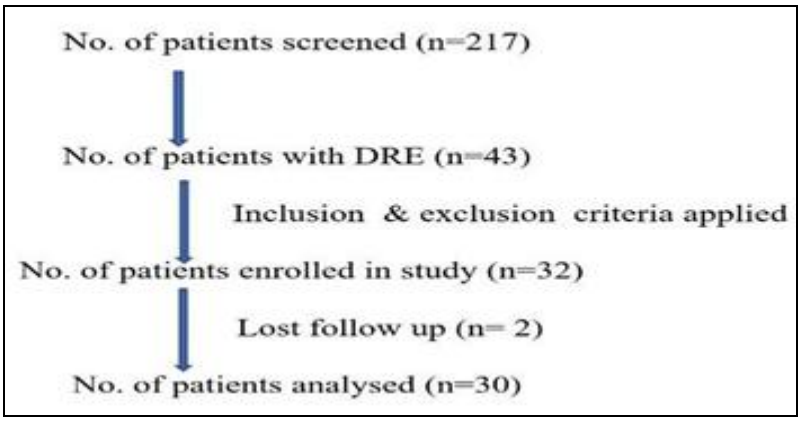

FIG. 1: STUDY FLOW CHART

RESULTS: A total of 247 patients with epilepsy were screened, out of which 43 patients were found to have Drug-Resistant Epilepsy. After applying inclusion and exclusion criteria, 32 patients were enrolled in the study. Two patients were lost in follow-up. Hence, 30 patients were taken up for analysis.

TABLE 1: BASELINE CHARACTERISTICS OF THE PATIENTS

Parameters	Categories	No of patients
Age	Average (years)	29.2 (+/-) 15
	Less than 18 years	8 (26.7%)

	18-65 years	21 (70.0%)
	More than 65 years	1 (3.3%)
sex	Male: Female ratio	16: 14
	Age at diagnosis (years)	25 (+/-) 14
Duration of epilepsy	Time since diagnosis (years)	3.8 years
Type of epilepsy	Focal	23 (76.6%)
	Generalized	7 (23.4%)
No. Of concomitant antiepileptics	2	7 (23.3%)
	3	16 (53.3%)
	4	5 (16.6%)
	5	1 (3.3%)
	6	1 (3.3%)
	Abnormal imaging (CT/MRI) (%)	7 (23.3%)
	EEG abnormality (%)	9 (30%)

Baseline patient demographics and characteristics are shown in **Table 1**. The study group contains both pediatric and adult populations, though about 3/4th of the patients were adults.

Males and females were almost equally represented. Patients with focal epilepsy constituted about 3/4th of the study population.

TABLE 2: POST-LACOSAMIDE SEIZURE FREQUENCY

Post Lacosamide seizure frequency overall	
More than 90% reduction	11 (36.6%)
More than 50% reduction	25 (83.3%)
Unchanged	5 (16.7%)
Post Lacosamide seizure frequency in focal seizures	
More than 90% reduction	9 (39.1 %)
More than 50% reduction	20 (87%)
Unchanged	3 (13%)
Post Lacosamide seizure frequency in generalized seizures	
More than 90% reduction	2 (28.6%)
More than 50% reduction	5 (71.4%)
Unchanged	2 (28.6%)
Post Lacosamide seizure frequency as 1st add-on	
More than 90% reduction	5/7 (71.4%)
More than 50% reduction	6/7 (85.7%)
Unchanged	1/7 (14.3%)
Post Lacosamide seizure frequency as 2nd add-on	
More than 90% reduction	5/16 (31.3%)
More than 50% reduction	13/16 (81.3%)
Unchanged	3/16 (18.8%)
Post Lacosamide seizure frequency as 3rd add-on onwards	
More than 90% reduction	1/7 (14.3%)
More than 50% reduction	5/7 (71.4%)
Unchanged	2/7 (28.6%)

Seizure frequency after starting lacosamide was shown in **Table 2**. lacosamide was found to be most effective in focal epilepsy when compared to generalised epilepsy, and it was most effective when added as a first or second add-on.

TABLE 3: ADVERSE EFFECTS

Adverse effects	Number of patients with ADR (%)
Dizziness	8 (25%)
Somnolence	8 (25%)
Nausea	6 (18%)
Headache	5 (15%)
Vomiting	2 (6%)
Weight gain	2 (6%)
Hyperactivity	1 (3%)

Table 3 shows the adverse effects. Almost half of the patients reported some adverse effects, as shown in the table. But none of them warranted the discontinuation of lacosamide.

DISCUSSION: In this study, we observed that adding lacosamide as an add-on drug resulted in decrease in seizure frequency of more than 90% in 37% of the patients and more than 50% in 83% of the patients. This higher percentage observed in our study was relatively higher than the majority of the studies reported, though a study by Maschio *et al.*[7] reported a similar percentage (86.4%). One possible reason for this better outcome could be excluding patients with intellectual disability (I.D), in whom the decrease in seizure frequency after lacosamide is limited (13% in one study by Kleist *et al.*) [8].

Overall, the outcome was better in patients with focal epilepsy. More than 90% reduction is 39% of the population compared to generalized epilepsy, which is 29% of the population, which is comparable with many other studies, notably the study done by Liu *et al.* [9]. The more the number of already failed Antiepileptic Drugs, the lesser was the effectiveness of adding lacosamide in our patient population. A similar observation is reported in various studies [10, 11, 14, 15]. Hence, it may be preferable to add lacosamide as a first or second

add-on when the primary Antiepileptic Drugs fail [12, 13]. We observed that adverse drug reactions were seen in 48.3% of patients. But none of them were severe enough to warrant discontinuation of treatment. Most common adverse drug reactions were dizziness and somnolescence. Most studies have reported dizziness as the most common adverse drug reaction [16, 17].

Limitations: The smaller sample size and shorter follow-up duration are this study's main limitations.

CONCLUSION: Lacosamide was found to be safe and effective in reducing seizure frequency in patients with drug-resistant epilepsy in our patient population, particularly when added as 1st or 2nd add-on. Further studies with more sample size and long-term follow-up are needed to support these findings.

ACKNOWLEDGEMENT: Nil

CONFLICTS OF INTEREST: Nil

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How to cite this article:
Prakash V, Balaji G and Devi TS: Lacosamide as an add-on therapy for drug resistant epilepsy: a prospective observational study at a Tertiary Care Hospital in South India. Int J Pharm Sci & Res 2023; 14(11): 5541-54. doi: 10.13040/IJPSR.0975-8232.14(11).5541-54.