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Research Article

The Effectiveness and Tolerability of Lacosamide Use in Children with Refractory Epilepsy - A Tertiary Care Hospital Experience in Riyadh, Saudi Arabia

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Abstract

Introduction: Epilepsy is the most common neurological disease globally which affects all age groups. Approximately 50 million people worldwide have epilepsy [1].

The goal of managing patients with epilepsy is to achieve seizures freedom while avoiding treatment side effects and optimizing the quality of life [2].

Lacosamide at the time of our study was approved by US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for partial-onset seizures as monotherapy or adjunctive therapy in patients 17 years or older. Recently in 2017, Lacosamide was approved by both the FDA and EMA as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adults, adolescents and children 4 years of age and above with epilepsy.

Objectives: To evaluate the effectiveness and tolerability of Lacosamide in Saudi children less than 17 years old.

Method: An Observational Retrospective Cohort study.

Results: Out of 54 cases of refractory epilepsy treated with Lacosamide as an adjunctive therapy, forty-six patients were analyzed. After Lacosamide was started, twenty-one patients (45.7%) became seizure-free (100% response), two patients (4.3%) achieved 75% reduction in seizure frequency and twelve patients (26%) improved up to 25% - 50%. Eleven patients (23.9%) didn't report any improvement in the number of seizure episodes after starting Lacosamide. The initial dose ranged between 1- 6.5 mg/kg/day divided to twice daily doses. The majority (84.78%) of patients were on 10 mg/kg/day in two divided doses as maintenance dose. Seven patients (15.2%) developed adverse drug reaction in the form of increased or loss of appetite, behavioral problems, nausea and vomiting.

Conclusion: Lacosamide is one of the effective and tolerable treatments in children with refractory epilepsy as an adjunctive therapy.

Keywords: *Lacosamide; Refractory Epilepsy; Adjunctive Therapy*

Introduction

Epilepsy is the most common chronic neurological disorder, approximately 50 million people worldwide have epilepsy. Epilepsy is characterized by recurrent, 2 or more, unprovoked seizures [1].

Managing patients with epilepsy focuses on controlling seizures while avoiding treatment side effects and optimizing the quality of life [2].

Drug resistant epilepsy occurs when a person has failed to become and remain seizure free with adequate trials of two antiepileptic drugs (AEDs). These AEDs must have been chosen appropriately depending on the seizure type and tolerated by the person. Drug-resistant epilepsy also referred to as intractable, refractory, uncontrolled or pharmacoresistant epilepsy [2,3].

Lacosamide is one of the newer generation AEDs which act by selectively enhancing slow inactivation of voltage-gated sodium channels, resulting in diminished pathological hyperexcitability without compromising physiological activity. It is FDA approved in partial-onset seizures as monotherapy or adjunctive therapy in patients 4 years or older. Lacosamide is also used as adjunct therapy in children with refractory seizures [4,5].

Although, few clinical trials have been conducted with younger patients on Lacosamide, they are limited in providing full effectiveness and safety information of the drug. However, we do not have data about Lacosamide use in the Saudi pediatric population. In this study, we intended to evaluate and assess Lacosamide effectiveness and tolerability in Saudi children with intractable epilepsy.

A retrospective study of 16 children with uncontrolled focal epilepsy showed a great response to adjunctive lacosamide therapy, median dose 4.7 mg/kg daily. Median seizure reduction of 37.5% with ≥ 50% seizure reduction without severe adverse events which includes seizure worsening, behavioral disturbance, and depression with suicidal ideation. These adverse events prompted lacosamide discontinuation in 25% of patients [6].

Another multicenter retrospective study includes eighteen pediatric (mean age 12.3 years) diagnosed with Lennox-Gastaut syndrome (LGS) receiving oral Lacosamide as adjunctive therapy. 33% of patients responded, but none of them was seizure-free during the study period. The overall seizure reduction rate was 29%. Adverse reactions reported in 44% of patients. Lacosamide was discontinued in four (22%) patients due to increase in seizure frequency (three cases) and walking instability (one patient) [7].

The results of adjunctive Lacosamide treatment were retrospectively reviewed in 18 pediatric patients with pharmacoresistant focal epilepsy receiving one to three other antiepileptic drugs. The final dose of Lacosamide ranged between 1.7 and 10 mg/kg. 36% of patients reported reduction in seizure frequency more than 50%. Side effects, mostly somnolence and irritability, were reported by 39% of patients [8].

A prospective study conducted at a tertiary care hospital included seventy-nine children (age 5 - 15 years) with refractory partial epilepsy failed to two or more AEDs. Lacosamide add on as an adjunctive therapy at a dose of 25 mg for the first week followed by 50 mg twice daily for the remaining period. Thirty-five patients (44.3%) were seizure free, thirty-two patients (40.6%) indicated ≥ 50% reduction in seizure frequency, three patients (3.8%) indicated 25 - 49% seizure reduction, and nine patients (11.4%) either had no change in seizure frequency or experience increase in seizure frequency. Three patients (3.8%) dropped out of the study, because of vomiting, aggressive behavior, and poor response [9].

Another multicenter prospective study was carried out where Lacosamide was added to the baseline therapy in different patients' age groups including children less than 17 years old with uncontrolled epilepsy to investigate the effectiveness and safety of Lacosamide as an adjunctive therapy. Lacosamide was initiated in patients aged < 16 years as add on medication. At 3-month follow-up 47.4% of children showed at least a 50% reduction in seizure frequency. 30.5% of this group developed side effects during therapy, mostly dizziness [10].

A prospective, open-label, observational, multicenter study involved 130 patients aged less than 16 years with refractory epilepsy who had started on lacosamide with initial dose 1 - 2 mg/kg/day. Patients were evaluated after 3 months of lacosamide therapy, 62.3% of patients achieved a > 50% reduction in seizure frequency, 13.8% of patients with complete seizure suppression. Thirty-nine patients (30%) developed adverse effects [11].

Methods

Overview

The Effectiveness and Tolerability of Lacosamide Use in Children with Refractory Epilepsy- A Tertiary Hospital Experience in Riyadh, Saudi Arabia.

The study has King Fahad Medical City (KFMC) IRB approval with log number: 16-045.

Study Design

Observational Retrospective Cohort study.

Study setting

Epilepsy clinics of the National Neuroscience Institute (NNI) in a tertiary care hospital, King Fahad Medical City in Riyadh, Saudi Arabia.

Subjects

Sample size and Data Collection

A retrospective review of data retrieved from medical records for all patients 17 years of age and younger who were started on Lacosamide for refractory epilepsy from November 2011(since the medication was added to the KFMC formulary) till November 2015. Patient's data was obtained from the electronic medical record system (CORTEX) and Health Information Management system (HIM) - Chart Viewer. Patients' caregivers were contacted to collect any missing data regarding patients' response and tolerability after starting Lacosamide.

Inclusion and exclusion criteria

Inclusion criteria

- Patients 17 years of age and younger with refractory epilepsy on Lacosamide following in the epilepsy clinic at King Fahad Medical City.

Exclusion criteria

- Patients older than 17 years of age.
- Patients 17 years of age and younger who lost follow up after Lacosamide was started.
- Patients with history of noncompliance to medication.
- Patients who could not be contacted to evaluate therapy outcomes.

Outcome Measures

Primary outcome: Lacosamide effectiveness

The primary outcome of the study is to measure Lacosamide effectiveness in Saudi patients 17 years of age and younger. In this study, the effectiveness is measured by the reduction in seizure episode frequency per month compared to baseline by 0% (no response), 25% response, 50% response,75% response and 100% response since the initiation of treatment till the time of last follow-up. This information was accessed through the patient's file during the epilepsy clinic follow up and a questionnaire.

Secondary outcome: Lacosamide tolerability

The secondary outcome of the study was an assessment of Lacosamide tolerability by reviewing the reported adverse effects, causes of dose reduction or medication withdrawal.

Statistical analysis

All categorical variables will be presented as numbers and percentages, while the continuous variables will be expressed as Mean ± SD. Chi-square/Fisher's exact test according to whether the cell expected frequency is smaller than five was used to determine the significant

relationship between categorical variables. One-way analysis of variance (ANOVA) was used to test for the statistical significance between the means of Lacosamide maximum dosing with the response, adverse reaction and seizure type. All statistical analyses will be performed using sing SPSS 22.0 software (SPSS Inc., Chicago, IL, USA) package; two-tailed a p-value of 0.05 will be considered significant.

Results

Demographics data

Overall, 54 cases of Saudi patients 17 years of age and younger with refractory epilepsy on Lacosamide following in the epilepsy clinic at King Fahad Medical City were reviewed.

Eight patients out of 54 were excluded as they lost follow up after the first visit within the study period.

Accordingly, forty-six pediatric patients with refractory epilepsy on lacosamide were analyzed.

Patients' ages ranged from 1 year to 17 years (Mean age 10 ± 5 years), 26 (56.5%) male and 20 (43.5%) female. (Table 1).

Gender	Number of patients (46)
Male	26 (56.5%)
Female	20 (43.5%)

Table 1: *Demographic Data.*

Mean age of epilepsy onset was 3.6 years ± 4.

Clinical Characteristics

Lacosamide was used by 20 (43.48%) patients with generalized seizures, 22 (47.83%) with partial seizures and 4 (8.7%)with Mixed type of seizures (Table 2).

Generalized seizures	20 (43.48%)
Tonic - clonic	13
Myoclonic	3
Tonic	4
Partial seizures	22 (47.83%)
Complex Partial	10
Focal	12
Mixed type of seizures	4 (8.7%)
Multifocal	2
Multiple semiology	2
Total	46

Table 2: *Seizure Type.*

Initial dose ranged from 1- 6.5 mg/kg/day divided to twice daily doses. One patient initiated on 26.8 mg/kg/day.

Majority of patients (84.78%) were on maintenance dose of 10 mg/kg/day in two divided doses. Seven patients (15.2%) exceed this range and reached dose up to 16 mg/kg/day divided to twice daily.

Nine (19.6%) patients were on one AED and twenty-eight (60.8%) patients were on more than two AEDs before Lacosamide had been started (Table 3).

Number of previous AED	N = 46
1 AED	9
2 AEDs	9
3 AEDs	4
4 AEDs	8
5 AEDs	10
6 AEDs	3
7 AEDs	2
8 AEDs	0
9 AEDs	1

Table 3: *Number of medications before start Lacosamide.*

Previous AEDs used before starting Lacosamide included; Clobazam, Clonazepam, Gabapentin, Lamotrigine, Levetiracetam, Oxcarbazepine, Phenobarbitone, Phenytoin, Rufinamide, Topiramate, Valproate sodium and Vigabatrin.

Effectiveness Outcomes

Out of 46 patients, Twenty-one (45.65%) patients achieved seizure freedom (100% response) after starting Lacosamide, 57.1% of them had partial seizures, and 33.3% had generalized seizures. Two (4.3%) patients reached 75% reduction in seizure frequency. Twelve (26%) patients improved up to 25% - 50% and eleven (23.9%) patients didn't report any improvement in the number of seizure episodes after starting Lacosamide. The maximum dose of Lacosamide did not show any statistically significant difference among different efficacy groups (p-value 0.763).

However, one patient reported an increase in seizure frequency and intensity with a dose of 12.5 mg/kg/day.

Table 4 displays comparison of Lacosamide final dose with effectiveness among different groups. We didn't find any statistically significant difference between the effectiveness of Lacosamide and seizure types (p-value 0.56) (Table 5).

Efficacy	N	Initial Mean Dose (mg/kg/day)	Maximum Mean Dose (mg/kg/day)
0%	11	2.25 (1.29-5.5)	5.25 (1.7 – 14.5)
25%	3	3 (2.25 - 4)	5.3 (2.4 - 8)
50%	9	2.1 (1 - 3.7)	5.8 (2.5 - 13.3)
75%	2	3 (1.5 - 4.5)	7.68 (6.16 - 9.2)
100%	21	4.1 (1.1 - 26.8)	6.8 (1.1- 16)

Table 4: *Comparison of Lacosamide Final Dose with Effectiveness Among Different Groups.*

Type of Seizure	Effectiveness					
	0%	25%	50%	75%	100%	Total
Generalized Seizure						
Tonic - clonic	4	1	4	0	4	13
Myoclonic	2	0	1	0	0	3
Tonic	0	0	1	0	3	4
Partial Seizure						
Complex Partial	2	1	0	1	6	10
Focal	3	1	2	0	6	12
Mixed Seizure						
Multifocal	0	0	0	1	1	2
Multiple semiology	0	0	1	0	1	2
Total	11	3	9	2	21	46

Table 5: *Lacosamide Effectiveness by Seizure Type.*

The number of AEDs used was decreased in 42.8% of improved cases.

Fifteen (32.6%) patients had increase in the number of AEDs from 1 to 3 medications.

Eleven (23.9%) patients had no change in number of their AEDs even after adding Lacosamide.

Tolerability

Only seven (15.2%) patients developed adverse drug reactions (Table 6). Adverse drug reactions include increased or loss of appetite, weight loss, ataxia, nystagmus, behavioral problems as aggression, agitation, anger, anxiety and increase in seizure frequency. Comparison of Lacosamide maximum dose among patients with and without adverse reaction did not show any statistical significance (p-value 0.57).

Adverse Reaction	N = 46	Mean maximum dose mg/kg/day
Yes	7 (15.2%)	6.5 (2.7 - 14.5)
No	39 (84.8%)	6.1 (1.1 - 16)

Table 6: *Comparison of Lacosamide maximum dose among patients with and without adverse reaction.*

Two patients who reached 100% reduction in seizure developed behavioral problems (including aggression, agitation, anger, anxiety) and increased appetite. However, they continued the therapy. Other five patients didn't show any efficacy (0%) or improvement after starting Lacosamide. Three patients of them, discontinued Lacosamide as they could not tolerate the side effects; nervousness, increase in seizures frequency, loss of appetite, ataxia and nystagmus or increase in seizure frequency.

Discussion and Conclusion

The results of this study indicates that Lacosamide is a useful treatment option in children with refractory epilepsy as 76% of patients reported 25 - 100% seizure improvement. 45.7% of patients had full (100%) seizure control. Lacosamide showed a remarkable response in patients with complex partial seizure, focal epilepsy and generalized tonic-clonic seizure (GTC).

Initial dose ranged from 1 - 6.5 mg/kg/day divided to twice daily doses. Maximum maintenance dose reached 16 mg/kg/day (range 1.1 -16 mg/kg/day|) divided twice daily, while in the previous studies the final dose of Lacosamide was ranged between 1.7 and 10 mg/kg [8].

Eleven patients (23.9%) didn't report any improvement; four of them had no response even after adding other AEDs to Lacosamide. There is no clear relation between better response and high dose.

Patients on Lacosamide can develop tolerable adverse drug reactions including increase or loss of appetite, weight loss, behavioral problems (e.g. aggression, agitation, anger, and anxiety), ataxia and nystagmus. Although adverse effects were observed in 15.2% of patients in our study, these resulted to drug withdrawal only in 3 patients.

However, we were unable to confirm if there is a relationship or correlation between adverse effects and the dose. Indeed, the patient who received the highest dose (16 mg/kg/day) of Lacosamide did not experience any adverse effects, although one patient (max dose 1.7 mg/kg/day) discontinued the medication due to ataxia and nystagmus.

Lacosamide can be a cost effective medication for better seizure control as after initiation of treatment, the number of AEDs decreased by 2 - 3 medications in 42.8% of patients who had good seizure control after Lacosamide was started.

Thus, Lacosamide is a good option as an add-on therapy to other AEDs to achieve better seizure control in pediatric patients 17 years of age and younger.

This study shows ≥ 50% of seizure reduction in 70% of children during follow-up, adding more evidence towards efficacy of Lacosamide in pediatric epilepsy patients. Our study does not demonstrate a significant difference between responders and non-responders with respect to the patient's age, maximal maintenance dose attained and the number of previous and concomitant AEDs.

The study had limitations inherent to its design. The study design allowed for the potential that the results might be affected by bias. The relatively small number of patients limited the study power. In general, we can implement the results to the Saudi population as there is no conflict between our study and previous studies in pediatric patients with refractory epilepsy. Another limitation is that seizures within our patient population were grouped according to the clinical description and not by EEG classification of partial and generalized seizures, since Lacosamide has been proven to be effective in refractory partial epilepsy with or without secondary generalization. Larger studies are needed to identify the relation between response and doses, doses and adverse events, and to determine the best combinations of Lacosamide and other AEDs to achieve effective control of refractory epilepsy.

In conclusion, our study adds to the evidence that Lacosamide appears to be an effective and well-tolerated AED as adjunctive treatment in pediatric patients with refractory epilepsy.

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The authors have no conflicts of interest to declare.

The authors confirm that they have read and affirmed that this report is consistent with King Fahad Medical City IRF final report guidelines.

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