Original Article

Efficacy of Lacosamide Add-on Therapy on Refractory Focal Epilepsies in Children and Adolescents: An Open-Label Clinical Trial

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Abstract

Objective: Epilepsy is a chronic neurological disorder that affects 0.5%–1% of children. 30%–40% of patients are resistant to current anti-epileptic drugs. Lacosamide (LCM) appeared to be effective, safe, and well tolerated in children and adolescents. This study was aimed to evaluate whether LCM could be an effective add-on therapy in children with refractory focal epilepsies. **Methods:** This study was conducted from April 2020 to April 2021 in Imam Hossein Children Hospital, Isfahan, Iran. We included 44 children aged 6 months to 16 years with refractory focal epilepsy (based on International League Against Epilepsy criteria). LCM was given in divided doses of 2 mg/kg/day, increasing by 2 mg/kg every week. The first follow-up visit was 6 weeks later, when all patients had reached the therapeutic dose. **Findings:** The average age of the patients was 89.9 months. 72.5% of children had focal motor seizures. Evaluation of percent change in seizure frequency and duration before and after treatment showed a 53.22% reduction in seizure frequency and 43.72% reduction in seizure duration after treatment. Our study group tolerated LCM well, with few side effects. Headache, dizziness, and nausea were common side effects. In line with other studies, none of the suspected risk factors could predict response to LCM treatment. **Conclusion:** LCM appears to be an effective, safe, and well-tolerated medication in children with uncontrolled drug-resistant focal epilepsy.

Keywords: *Drug resistant epilepsy, Lacosamide, partial epilepsy, pediatrics*

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Introduction

Epilepsy is one of the most common chronic neurological disorders which affects 0.5%–1% of children.[1,2] Recent evidence indicates that 60% of patients might respond to standard medical treatment and achieve remission, nevertheless, 30%–40% of patients will be resistant to current anti-epileptic drugs (AEDs).[3,4] Patients with refractory epilepsies refer to those who failed to respond to at least two appropriately indicated and tolerated AEDs. Nonpharmacologic interventions such as epilepsy surgery, vagal nerve stimulation, and the ketogenic diet have limited indications, due to difficulty of administration and poor response rates among most patients.[5] Thus, this is the necessary to find a new and well-tolerated treatment to provide an optimal quality of life for these patients.

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Lacosamide (LCM) is a third-generation AED, currently, approved by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) for use in patients older than 16 (EMA) and 17 (FDA) years old.[6] While, yet there is growing evidence suggesting that LCM is effective, safe, and well-tolerated in children and adolescents. Although the mechanism of action of LCM is unknown, researchers suggest that it selectively enhances the slow inactivation of voltage-gated sodium channels. It is also thought to have a neuroprotective effect in the brain, preventing the formation of abnormal neuronal connections.[7-9] Unlike other sodium channel blockers, this mechanism

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reduces pathological hyperexcitability without affecting physiological activity. LCM has low drug-drug interaction and adverse effect profile, because of its unique method of action, lack of induction or inhibition by hepatic enzymes, low rate of binding to serum proteins, high renal clearance rates, and linear pharmacokinetics.[10]

LCM has 100% oral bioavailability and a very low plasma protein-binding rate (<15%); it is removed through metabolic biotransformation and urine excretion. It has a low drug-drug interaction and the most commonly observed adverse effects include dizziness, headache, diplopia, and nausea.[11]

We aimed to assess the efficacy of LCM as add-on therapy in children and adolescents with refractory focal epilepsy.

Methods

This study is an experimental study (a pre-post-trial) conducted from April 2020 to April 2021 in Imam Hossein Children Hospital, Isfahan, Iran. This study was approved by the Ethics Committee of Isfahan University of Medical Sciences.(Ethical approval ID: IR.MUI.MED.REC.1399.1163). We recruited all children, 6 months to 16 years of age, with refractory focal epilepsy, as defined by International League Against Epilepsy (ILAE) criteria.[12] We excluded children who were under the treatment of LCM at least for 2 months before our study. The demographic characteristics including age and gender, as well as the type of delivery and delivery complications, family history of epilepsy, history of children's neurodevelopmental delays (NDDs), age at seizure onset, type of epilepsy, epilepsy etiology, number of AEDs, and findings on patients' electroencephalogram (EEG), and magnetic resonance imaging (MRI), were collected. The etiology of epilepsy was classified according to the ILAE classification of epilepsies[13] and codified as genetic, structural/metabolic, and unknown. According to etiology, epilepsy was also considered as fixed (including genetic, structural as cortical malformations, infectious, and immune conditions) or progressive (including metabolic and structural as tumors). Seizure frequency was recorded in a diary commonly used in our epilepsy clinic and updated at each follow-up visit. Routine laboratory investigations and electroencephalogram (EEG) recordings, while awake and asleep were performed according to clinical indications. Seizure frequency at baseline was defined as the monthly number of seizures in the previous 3 months before starting LCM.

We administered LCM as an add-on therapy for all eligible children. Drug scheme administration consisted of a starting dose of LCM of 2 mg/kg/day in divided doses with 2 mg/kg increments every week, up to a maximum of 12 mg/kg/day, based on both age and weight. The first follow-up visit was held after 6 weeks when the therapeutic dose was reached in all patients, and then 3 months after the first visit.[14] In each visit, average frequency and duration of seizures, new adverse effects on LCM add-on therapy, or any discontinuation of LCM and the reason were recorded.

A reduction of monthly seizure frequency and seizure duration ≥75%, 50%–74%, 26%–49%, and ≤25% from baseline after reaching the target dose were considered as "complete response," "partial response," "poor response," and "no response," respectively. Finally, we consider a reduction of monthly seizure frequency and seizure duration ≥50% as responders.

Quantitative variables were reported in the form of mean and standard deviation and categorical variables were reported with frequencies and percentages. The normality of quantitative variables was evaluated using the Shapiro–Wilk test and histogram plot. The comparison of means between groups was performed using the analysis of variances and two-sample independent *t*-test. The comparison regarding qualitative variables was done using the Chi-square test or Fisher's exact test, when appropriate. The logistic regression model was used to evaluate the association between probable prognostic factors and dichotomous variable (being responder/nonresponder). Data analysis was performed using the SPSS software (IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY., USA). The significance level of tests was considered <0.05, otherwise stated.

Results

In this prospective study, we recruited 44 patients with refractory focal epilepsies. All of them were uncontrolled with more than one AEDs, satisfying the criteria for refractory seizures. Four patients were excluded from the study due to the lack of follow-up given the unresponsiveness of parents. Fifty-five percent of children were boys and average age of patients was 89.9 (45.18) months. On average, they experienced 63.8 (39.88) months of seizures, from the onset to their current age. The onset of seizures varied in different patients, but on average, it started from at 28.05 (34.15) months of age. Sixty-five percent of participants were born through cesarean section delivery and others were born through normal vaginal delivery. The rate of NDD (in any fields), positive family history of seizures, and NDD and complications at birth were 60, 42.5, and 20% across all the participants. Most of the participants showed focal motor seizures (72.5%).

Most of the patients had abnormal EEG (97.5%) and MRI findings (62.5%). The most common prescribed drugs (except for Locasamide that was prescribed for all the patients) for them clobazam (47.5%), valproate (40%), and Tegretol (27.5%) [Table 1].

As shown in Table 1, there was no statistically significant difference regarding aforementioned demographic and clinical characteristics of the patients between responder and nonresponder groups [Table 1].

Next, we assessed the treatment response based on the percent changes in the frequency and duration of seizures before and after treatment. There was a 53.22% reduction in average frequency of seizures and 43.7% decrease in average duration of seizures [Table 2]. Given the nonaccurate reports by the parents, we categorized the treatment responses into 5 groups including "Complete response," "partial response," "poor response," "no response" and "progression." However, there is one patient who worsen after addition of Locasamide to treatment regimen, the number of patients with complete response and no response, based on either frequency or duration of seizures, were considerable [Figure 1]. Hence, we categorized the patients into responders (having complete or partial response) and nonresponders (having poor response, no response, or progression) for further analysis.

Next, we assessed the probable prognostic factors for being responder to Locasamide treatment. As shown in Table 3, we used univariate logistic regression with being responder as dependent variable. As mentioned above, a responder is defined as more than 50% decrease in frequency or duration of seizures. None of the assessed factors were associated to being responder except for using more than three drugs (in addition to locasamide) that significantly associated to being nonresponder based on seizures frequency 0.220 (0.057–0.846) ($P = 0.028$). All the variables with $P < 0.2$ were entered into multivariate logistic regression models. None of the association was significant in multivariate models; therefore, none of the assessed risk factors could successfully predict responsiveness [Table 3].

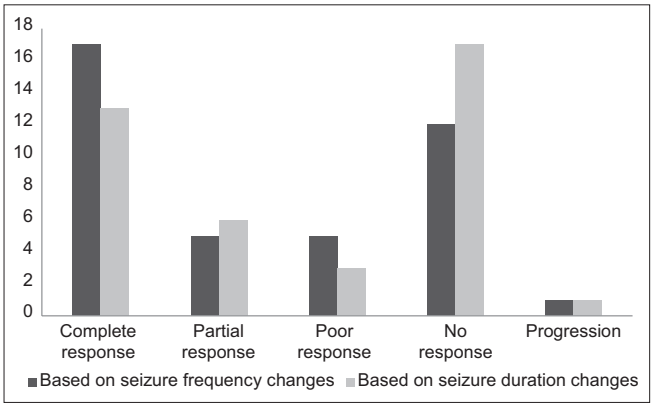

Figure 1: Response to Lacosamide add-on therapy in children and adolescents

Discussion

Our study evaluated the efficacy of adjunctive LCM therapy in a pediatric population. Nearly 44.8% of the 39 patients treated with LCM were responders based on seizure frequencies, also 48.56% of them were responders based on seizure duration. This result is consistent with Rosati *et al*.'s findings that over 44% of children and adolescents treated with LCM were responders.[15] Although LCM is used off-label in the pediatric population for the treatment of drug-resistant epilepsy, since 2010, various clinical trials have been focused on the benefits of LCM treatment in children. The mean response rate, defined as at least a 50% reduction in seizure frequency was between 30% and 84% in previous studies.[16-20] The results of a systematic review currently published showed that half of the patients had ≥50% reduction in seizure frequency at a mean follow-up of 10 months.[21] In addition, recent adult clinical trials showed that 35%–84.9% of adults with refractory seizures treated with LCM experienced a ≥50% reduction in seizure frequency.[22,23] Although almost all studies revealed a beneficial effect of LCM in 50% of patients with focal epilepsies, we found seizure worsening in one of our patients (2.56%). Ortiz de la Rosa *et al*. in their systematic review demonstrated that 17% of cases experienced worsened seizures following LCM add-on therapy.[21] All AEDs may theoretically have a paradoxical seizure-inducing effect in certain conditions. It is often difficult to distinguish between the effect of an AED and the natural course of the disease.[19]

We compared responders and nonresponders on the following variables: age, gender, type of delivery, delivery complications, history of NDD, family history of epilepsy, age of epilepsy onset, duration of epilepsy, type of epilepsy, etiology of epilepsy, EEG findings, MRI findings, and contaminant drugs; however, no statistically significant differences were detected between the two groups. Similar to our findings, the majority of studies concluded that there was no main factor affecting LCM efficacy in the pediatric population, while Toupin *et al*.[24] reported that females were more likely to respond to LCM than males in a study of 22 children with refractory epilepsy.

LCM has a nearly 100% oral bioavailability and a 15% plasma protein-binding rate. It is eliminated through metabolic biotransformation and urinary excretion.[11] It has been described as a safe and

Table 1: Patients' demographic and clinical characteristics

Variable	Clinical response based on seizure frequency		*P*	Clinical response based on seizure duration		*P*	Total, *n* (%)
	Nonresponder, *n* (%)	Responder, *n* (%)		Nonresponder, *n* (%)	Responder, *n* (%)		
Age (months), mean (SD)	92.33 (47.59)	86.82 (44.08)	0.706	84.33 (42.27)	94.79 (48.76)	0.472	89.9 (45.18)
Gender							
Male	8 (44.44)	14 (63.64)	0.225	10 (47.62)	12 (63.16)	0.324	22 (55)
Female	10 (55.56)	8 (36.36)		11 (52.38)	7 (36.84)		18 (45)
Delivery							
NVD	7 (38.89)	7 (31.82)	0.641	9 (42.86)	5 (26.32)	0.273	14 (35)
C/S	11 (61.11)	15 (68.18)		12 (57.14)	14 (73.68)		26 (65)
Delivery complication	4 (22.22)	4 (18.18)	0.751	6 (28.57)	2 (10.53)	0.154	8 (20)
NDD	13 (72.22)	11 (50)	0.154	15 (71.43)	9 (47.37)	0.121	24 (60)
Family history	6 (33.33)	11 (50)	0.289	9 (42.86)	8 (42.11)	0.962	17 (42.5)
Age of epilepsy onset (months), mean (SD)	31.72 (39.45)	25.06 (29.75)	0.546	27.39 (37.93)	28.79 (30.45)	0.898	28.05 (34.15)
Duration of epilepsy (months), mean (SD)	66.39 (39.38)	61.68 (41.09)	0.716	61.9 (31.95)	65.89 (47.99)	0.762	63.8 (39.88)
Type of epilepsy							
Motor	13 (72.22)	16 (72.73)	0.330	15 (71.43)	14 (73.68)	0.073	29 (72.5)
Nonmotor	2 (11.11)	5 (22.73)		2 (9.52)	5 (26.32)		7 (17.5)
Mixed	3 (16.67)	1 (4.55)		4 (19.05)	0		4 (10)
Etiology							
Genetic	2 (11.11)	4 (19.05)	0.821	3 (14.29)	3 (16.67)	0.970	6 (15)
Metabolic/structural	4 (22.22)	6 (28.57)		5 (23.81)	5 (27.78)		10 (25)
Unknown	7 (38.89)	6 (28.57)		7 (33.33)	6 (33.33)		13 (32.5)
Perinatal insult	5 (27.78)	5 (23.81)		6 (28.57)	4 (22.22)		10 (25)
EEG finding							
Normal	0	1 (4.55)	0.091	0	1 (5.26)	0.449	1 (2.5)
Mild/moderate abnormal	13 (72.22)	20 (90.91)		17 (80.95)	16 (84.21)		33 (82.5)
Definitive abnormal	5 (27.78)	1 (4.55)		4 (19.05)	2 (10.53)		6 (15)
MRI finding							
Normal	6 (33.33)	9 (40.91)	0.175	8 (38.10)	7 (36.84)	0.368	15 (37.5)
Structural/genetic	4 (22.22)	9 (40.91)		5 (23.81)	8 (42.11)		13 (32.5)
Acquired/traumatic	8 (44.44)	4 (18.18)		8 (38.10)	4 (21.05)		12 (30)
Concomitant AEDs							
Clobazam	11 (27.5)	8 (20)		13 (32.5)	6 (15)		19 (47.5)
Valproate	9 (22.5)	7 (17.5)		9 (22.5)	7 (17.5)		16 (40)
Tegretol	5 (12.5)	6 (15)		5 (12.5)	6 (15)		11 (27.5)
Levetiracetam	6 (15)	4 (10)		6 (15)	4 (10)		10 (25)
Topiramate	6 (15)	3 (7.5)		6 (15)	3 (7.5)		9 (22.5)
Lamotrigine	3 (7.5)	3 (7.5)		3 (7.5)	3 (7.5)		6 (15)
Phenobarbital	3 (7.5)	2 (5)		4 (10)	1 (2.5)		5 (12.5)
Clonazepam	2 (5)	3 (7.5)		2 (5)	3 (7.5)		5 (12.5)
Carbamazepine	1 (2.5)	3 (7.5)		3 (7.5)	1 (2.5)		4 (10)
Ketogenic diet	0	3 (7.5)		1 (2.5)	2 (5)		3 (7.5)
Phenytoin	1 (2.5)	2 (5)		1 (2.5)	2 (5)		3 (7.5)
Oxcarbazepine	1 (2.5)	2 (5)		1 (2.5)	2 (5)		3 (7.5)
Pregabalin	2 (5)	0		2 (5)	0		2 (5)
Prednisolone	2 (5)	0		2 (5)	0		2 (5)
Primidone	2 (5)	0		1 (2.5)	1 (2.5)		2 (5)
Ethosuximide	2 (5)	0		1 (2.5)	1 (2.5)		2 (5)
Nitrazepam	1 (2.5)	1 (2.5)		1 (2.5)	1 (2.5)		2 (5)
ACTH	1 (2.5)	0		1 (2.5)	0		1 (2.5)

EEG=Electroencephalogram, MRI=Magnetic resonance imaging, NDD=Neurodevelopmental delays, AEDs=Anti-epileptic drugs, NVD=Natural vaginal delivery, ACTH=Adrenocorticotropic hormone, SD=Standard deviation

well-tolerated medication. Although the absence of pharmacokinetic interaction is well documented, with only one decade of use, the potential drug-drug interactions are yet to be described. In adult studies, the common adverse effects were dose-dependent and reversible with dose reduction or interruption.[25] Numerous adult and childhood studies established that the adverse effects mainly involve the gastrointestinal and nervous systems. The main reported side effects were headache, dizziness, and nausea in up to 50% of children receiving LCM therapy. Moreover, ataxia, fatigue, vertigo, vision abnormalities, nystagmus, coordination, and gait problems were reported.[23,26,27] LCM was well-tolerated in our study group and the majority of the children reported no side effects. A 4.5-year-old boy with an unknown etiology of focal epilepsy had a significant increase in seizure frequencies which led to discontinuing the treatment. In addition, two 5-year-old girl with cerebral palsy and unknown etiology of epilepsy had fatigue and dizziness. Furthermore, inconsolable crying with no other apparent reason within nausea was reported in two 3.5-year-old and 5-year-old girls.

Table 2: Clinical response based on seizure frequency and duration

	Based on seizure frequency changes	Based on seizure duration changes
Percent of improvement, mean (SD)	53.22 (43.5)	43.7 (45.48)
Clinical response, count (%)		
Complete response	17 (42.5)	13 (32.5)
Partial response	5 (12.5)	6 (15)
Poor response	5 (12.5)	3 (7.5)
No response	12 (30)	17 (42.5)
Progression	1 (2.5)	1 (2.5)

SD=Standard deviation

Table 3: Univariate logistic regression analysis of patient's responses based on seizure frequency and duration

Variable	Responder based on seizure frequency	Responder based on seizure duration
Age (months)	0.997 (0.983-1.011)	1.005 (0.991-1.020)
Gender (reference: Female)	2.188 (0.613-7.808)	1.886 (0.532-6.687)
Delivery (reference: NVD)	1.364 (0.370-5.028)	2.100 (0.551-8.002)
Delivery complication (reference: Negative)	0.778 (0.165-3.672)	0.294 (0.051-1.683)*
NDD (reference: Negative)	0.385 (0.102-1.451)*	0.360 (0.097-1.330)*
Family history (reference: Negative)	2.000 (0.552-7.251)	0.970 (0.276-3.403)
Age of epilepsy onset (months)	0.994 (0.976-1.013)	1.001 (0.983-1.020)
Duration of epilepsy (months)	0.997 (0.981-1.013)	1.003 (0.987-1.019)
Type of epilepsy		
Motor	Reference	Reference
Nonmotor	2.031 (0.337-12.236)	2.679 (0.445-16.112)
Mixed	0.271 (0.025-2.922)	N/A
Etiology		
Genetic	Reference	Reference
Metabolic/structural	0.750 (0.090-6.230)	1.000 (0.132-7.570)
Unknown	0.429 (0.057-3.222)	0.857 (0.124-5.944)
Perinatal insult	0.500 (0.061-4.091)	0.667 (0.087-5.127)
EEG finding		
Normal	N/A	N/A
Mild/moderate abnormal	7.692 (0.805-73.549)*	1.882 (0.302-11.729)
Definitive abnormal	Reference	Reference
MRI finding		
Normal	Reference	Reference
Structural/genetic	1.500 (0.313-7.186)	1.829 (0.404-8.270)
Acquired/traumatic	0.333 (0.068-1.624)*	0.571 (0.119-2.751)
Number of drugs at seizure control (>4)	0.220 (0.057-0.846)**	0.448 (0.126-1.589)
Contaminant AEDs		
Ketogenic diet	N/A	2.353 (0.196-28.266)
Carbamazepine	2.684 (0.254-28.311)	0.333 (0.032-3.515)
Oxcarbazepine	1.700 (0.142-20.422)	2.353 (0.196-28.266)
Levetiracetam	0.444 (0.103-1.915)	0.667 (0.156-2.852)

*P<0.2 (All the variables with P < 0.2 were entered into multivariate logistic regression models), **P<0.05. N/A=Not applicable, EEG=Electroencephalogram, MRI=Magnetic resonance imaging, NDD=Neurodevelopmental delays, AEDs=Anti-epileptic drugs, NVD=Natural vaginal delivery, SD=Standard deviation

To the best of our knowledge, this study is the first study evaluating LCM in an Iranian pediatric population. Furthermore, we tried to collect the data on a wide variety of factors that might be associated with response to LCM add-on therapy. However, despite determining the sample size through power analysis and a comprehensive review of previous studies in our study, the higher sample size could help detecting probable associations and differences.

This pre-post-trial confirmed that LCM appears to be an effective, safe, and well-tolerated medication in children with uncontrolled drug-resistant focal epilepsy. A significant response was seen after the 6 months of the treatment course. Further studies are needed to validate the use of LCM as a first-line and widely prescribed AED for the treatment of focal epilepsy in children and adolescents.

Authors' Contribution

TM and JN contributed to the study conception and design. Material preparation and data collection were performed by TM, JN, OY, MG, and NH. Data analysis was performed by TM The first draft of the manuscript was written by TM and then critically revised by JN. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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