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Original Article

"EFFECT OF LACOSAMIDE ON BEHAVIOUR OF CHILDREN WITH REFRACTORY PARTIAL EPILEPSY"

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ABSTRACT

Objective: A unicentre, prospective study was carried out to investigate the behavioral effects of lacosamide as adjunctive therapy with refractory partial epileptic children in tertiary care hospital with prior approval from the Institutional Human Ethical Committee.

Methods: Seventy nine patients (age 5- 15 years) with refractory partial epilepsy patients were enrolled after fulfilling the inclusion and exclusion criteria. And those who had failed≥ 2 antiepileptic drugs in whom lacosamide was added as add on drug therapy. Lacosamide tablets was administered orally twice daily. Influence of Lacosamide on children's behaviour was performed at every visit of titration, maintenance period and 2 follow ups at monthly interval. Patient's caregiver or investigator observed adverse events were recorded.

Results: Out of 79 patient's, 53 were males and 26 females. Patients completing 3 months, of study therapy showed significant ($p<0.001$) decrease in frequency of seizure and improvement in behaviour at end of the treatment period and few patients had mild transient adverse events. Three patients were dropped from the study.

Conclusion: Lacosamide signifies a beneficial drug that is effective and concurrently improved patient's behaviour in refractory partial epilepsy paediatric patients.

Keywords: Inclusion, Behavior, Prospective study, Lacosamide, Influence.

INTRODUCTION

Epilepsy is a neurological disorder characterized by recurring seizures and is generally defined by two or more unprovoked seizures with abnormal and excessive discharge from set of neurons in the brain. The condition comprises different seizure types and syndromes [1-2]. This has created complexities in establishing the incidence and prevalence and prognosis of epilepsy [3]. It was estimated that the risk of premature death among individuals with epilepsy is 2–3 times higher than in the general population [4]. There may be about 5-10 million people with epilepsy (PWE) in India accounting for almost one-fifth of the global figures [5]. Many people die each year from causes directly related to epilepsy. Around half of these are due to sudden unexpected death in epilepsy (SUDEP). However, establishing the exact number and nature of epilepsy-related deaths from national data is difficult [6].

Prevalence increased over the age-span in both sexes, although was higher in men over 55 years old than in women of the same age group. Prevalence was <2 per 1000 in the under 5-years-old age group increasing to over 4 per 1000 in 5–15 years old and also increased to 15.1 per 1000 in men and to 11.0 per 1000 in women aged ≥ 85 years. This confirms earlier findings that incidence and prevalence is highest in the elderly population [7, 8].

Epilepsy does not have one underlying cause. Attributable cause in adults include hippocampal sclerosis, cortical dysgenesis, vascular insults, head injuries and drug or alcohol abuse [9]. Onset of epilepsy can occur at any age, but is most common during childhood or older age. Not all patients with seizures develop the chronic condition; some children have seizures that do not progress into adulthood and some adults may experience remission.

The most commonly used AED (antiepileptic drugs) are carbamazepine, valporic acid and phenytoin [9, 10]. The newer drugs are licensed for adjunctive therapy only lacosamide (LCM), lamotrigine (LTG) and oxcarbamazepine (OXC) are licensed for monotherapy or adjunctive therapy [11]. Despite the introduction of several new antiepileptic drugs (AEDs) over the past 20 years, about 30% of patients with epilepsy become refractory to current treatments or experience significant adverse events [12-14]. Therefore, attempts are being made to identify novel drugs therapies that reduces the seizure frequency and may improve patient's quality of life. Lacosamide pharmacokinetic-pharmacodynamics (efficacy) analysis was performed based on the pooled data from the 3 efficacy trials for partial-onset seizures. Lacosamide exposure is correlated with the reduction in seizure frequency [15]. Lacosamide showed favourable pharmacokinetics properties, a low potential for drug - drug interactions and is thus well suited for polytherapy and use in children [16]. Although it is not approved for use in children, but have an active role in the management of pediatric epilepsy because of focal seizures are the most common seizure in children [17]. The goal of the present prospective study was to assess the influence of lacosamide on behaviour of children with refractory partial epilepsy using Connor's rating scale index [18]. It was part of our study on effect and tolerability of lacosamide in children with refractory partial epilepsy [19].

MATERIALS AND METHODS

Patients

This is an open label study, out of 531 screened patients, 79 patients were enrolled and 3 (3.79%) patients were dropped from the study. 76(96.20%) patients completed the titration, maintenance period with two follow up period of one month each.

Study design

This is a prospective study carried out for a period of 30 months. Prior approval from the Institutional Human Ethics Committee was obtained. In this study all patients or their legal representatives gave written informed consent before trial participation. Patients were enrolled based on inclusion criteria of those aged between 5-15 years with uncontrolled focal epilepsy, who have had at least 3 months duration of epileptic seizures and not controlled after sequential or additives use of at-least two Antiepileptic drugs (AEDs). Diagnosis of seizures and epileptic syndromes was based on the classification of Epileptic seizures (Commission on Classification

and Terminology of the International League against Epilepsy 2011 [20] after going through their electroencephalography (EEG) reports and or either magnetic resonance imaging (MRI).

Lacosamide was administered orally in the form of tablets with increment dose of 25mg twice a week followed by 50mg twice a day for the remaining period. During the study period, in case of any adverse event or any discrepancies, patient were said to report or call principal investigator (PI).

Study assessments

Routine examinations of vital signs, body weight, physical and neurologic examinations were done at every visit. Plasma samples were drawn to investigate transaminase (SGOT/SGPT) levels, electroencephalogram (EEG) and electrocardiogram (ECG) were recorded.

Patients were categorized based on etiological classification idiopathic/genetic, structural/metabolic and cryptogenic/ unknown. Seizure type was based on the semiology, EEG findings (temporal epilepsy, focal lobe epilepsy, occipital lobe epilepsy, centro-temporal epilepsy, multifocal and others).

In our study, we also measured tolerability based on global 5 point scale (score of 5 was given when there was decrease in side effects; a score of 4 when there were no side effects; score of 3 when there was one new side effect; score of 2 when there were 2-3 side and score of 1 when there were > 3 side effects). Patients who were unable to tolerate protocol medication and those experiencing adverse effects were made to discontinue treatment.

Attenders/caretakers were provided with record diary card, which captures the details of per month treatment days, seizure occurrence, loss of consciousness, total number of seizure for 24 hours, duration of seizure and medication taken in the morning and evening, from the beginning of titration period till last evaluation.

Statistical analysis

Outcome of lacosamide in refractory partial epilepsy was measured using SPSS 20.0 for Windows (IBM Corporation, Armonk, NY, USA) was used for the statistical analysis. Statistical significance was set at $p < 0.05$.

RESULTS

Patient disposition

Out of 531 screened patients, 79 patients were enrolled with intention to treat (ITT). 76(96.2%) patients completed 3 months of maintenance period. Three (3.79%) patientsdropped from the study. One (1.26%) patients developed severe hyperactivity and behavioural changes and other two (2.53%) withdrew from the study because of vomiting and lack of seizure control as shown in Table 1**.**

Demographics data and patient characteristics

The clinical characteristics of 79 patients with refractory partial epilepsy are presented in Table 2. Patient mean age was 8.84±3.09years with age range of 5 - 15years; of which 53 (67%) maleand 26 (32.9%) females with mean weight of 24.44±9.84. The mean age at epilepsy onset in males 6.46±3.49 and females 6.38±3.39. Forty nine (62.02%) patients continued investigational drug even after end of the study (EOS) treatment period was and 30 (37.9%) stopped afterend of the study (EOS).

Table 1: Patient disposition

S. No.	Study details	Value
1	No. of patient enrolled	79
2	No. of patients completed during study period	76 (96.2%)
3	Patients completed 3 months of treatment duration	46 (58.2%)
4	No. of patients continued even after treatment period	30 (37.9%)
5	No. of patients discontinued the study	3 (3.79%)

Table 2: Demographic data and patient characteristics

S. No.	Characteristics	Value
1.	**Age, year**	8.84±3.09
2.	**Sex, n** (mean±SD)	
	Male (53)	8.93±3.09
	Female (26)	8.65±3.31
3.	**Weight,** Kg (mean±SD)	24.44±9.84
4.	**Follow up Duration on Lacosamide**	
	Continued	49 (62.02%)
	Discontinued	30 (37.97%)
5.	**Onset of Seizure(mean±SD)**	
	Males	6.46±3.57
	Females	6.38± 3.39

Table 3: Drugs -Antiepileptic therapy process

S. No.	Antiepileptic Drugs	n (%)
1.	LCM + SVA	19 (24%)
2.	LCM + SVA + 1AED	17 (21.5%)
3.	LCM + SVA + 2AED	3 (3.8%)
4.	LCM + LMT	1 (1.3%)
5.	LCM + LMT + 1AED	2 (2.53%)
6.	LCM + LEV + 1AED	7 (8.9%)
7.	LCM + LEV + 2AED	2 (2.5%)
8.	LCM + CBZ	6 (7.6%)
9.	LCM + CBZ + 1AED	5 (6.3%)
10.	LCM + CBZ + 2AED	1 (1.3%)
11.	LCM + 1AED	12 (15.1%)
12.	LCM + 2AED	4 (5.06%)

Co-administered Drugs: SVA: sodium volporic Acid, CBZ: Carbmazepine, LMT: Lamotrigine LEV: Levetiracetam, Other Antiepileptic drugs (AEDs)includes: CLB: Clobazam, OXC: Oxcarbamazepine, TPM: Topiramate, PHT: Phenytoin, ZNS: Zonisamide, PB: Phenobarbitone, CNZ: Clonazepam, NPM: Nitrazepam.

During the study period, concomitant administration of one or more antiepileptic drug (AED) along with lacosamide (LCM) was evaluated. Lacosamide with sodium valporic acid (SVA) was 24%, followed by addition of another AED drug was 21.5% and two AED was 3.8% respectively, was used in highest consumed drug in this study period, when compared to other co-administered AED. Lacosamide with one AED was 15.1% showed second highest consumed drug during the study period. Remaining AED drugs along with LCM are shown in Table 3.

Co-administered AED drugs Includes

SVA: Sodium valporate, CLB: Clobazam, CBZ: Carbmazepine, OXC: Oxcarbamazepine, LMT: Lamotrigine LEV: Levetiracetam, TPM: Topiramate, PHT: Phenytoin, ZNS: Zonisamide, PB: Phenobarbitone, CNZ: Clonazepam, NPM: Nitrazepam. LCM: Lacosamide

Diseases and Drug characteristics with behavior of children

As shown in Table 4, among the study population, majority of the patients 30 (38.1%) had occipital lobe of epilepsy, followed by frontal lobe epilepsy in 20 (25.3%) patients. Based on etiological classification 19(24.1%) with idiopathic/genetic, 50(63.3%) with structural/metabolic and 10(12.7%) patients with cryptogenic/ unknown.

The behavioural life of the remaining 76 patients was assessed using 25 item questionnaire that was filled by parents/ care takers/ attenders. Mean total scores at baseline was 48.04 ± 10.57**;** after 3 month of maintenance period, mean behavioral life was 19.27 ± 08.03 and subsequent follow up visit was. The scores improved significantly with treatment (ANOVA test with P < 0.001). The behavioural scores remained relatively constant from baseline to treatment period to all subsequent follow up visits was 19.05 ± 05.29.

Table 4: Diseases and Drug characteristics

S. No.	Clinical Findings	Values	
		Males	Females
1	**Seizure Type**		
	Temporal Lobe Epilepsy	3 (5.8%)	1 (3.84%)
	Frontal Lobe Epilepsy	13 (25.0%)	7 (26.6%)
	Occipital Lobe Epilepsy	24 (44.2%)	6 (23.0%)
	Centro temporal Epilepsy	01 (1.9%)	3 (11.5%)
	Multifocal	06 (11.5%)	9 (34.5%)
	Others	06 (11.5%)	0 (0.0%)
2	**Tolerability**		
	0	03 (3.8%)	
	1	04 (5.1%)	
	2	11 (13.9%)	
	3	32 (40.5%)	
	4	27 (34.2%)	
	5	02 (2.5%)	
3	**Seizure frequency per 28 days:**		
	Mean ± SD - Baseline	13.3 ± 24.11	
	End of the study seizure frequency:		
	Mean ± SD	4.53 ± 13.22	
	% Reduction (p<0.001)#:	59.9 ± 99.9	
4	**Connors Comprehensive Behaviour Rating Scale**		
	Baseline - Mean ± SD	48.04 ± 10.57	
	End of the study **-** Mean ± SD*	19.27 ± 08.03	
	Follow Up*	19.05 ± 05.29	

#p<0.001, showed significant difference using Wilcoxson signed ranks test., *P < 0.001, showed significant difference using ANOVA test

Efficacy and tolerability

At the end of the study (EOS), 76 patients entered the maintenance period with a mean reduction in seizure frequency per 28 days from 13.35 ± 24.12 at baseline to 4.53 ± 13.23 at the EOS (Wilcoxson signed ranked test p < 0.001). At the end of the follow up period, mean reduction in seizure was 3.9 ± 11.81 as shown in Table 4.

Tolerability was assessed by investigator and patients at the last visit on a 5 point scale. Two (2.5%) patients had reduction in side effects after lacosamide therapy; 27 (34.2%) did not have any new side effects. Thirty two patients (40.5%) had one new side effect while 11 patients (13.9%) had 2-3 side effects. Four of our patients (5.1%), developed more than 3 side effects as shown in Table 4.

Adverse effects

The common adverse events were hyperactivity, ataxia, drowsiness, insomnia, weight gain, nausea, abdominal discomfort, giddiness, headache, and vomiting. Most of the reported side effects were mild to moderate in intensity and did not need discontinuation of treatment. Overall results of clinical laboratory tests, physical examinations, neurological examinations and assessments of vital signs did not reveal any changes with lacosamide treatment.

Lacosamide was withdrawn in three patients (3.79%). Reasons for discontinuation were unsatisfactory seizure control (one patient) and aggressive behavior (one patient) during the titration and one patient had severe vomiting.

DISCUSSION

This prospective demonstrates that adjunctive therapy with twice-daily dose of up to 50mg of oral lacosamide not only reduces seizure frequency with better safety profiles and fewer side effects in pediatric patients with uncontrolled epilepsy. The study confirms the clinical efficacy and tolerability of lacosamide in refractory epilepsy and corroborates findings from previous studies.

In randomized controlled trials conducted in adults, lacosamide has shown to be an effective and safe AED in treating refractory seizures, with 30-40% of patients achieving ≥ 50% reduction in seizure frequency at doses of 400-600 mg/day [20-23].

In a multicenter, prospective study by Verrotti et al. (2013) compared lacosamide in pediatrics and adults. A total of 118 patients (59 group A, 59 group B) with uncontrolled generalized and focal epilepsy were enrolled. At 3-month evaluation, 118 treated patients 56 subjects (47.4% group A; 47.4% group B; p = 0.8537) experienced at least 50% reduction in seizure frequency respectively [15].

Diagnosis criteria used in our epilepsy study is similar to previous studies evaluating lacosamide therapy in children [20-22,24] . butwith large sample size.

In our study, we compared baseline seizure frequency with 2 month of maintenance period, end of the study (EOS) and after 2 follow ups. It was found that at 2 months of the treatment period the mean % reduction in seizure was 50.2($p<0.001$) and at the end of the study there was increase in mean reduction of seizure from baseline to 59.9% ($p<0.001$). At the end of two months follow ups period the mean reduction found to be 67.5% ($p<0.001$).

Lacosamide has been reported to be a well-tolerated, relatively safe drug [25]. Adverse reactions, such as dizziness, headache, diplopia, nausea and somnolence, drowsiness, dizziness observed in pediatric case reports and case series [25-28]. Adverse events were noted in half of our subjects. The most common adverse event observed in our study were almost congruent with those reported by Gavatha et al (2011). Adverse effects seen with lacosamide in adults are dose-related [25] and reversible upon discontinuation or dose reduction.

Lacosamide was discontinued in only one patient (1.26%) because of severe hyperactivity, aggression and inattention one week after starting the drug. It continued for one month till the drug was continued and the behavioral symptoms reverted back to normal status after the drug was stopped [29] and remaining two (2.53%) were withdrawn from study due to vomiting and lack of seizure control.

CONCLUSION

In conclusion, lacosamide is one of the newest additional drug to the AED category and represent a possible option, currently indicated for refractory partial epilepsy. Lacosamide showed favorable safety, tolerability profile with no increase in seizure frequency and improved children behavior during the study period.

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None

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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