

Efficacy and Safety of Levetiracetam in Refractory Seizures in Children

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ABSTRACT

Objective: To assess efficacy and safety of Levetiracetam (LEV) as add-on therapy in children with refractory seizure.

Methodology: This prospective observational cohort study was conducted in the Outpatient Department of Paediatric Neurology, "The Children's Hospital & Institute of Child Health, Multan", Pakistan from 15th January 2020 to 14th January 2021. Fifty children of aged 2 months to 14 years of both genders with refractory epilepsy were enrolled and received oral LEV. Data on LEV efficacy and side effects were recorded. The medication was considered as "effective" when all seizures had ceased within 3 months, "partially effective" when seizure frequency was decreased by $\geq 50\%$ and "ineffective" when seizure frequency was decreased by $< 50\%$ or seizure frequency remain unchanged during a period of 3 month.

Results: Out of a total of 50 participants, there were 35 (70.0%) male. Mean age was 4.81 ± 3.79 years while mean age at onset of seizures was 2.51 ± 2.85 years. Most frequent type of seizures was generalized tonic clonic seizures in 19 (38.0%) patients followed by focal clonic seizures in 13 (26.0%) patients. Levetiracetam was effective in 14 (28%) patients, partially effective in 24 (48.0%) and not effective in 12 (24.0%) patients.

Conclusion: Levetiracetam as add-on therapy reduced the seizure frequency in 76% of the participants without any significant side effects.

Keywords: Levetiracetam, refractory seizure, epilepsy, add-on therapy, efficacy.

INTRODUCTION

Considering neurological diseases, epilepsy is the commonest yet non transmissible disorder by which roughly 0.6-0.8% of the general public is affected.¹⁻³ Majority of the epileptic children attain respectable seizure regulation by the use of anti-seizure medicines, but some of them are unmanageable even after the use of several other medicines. Usually, if two or more medications fail to respond and one or more seizures occur every month for about 18 months then it is labeled as refractory seizures, happening in 20-30% of the epileptic children.⁴ While treating epilepsy, most of the time the ineffectiveness of the medication is quite evident in the beginning. But there have not been standards in medicine to define this drug-resistant epilepsy. It is very important to diagnose the intractable epilepsy as early as possible, so that further suitable treatments could be started to treat the patient.⁵

Although, the mortality in the drug-resistant epileptic patients, is about 5-15 times higher as compared to general public,⁶⁻⁹ but once patients get free of seizures, the rates become comparable to the general public.¹⁰⁻¹² Hence, in order to get rid of seizures and broaden the life span, particularly of the pediatric patients, as they are expected to live longer, curative perspective is needed.¹³ Traditionally, phenobarbital and phenytoin are exclusively used to treat refractory epilepsy but only 50%-80% of the patients are comprehensively managed by these drugs.¹⁴ It is a matter of concern that in the long run, some negative effects are associated with phenobarbital as observed in animals that there was an increase in neuronal apoptosis and in children induced cognitive impairment.^{15,16}

To treat epilepsy of various kinds, an antiepileptic drug (AED), levetiracetam (LEV) has extensively been used over the past few years. While treating partial onset, myoclonic, and/or primary generalized tonic-clonic seizures, its usage is as adjuvant therapy.¹⁷⁻¹⁹ Among the doctors it was fascinating to use LEV due to the features like minimum of its metabolism through liver, less chances of drug interaction, effective against seizures of many kinds, and it enabled the start of effective dose from the first day.²⁰ The accurate mode of action in epilepsy is not known, however, this drug gets bound to a synaptic vesicle protein, SV2A, as it is thought that it is responsible for the conduction through synapses.²¹ As uncontrolled seizures in children is matter of serious concern and has very poor prognosis so we planned this study with the aim to assess efficacy and safety of Levetiracetam in refractory seizure in pediatrics.

METHODOLOGY

This prospective observational cohort study was done at the Outpatient Department of Paediatric Neurology, The Children's Hospital & Institute of Child Health, Multan, Pakistan from 15th January 2020 to 14th January 2021. Inclusion criteria were children of both genders aged 2 months to 14 years with refractory epilepsy. Children with progressive neurological disorders were excluded. Children with hematological disorders or endocrine disorders were also not included. Refractory epilepsy was labeled as recurrent seizures that failed to respond to at least 2 appropriate AEDs used in combination, despite using the maximum dosage, or dosage resulting in therapeutic drug levels. Approval from "Institutional Ethics Committee of The Children's Hospital & Institute of Child Health, Multan", Pakistan was sought (Letter number ERC/2020/93). Informed and written consents were taken from parents/caregivers.

Seizures were classified in accordance with the "International League against Epilepsy" classification. Levetiracetam was initially administered 2 times a day with a starting dose of 10-20 mg/kg per day. Further doses were titrated weekly until cases were seizure-free or till the maximum dose. The patients were monitored clinically monthly for at least 6 months after starting of LEV. Clinical response to the treatment was evaluated by the comparison of seizure frequency in the preceding 3 months and following LEV treatment initiation, respectively. The medication was considered as "effective" when all seizures had ceased within 3 months, "partially effective" when seizure frequency was decreased by $\geq 50\%$ and "ineffective" when seizure frequency was decreased by $< 50\%$ or seizure frequency remain unchanged during a period of 3 month. For data analysis, "Statistical Package for the Social Sciences (SPSS)" version 26.0 was used.

RESULTS

Out of a total of 50 children, mean age was 4.80 ± 3.80 years (ranging from 2 months to 14 years) while mean age of onset of seizures was 2.51 ± 2.85 years. Majority of the patients, 35 (70.0%) were male. Mental retardation was observed in 31 (62.0%) patients. Daily episodes of seizures were reported in 33 (66.0%) patients while 2 (4.0%) had weekly, 1 (2.0%) bimonthly and 14 (28.0%) patients had monthly episodes of seizures. Table-1 is showing baseline characteristics of all the patients.

Table-1: Characteristics of Patients with Refractory Seizures

Variable	No. of Patients	%
Gender		
Male	35	70.0
Female	15	30.0
Age Groups		
6 months to 5 years	29	58.0
6 years to 10 years	16	32.0
11 years to 14 years	5	10.0
Mental Retardation		
Positive	31	62.0
Negative	19	38.0
Family History of Seizures		
Yes	14	28.0
No	36	72.0
Seizure Frequency Before adding Levetiracetam		
Daily	33	66.0
Weekly	2	4.0
Bimonthly	1	2.0
Monthly	14	28.0
Descriptive	Mean	±S.D.
Age of the patients (years)	4.80	3.80
Age at onset of seizures	2.51	2.85

Most frequent type of seizures was generalized tonic clonic seizures present in 19 (38.0%) patients followed by focal clonic seizures present in 13 (26.0%) patients, myoclonic and atonic seizures were evident in 4 (8.0%) and 2 (4.0%) patients respectively. Other type of seizures including absence seizures, complex partial seizures and mixed type were present in 12 (24.0%) patients (Table-2).

Table-2: Types of Seizures

Type of Seizures	No. of Patients	%age
Generalized Tonic Clonic	19	38.0
Focal Clonic	13	26.0
Myoclonic	4	8.0
Atonic	2	4.0
Others (mixture of fits)	12	24.0
Total	50	100%

Levetiracetam was effective in 14 (28.0%) patients, partially effective in 24 (48.0%) and not effective in 12 (24.0%) patients (table-3). Adverse effects of LEV were evident in 3 (6.0%) patients only while 47 (94.0%) had no adverse effects (Table-3).

Table-3: Efficacy and Adverse Effects of Levetiracetam

Outcomes	No. of Patients	%age	
Efficacy	Effective	14	28.0
	Partially effective	24	48.0
	Not effective	12	24.0
Adverse Effects	Irritability	2	4.0
	Hyperactivity	1	2.0
	No side effect	47	94.0

DISCUSSION

In the patients presenting intractable epilepsy, the usage of the newly discovered antiepileptic medicines has shown improvement in seizure outcome and it seems that their tolerability is also far better than of the previously used antiepileptic drugs (AEDs).^{17,18} Now a days, among the frequently used innovative AEDs, levetiracetam LEV is one of them to treat epilepsy in children. We find it to have linear pharmacokinetics, nearly complete absorption through oral route and an insignificant metabolism, and the chances of its interaction with other AEDs are rare. The execution of this study made us to evaluate effectiveness and safety of LEV as an adjuvant therapy for the treatment of refractory seizure in children. There are similarities between our study results and the findings of the existing literature. In Saudi Arabia, Ahmed A. Elberry and Associates conducted a study and found that generalized tonic-clonic (59%) and tonic seizure (27%) were the major seizure types when they studied 22 patients.²² It is quite

evident from the results that it took near about 7 months to 1 year for the patients (45%) to become seizure free. Normalized EEG was observed in patients (80%) out of 10 patients. The reduction of the seizure frequency was noted in patients (41%) and seizures continued in patients (14%). Only one patient came out to be with side effects among all patients who were treated with LEV. It was established by the researchers that to treat epilepsy in children, more specifically tonic-clonic seizure, LEV might be productive when given concomitantly, showing less incidence of side effects. According to another study, when patients were treated with LEV as a single drug, the retention rate for the drug at 3 months was (66%) and at 12 months, it was (63%).²³ The patients with idiopathic epilepsy were (47%) and with symptomatic-cryptogenic epilepsy (53%). In 65% of the patients the rate of seizure reduction was more than 90% and in 14% of the patients the rate of seizure reduction was 50-90%, 3 months after the treatment. In the same way, after 12 months of treatment, more than 90% rate of seizure reduction was observed in 63% of the patients, and in 15% patients it was in-between 50-90%. In 47% of the patients, satisfactory EEG signals (normal EEG) were acquired. Only 17% of the patients were reported with adverse events. Commonly observed side effects were irritability (67%), hyperactivity (8%), somnolence (6%), behavioral changes (5%), restlessness (5%), increased seizure frequency (3%), enuresis (2%), headache (2%) and attempts to commit suicide (2%). In the treatment of partial and generalized seizures, extraordinary effectiveness of LEV as an adjuvant therapy is established. According to several studies, majority of the patients with refractory epilepsy were effectively shifted to LEV as a single drug.

Ben-Menachem et al evaluated the effectiveness and tolerance of LEV as a single therapeutic drug to treat intractable partial epilepsy by conducting a multicenter double-blind trial.²⁴ Results showed that in the LEV single drug group, the frequency of partial seizure was reduced to the median percent 73.8% in a comparison with baseline, giving a rate of response 59.2%. An open study conducted by Alsaadi et al revealed that the percentage of the patients who continued LEV up to 12 months leaving above 50% of them seizure free, was 82%.²⁵ Ozkale et al described in another study that a high dose of 300 mg/kg/d of LEV was given to a patient accidentally for 35 days, no side effects were reported in the patient.²⁶ Shahid Mahmud and Syed Qamar Zaman stated that among children, they found 58% of them with generalized seizure and 32% with focal seizures.²⁷ Statistics showed that there was significant relation between age group types of seizures ($p=0.046$); accurate dosage of antiepileptic drugs and seizures management ($p=0.007$); medication adherence and management of seizures ($p=0.007$). Generalized seizures are the most common condition and focal seizures are next to come. Among children of all age groups, the most frequently observed cause of seizures came out to be epilepsy.

The effectiveness and tolerance of LEV as an adjunct AED was described in a review as 42.24%, among the children ≤ 18 years with intractable epilepsy, reducing the frequencies of seizure beyond 50%, out of which 11.8% had become free of seizure.²⁸ Some others also noted comparable results.^{29,30} In a report presented by Opp et al. described that above 50% reduction in seizure was observed in 24.9% of the individuals when treated with LEV.³¹ According to a systemic review involving 13 studies (including 3 randomized controlled trials), most adverse effects related to LEV were mild in nature while only 2% patients discontinued LEV treatment due to drug related adverse effects.³²

CONCLUSION

Levetiracetam was able to reduce seizures in 76% of the children with refractory seizures and minimal tolerable side effects were observed. Further studies comparing levetiracetam with other contemporary add-on AEDs should be conducted to strengthen our beliefs about the role of levetiracetam in refractory seizures among children.

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