EVALUATION OF SAFETY AND EFFICACY OF LEVETIRACETAM IN PAEDIATRIC EPILEPSY

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ABSTRACT
Objective: To evaluate safety and efficacy of levetiracetam therapy in paediatric epilepsy. Study design: A 6 months cohort prospective open label, uncontrolled, observational study was carried out at St. Philomena’s Hospital. Total of 69 patients were included in the study. Upon enrolment, 1st and 2nd follow-up of the patients were carried out at the interval of 3months to document ADRs, frequency of seizures and EEG reports of patients and statistical analysis of the data was carried out using wilcoxon signed rank test. Result: The results showed that out of 69 patients, 37 patients became 100% seizure free at 2nd follow up. A ≥50% reduction in seizures was observed in 15 patients at 2nd follow up.3 of 69 patients had <50% seizure reduction at 2nd follow up (P<0.001). ADRs reported were aggressiveness in 7 patients, hyperactivity in 4, rash in 3, drowsiness in 2 and 1 was prone to infection. Conclusion: Levetiracetam is found to be efficacious and safe in paediatric epilepsy.

KEYWORDS: ADR, antiepileptics, seizure.

INTRODUCTION
Epilepsy is a chronic neurological disorder which is characterised by repeated unprovoked epileptic seizures. Epileptic seizures are the clinical manifestations including signs and symptoms of an unusual and excessive electrical discharge of neurons in the brain. So,
seizure is a symptom.\(^1\) Paediatrics is one of the branches of medical science that deals with health related problems of infants, children and adolescents as well as their growth and developmental aspects.\(^2\)

Epilepsy is a common disorder in paediatric population in which its prevalence in India is almost similar to other developed countries.\(^3\) Seizures usually happen after abnormal firing of neurons in brain and excessive neuron discharges in cortex which the inhibitory activity of brain goes down and excitatory activity spreads throughout the brain and gives different type of spreading as focal or generalised seizures.\(^4\)

Abnormal electrical activity of brain can be easily monitored by conducting the test called EEG (electroencephalogram) which the electrical activity of brain is recorded as wavy lines. Different parts of brain have their specific functions and firing of neurons can happen in different parts and as a result the clinical presentations of seizures depend on the area which seizure originates from.\(^5\) Levetiracetam (LEV) is one of newer drugs which is not chemically similar to AEDs. Its mechanism of action also is not completely understood, it will bind to synaptic vesicle protein SV2A in the brain. It has fast and complete oral absorption. 66% of drug will eliminate in unchanged form from renal route and dose adjustment is required for renal impairment patients. It is metabolised by non hepatic enzymatic hydrolysis to inactive metabolites and has 40% higher clearance in children than adults.\(^4\)

The purpose of this study was to evaluate safety and efficacy of levetiracetam in paediatric epilepsy which is recently approved as adjunctive treatment for various types of seizures in children (refractory partial seizures in ≥4 years old patients, myoclonic seizures in ≥12 years old patients and for primary generalised tonic clonic seizures in ≥6 years old) and it is approved the most recently by FDA in 2012 as adjunctive therapy in partial onset seizures in children of 1 month age and older.\(^6-7\)

**MATERIAL AND METHODS**

The study was approved by Institutional Review Board of St.Philomena’s Hospital. A 6 months cohort prospective open label, uncontrolled, observational study was carried out. All paediatric out patients and patients who were admitted to the hospital due to convulsions and prescribed with levetiracetam, all neonates (new borns) with convulsions and prescribed with levetiracetam and a group of patients who were on levetiracetam along with other AEDs to
compare the efficacy of LEV with/without other AEDs included in the study and all patients diagnosed with degenerative disorder and patients above 18 years of age excluded.

Patients were enrolled in the study after obtaining the informed consent from the parents/guardians as the study group is paediatrics. Complete demographics of patients including age, weight, frequency of seizures before starting levetiracetam, EEG reports of patients before and after starting levetiracetam, initial dose and final dose of levetiracetam and other concomitant AEDs, type of seizures and etiology of seizures were collected. The reported ADRs, frequency of seizures and EEG reports of patients were documented after taking levetiracetam during 6months period of 1st and 2nd follow up and safety and efficacy of drug were assessed and statistical analysis of the data was carried out using wilcoxon signed rank test to evaluate the significant difference at the baseline and follow ups.

RESULTS
As our population group was paediatric, dose of levetiracetam was given according to weight of each patient. The results showed that the selected dose range was between 10 – 55.9 mg/kg/day. The enrolled 69 patients were distributed into different age groups. Majority of patients had age range of 2-6 years. The results of this study showed that partial seizure distribution is higher than generalised seizures (Generalised tonic-clonic, myoclonic, tonic, atonic) and epilepsy syndromes (IS, LGS, benign rolandic epilepsy). The results demonstrated that the most common etiology of seizures was genetic. The results of present study showed that frequency of seizures reduced to certain level for each patient at 1st and 2nd follow up and for few patients it did not change compared to baseline. Total number of patients at 2nd follow up were less than 1st follow up, because drug was changed after 1st follow up in 3 patients due to ADR (rash) details of which are given in table 1 and fig 1.

The result of present study showed the most common ADR was aggressiveness in 7 patients which was found to be mild according to the modified overt aggression scale (MOAS).[8] Other reported ADRs were found to be hyperactivity in 4 patients, rash in 3, drowsiness in 2 and prone to infection in 1 and 75% of patient did not have any ADR which is described in table 2 and fig 2.

There was second group of patients in our study who were on combination therapy along with LEV. The most concomitant drug was sod.valproate. Comparing the baseline on 69 seizure cases on levetiracetam as monotherapy with 2nd follow up of 66 cases (excluding 3
drop out cases) it may be observed here that there are 37 cases of 100% seizure free and 29 cases with different category of seizure. The change in 69 seizure cases to 37 seizure free cases in the 2nd follow up is found to be statistically highly significant (Z= 6.0083, P< 0.001) using wilcoxon signed rank test. Comparing the baseline on 30 seizure cases on combined drug therapy it may be observed that the change in 30 seizure case to 17 seizure free cases in 2nd follow up is found to be statistically highly significant (Z=4.123, P<0.001) using wilcoxon signed rank test details of which are given in table 3.

Table 1: Distribution of patients with respect to seizure frequency at 1st and 2nd follow up.

<table>
<thead>
<tr>
<th>FOLLOW UP</th>
<th>SEIZURE FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100% seizure free</td>
</tr>
<tr>
<td>1st Follow Up</td>
<td>34</td>
</tr>
<tr>
<td>2nd Follow Up</td>
<td>37</td>
</tr>
</tbody>
</table>

*baseline values contemplate to 100% in each case

![Distribution of patients with respect to seizure frequency at 1st & 2nd follow up](image)

Fig. 1: Distribution of patients with respect to seizure frequency at 1st & 2nd follow up

Table 2: Distribution of Patients with respect to ADR

<table>
<thead>
<tr>
<th>ADR</th>
<th>NO.OF PATIENT</th>
<th>SEVERITY ASSESSMENT</th>
<th>ACTION TAKEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressiveness</td>
<td>7</td>
<td>Mild</td>
<td>No action taken</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>2</td>
<td>Mild</td>
<td>01:Dose reduced</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>4</td>
<td>Mild</td>
<td>01: No action taken</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>Mild</td>
<td>Drug changed</td>
</tr>
<tr>
<td>Prone to infection</td>
<td>1</td>
<td>Mild</td>
<td>No action taken</td>
</tr>
<tr>
<td>No ADR</td>
<td>52</td>
<td>_</td>
<td>_</td>
</tr>
</tbody>
</table>
Table 3: Distribution of patients with respect to combined drug therapy

<table>
<thead>
<tr>
<th>NO. OF PATIENT</th>
<th>LEVETIRACETAM ADDED</th>
<th>EFFICACY</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>At baseline</td>
<td>5/7</td>
</tr>
<tr>
<td>22</td>
<td>At 1&lt;sup&gt;st&lt;/sup&gt; follow up</td>
<td>18/22</td>
</tr>
<tr>
<td>1</td>
<td>At 2&lt;sup&gt;nd&lt;/sup&gt; follow up</td>
<td>1/1</td>
</tr>
</tbody>
</table>

DISCUSSION

Various etiologies of seizures in 69 patients were mainly genetic in 49 patients (71%), birth injury in 18 patients (26%) and brain injury in 2 patients (3%) which in 1 patient was due to stroke and other one was due to child abuse. Study findings exhibited that out of 69 patients, 34 and 37 patients became 100% seizure free compare to base line at 1<sup>st</sup> and 2<sup>nd</sup> follow up respectively. ≥50% reduction in seizure frequency in 17 and 15 patients at 1<sup>st</sup> and 2<sup>nd</sup> follow up was observed .3 of 69 patients had <50% reduction in seizures at 1<sup>st</sup> follow up and 3 of them had <50% reduction in seizures at 2<sup>nd</sup> follow up. Seizures frequency remained same when compared to base line for 15 and 12 patients at 1<sup>st</sup> and 2<sup>nd</sup> follow up respectively.

EEG findings also were found to be normal in 9 patients at 1<sup>st</sup> follow up and also in 17 patients at 2<sup>nd</sup> follow up. Similarly EEG findings was mild normal in 18 and 24 patients at 1<sup>st</sup> and 2<sup>nd</sup> follow up and it was found to be abnormal in 42 patients at 1<sup>st</sup> follow up and in 25 patients at 2<sup>nd</sup> follow up but Goraya et al retrospectively analysed 10 patients who received intravenous levetiracetam. Their results showed 75% of patients became seizure free and 25% had partial reduction in seizures frequency.\(^9\)
In our study the dose range was 10-55.9 mg/kg/day where, of 69 patients, 9 patients had the initial dose change according to efficacy of drug in each individual and occurrence of ADRs. Our results also showed that out of 69 patients, in 10 patients levetiracetam was changed to other drug (including sod.valproate, clobazem, carbamazepine, lamotrigine) which in 1 patient was due to occurrence of ADR (rash) and in other 9 patients was due to no control of seizures. In the study carried out by S.Grosso, E. Franzoni et al the levetiracetam dosage varied from 10-60 mg/kg per day.[10]

In the present study the reported ADRs were found to be aggressiveness in 7 patients (10%), hyperactivity in 4 (6%), rash in 3 (4%), drowsiness in 2 (3%) and prone to infection in 1 (2%) and 75% of patients had no ADR. All reported ADRs were found to be mild in severity according to the modified overt aggression scale (MAOS) for aggressiveness and Hartwig’s severity assessment scale for other ADRs and no specific action was taken except for those who developed rash that the drug was changed and for 1 of patients with drowsiness dose of drug was reduced. But in another study carried out by Legae L et al Side effects were less common in the mono-therapy trial. Tiredness (7.8%) and aggressiveness (5%) were the most common side effects, and were dose-related, but was no reason to discontinue levetiracetam.[11]

During the study there were certain group of patients with combined therapy also and the drugs given along with levetiracetam were carbamazepine (16.6%), clobazem (3.3%), oxcarbazepine(3.3%), vigabatrin (3.3%), sod.valproate (33.3%), phenytoin (6.6%), elisacarbazepine with carbamazepine (3.3%), lamotrigine with sod.valproate (3.3%), clonazepam with sod.valproate and vit B6 (3.3%), sod.valproate with clobazem (6.6%), sod.valproate with phenytoin (3.3%), sod.valproate with oxcarbazepine (6.6%), clobazem with oxcarbazepine (3.3%), carbamazepine with clobazem (3.3%). For the multiple therapy group, levetiracetam was added at 1st follow up for 22 patients that 18 of them showed efficacy, it was added at 2nd follow up for 1 patient that showed efficacy and it was given at baseline for 7 patients that 5 of them showed efficacy.

Statistical analysis of the data was carried out using wilcoxon signed rank test. It was found that there is a highly significant difference in the reduction of seizure frequency between the baseline and 2nd follow up (Z=6.0083, P< 0.001).
CONCLUSIONS
Levetiracetam is found to be efficacious in the treatment of paediatric epilepsy which can be justified by the reduction of seizure frequency from baseline to second follow up and also the ADRs observed during the study were few and mild. Hence levetiracetam is comparatively safe medication to be used in paediatric epilepsy.

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