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The clinical efficacy and safety of levetiracetam add-on therapy for child refractory epilepsy

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Abstract. – OBJECTIVE: To investigate the clinical efficacy and safety of Levetiracetam (LEV) add-on therapy for child refractory epilepsy.

PATIENTS AND METHODS: Levetiracetam add-on therapy was tested on 65 children who suffered refractory epilepsy, and clinical seizures. Electroencephalogram (EGG) changes and adverse reactions were observed in these children respectively in three, six and twelve months after the therapy.

RESULTS: The complete control rates observed after 3, 6 and 12 months were respectively: 6.9%, 10.3% and 3.4%, while the response rates were accordingly 44.8%, 58.6% and 39.6%. The ameliorative rate of EGG reached 65.5%, appearing in positive correlation with the clinical efficacy (r = 0.436, p = 0.001). The retention rate after one year was 89%. Adverse reactions were expressed in 3% of the child patients, and the symptoms were dysphoria, mental and behavior disorders.

CONCLUSIONS: The levetiracetam add-on therapy for child refractory epilepsy, demonstrates fast and obvious efficacy as well as fewer adverse reactions.

Key Words:
Levetiracetam, Epilepsy, Therapeutic efficacy.

Introduction

Epilepsy ranks as one of the most common childhood nervous system diseases and children account for one-fourth of the epileptic patients worldwide[1,2]. There is still some 20 to 30% of childhood epilepsy, even though regular anti-epilepsy treatment evolves into refractory epilepsy annually[3]. Unlike the adult epilepsy, the childhood epilepsy requires efficacious treatment with good tolerance and less adverse reactions. Transparent, prospective and self-controlled, this study aims to evaluate the efficacy and safety of levetiracetam add-on therapy of child refractory epilepsy by analyzing the clinical seizures, electroencephalogram (EGG) changes, retention rates and adverse reactions before and after the treatment.

Patients and Methods

Patients

There were altogether 65 cases of confirmed child refractory epilepsy recorded from June 2012 to September 2013 in Xuzhou Children's Hospital. The diagnosis was explicit. Selected patients were those who had undergone right medication of 2 kinds of tolerable anti-epilepsy drugs or ample dose (a seizure free phase requires 3 times the length of the longest stage of attack or a 12-month phase), but showed no seizure-free recovery, and those who were clinically proven to be infected with refractory epilepsy and epileptic syndromes. All the participating patients had less than the 3-month stage of the attack, thus only those who were not fully recovered after a 12-month traditional treatment were selected.

The average age of patients was 3.16 ± 0.4 years (ranging from one year and three months to 12 years). Among these patients, 39 were male while 26 were female (with reference to the 2010 classification of epilepsy)[4]. Cases with generalized seizures were 29, partial seizures 34, and 2 cases with epileptic spasm. EEG of 62 cases read sharp waves of varied degrees, spike waves, and pike-and-slow wave complex. Abnormal waves were more likely to be seen in the temporal lobe and the frontal lobe. One case showed hypsarrhythmia and the remaining three showed no abnormal EEG.

MRI (magnetic resonance imaging) analysis of the brain detected 9 cases with abnormal brain parenchyma, among which one case had long T1 and long T2 signals in the basal area. That patient

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had a medical history of jaundice. Magnetic resonance imaging analysis showed no abnormality in rest of the 56 cases.

Methods

LEV add-on therapy is practiced by maintaining the original therapeutic schedule of all the participating patients (the original dose was regulated if any change in weight was observed and drug concentration changes were also noted). The starting dose was 10 mg/kg per day, in two separate dosages. After every one or two weeks, the same amount of dosage was added, until epileptic seizures were stopped or the total dosage reached to 60 mg/kg per day. The epileptic seizures, a 10-minute EGGs rest state and untoward reactions of every participating patient were recorded 3 months before the add-on therapy as well as 3, 6 and 12 months after the therapy. The LEV dosage was adjusted according to the patient's weight during the follow-up period. The LEV tablet (250 mg) was produced by the UCB Company, Belgium.

Efficacy Evaluation Index (Curative Effect Index)

Concerning the seizure frequency of the baseline phase, the efficacy percentage of the follow-up point was regarded as the curative effect index[5]: a complete control was with zero occurrence of seizure. Effective therapy required a reduction in seizure frequency by not less than 50%; otherwise, the therapy was reckoned as ineffective.

Follow-up seizure frequency = the exact epilepsy attacks (n)/follow up time (d) × 30.

Efficacy percentage (%) = (the epileptic frequency at the baseline phase – the follow-up seizure frequencies)/the epileptic frequency of the baseline phase × 100%.

Retention rate = the number of patients in the group during the follow-up time/the number of the total patients enrolled in the group × 100%.

EGG Amelioration Index

The total number of epileptiform discharge within 24 hours was calculated based on the epileptiform discharges recorded for the 10-minute long EGG. The measure of reduced epileptiform discharges was reckoned as the EGG amelioration index. Complete improvement required no epileptiform discharges; marked improvement required at least 50% reduction of epileptiform discharges; null improvement occurred when epileptiform discharges were reduced by less than 50%.

The number of epileptiform discharges within 24 hours = the epileptiform discharges within 10 minutes × 6 × 24.

EGG amelioration index = (the epileptiform discharges within 24 hours of baseline phase – the epileptiform discharges within 24 hours of follow-up period)/the epileptiform discharges within 24 hours of baseline phase × 100%.

Statistical Analysis

All the data gathered were processed by SPSS 16.0 (SPSS Inc., Chicago, IL, USA). The measurement data are indicated by the average ± standard deviation (X ± SD). The statistical normality was verified by Kolmogorov-Smirnov. Friedman test was applied to compare different efficacy rates drawn from varied follow-up points, while Kruskal-Wallis *H* test was employed to compare the seizure rates among different groups. Still, Spearman correlation test was used to detect the relevance among factors like gender, age of onset, and incongruent courses of disease against normal distribution, and $p < 0.05$ indicates the difference to be statistically significant.

Results

Clinical Efficacy

The follow-up period was supposed to last for 12 months starting from the day the participating patients were treated, but the actual follow-up periods of 58 patients among whom 30 were males, lasted over 12 months. And the overall complete control rates calculated in a 3-month phase, 6-month phase and 12-month phase, were respectively 6.9%, 10.3% and 3.4%. The corresponding efficacy rates (complete control rates + marked efficacy rates) were 44.8%, 58.6% and 39.6% (Figure 1). The overt discrepancy was detected among three efficacy rates ($X^2 = 11.7$, $p = 0.003$). The efficacy rate reached to the highest after 6-month therapy, with 6 patients (10.3%) had no seizures; 28 patients (48.3%) showed marked improvement; and 24 patients (41.4%) showed null improvement (Figure 2). The average age of patients showing improvements was 2.3 ± 0.5 years, while for patients showing no improvement was 3.7 ± 0.6 years. These two figures exhibited no statistical difference (p =

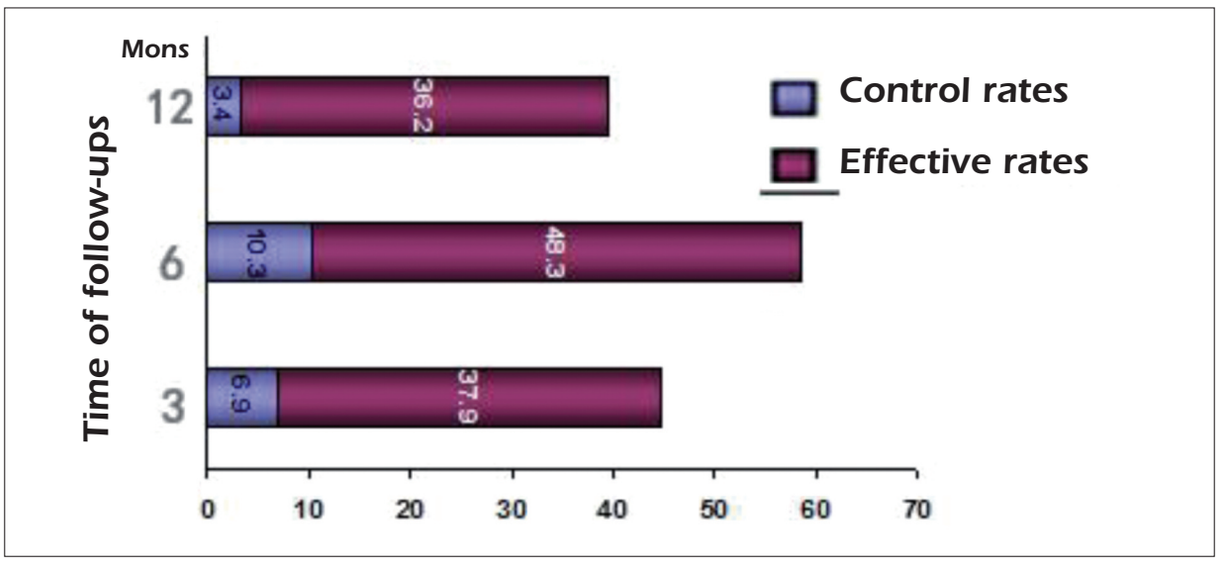

Figure 1. Control rates and effective rates after treatment at three different time points.

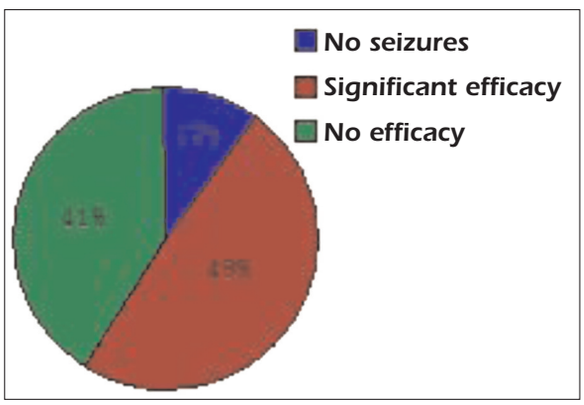

Figure 2. The effective rate of LEV add-on therapy following 6 months of treatment.

0.109). LEV was effective for 62.0% of patients with partial seizures and 51.8% of generalized seizures. No obvious difference was detected between these two groups ($p = 0.363$). The efficacy recorded after a 6-month follow-up showed no relevance to the gender (r = -0.137, $p > 0.05$), age of onset (r = -0.021, $p > 0.05$), or the course of disease (r = 0.129, $p > 0.05$) among patients.

EEG

There were two EEGs of baseline phase showing abnormal hypsarrhythmia; the remaining EEGs showed abnormal brain waves featuring a combination of spike waves, sharp waves and spike-and-slow wave complex detected mainly in the temporal lobe and the frontal lobe. After a 6-month LEV add-on therapy, 8 (13.8%) EEGs showed no epileptiform discharges, 30 (51.7%) EEGs showed marked amelioration with the improvement rate being 65.5% and the amplitude of spike waves and sharp waves being decreased at varied degrees. Among the above mentioned 8 patients featuring complete control, 3 EEGs showed complete improvement. Plus among the above mentioned 28 patients featuring marked amelioration, 4 EEGs showed complete improvement (Table I).

Table I. Correlation between clinical efficacy and improvement of the EEG (%).

Clinical efficacy	Complete improvement of EEG	Marked improvement of EEG	Null improvement of EEG	Sum
Complete control	3 (5.2)	3 (5.2)	0	6 (10.3)
Marked efficacy	4 (6.9)	17 (29.3)	7 (12.1)	28 (48.3)
Null efficacy	1 (1.7)	10 (17.2)	13 (22.4)	24 (41.4)
Sum	8 (13.8)	30 (51.7)	20 (34.5)	58 (100)

A positive correlation was detected between the improvement of the EEG and the clinical efficacy (r = 0.436, p = 0.001).

Retention Rate and Safety

The retention rate of treatments of 3, 6 and 12 months were respectively 97%, 90.7% and 89% (Figure 3). Note that 2 patients had dropped out of the therapy due to no improvement after a 6-month treatment. In addition, 2 patients were showing good signs of improvement, but ceased the add-on therapy because of unbearable mental disorder and drastic personality change. Still one more patient decided to stop to take in LEV due to the meager signs of improvement and the high cost of medication. Altogether 7 patients (11%) had dropped out of the therapy by the end of the 12-month follow-up. During the follow-up phase, untoward reactions due to LEV were noticed in12 patients, and among them 7 showed dysphoria and personality change within the first 4 months; 5 showed feeling of fatigue and rash within the first month of treatment. Except for the above mentioned 2 dropouts who were intolerant of mental disorder, the untoward reactions of rest of the patients were gradually diminished with the time during their therapy. No hepatic or renal dysfunction, electrolyte disturbance and abnormal blood parameters were detected during the follow-up phase.

Discussion

LEV is the newly-devised anti-epileptic drug, which was first approved for marketing by FDA in 1999 and is widely used as epilepsy therapy for both adults and children. LEV boasts optimal bioavailability (100%) yet a low protein binding rate (< 10%). A stable concentration is attainable within 48 hours[6]. Moreover, it undergoes no liver metabolism, involves no electrolyte balance within the plasma, and features null cross-reaction with traditional anti-epileptic drugs[7]. Thus, LEV is with good reason to be the ideal second-line anti-epileptic drugs (nAEDS). Recently, researchers found that LEV can be integrated with the synaptic vesicle protein 2A (SV2A)[8,9], but its exact anti-epileptic rationale is not clear yet. Since 2007, LEV tablets, oral liquid, and injections have entered China's market one after the other, and their efficacy is more or less confirmed[10].

In this study, we found that the corresponding efficacy rates calculated in 3-, 6- and 12-month phase are respectively 44.8%, 58.6% and 39.6%, and that the efficacy ranks highest after a 6-month phase, which is also the case with the complete control rate (10.3%). These findings suggest that the LEV add-on therapy is effective in child refractory epilepsy, and that the efficacy is expressed most obviously after 6 months. But differences as to the efficacy rate and the complete control rate, have been reported among domestic and foreign studies. Kanemura et al[11] followed up 61 children with refractory epilepsy who had undergone the add-on LEV therapy and showed that the complete control rate was 24.6% after a 6-month treatment. In 2012, Goldberg-Stern et al[12] reported a 12% control rate and a 46% efficacy rate after a yearlong LEV add-on treatment of a group of 78 patients among them there were chil-

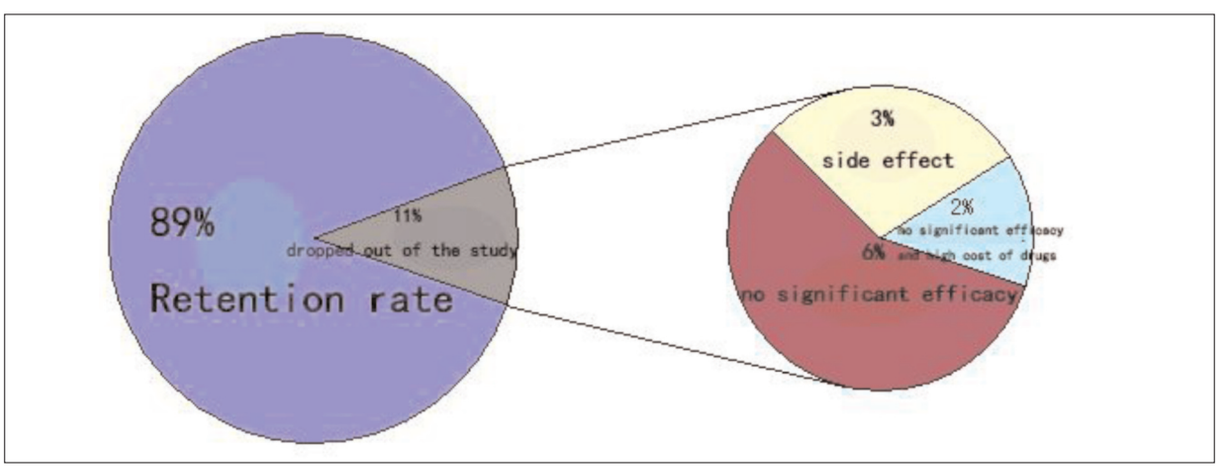

Figure 3. One year retention rate after add-on therapy treatment for children with intractable epilepsy and reasons for dropping out of the study.

dren, adolescents and youths. Whereas, Mandelbaum et al[13] showed a 59% of efficacy rate and 22% patients having no seizure attacks after a year of treatment to a group of 59 children with refractory epilepsy. It is patent that all aforementioned researchers show higher efficacy rates and high control rates than this study, which could be due to the age of participants and the LEV dosage. Children have a clearance rate of 30-40%, which is higher than that of the adults. Clearance rate features a negative correlation with age. Both the studies of Goldberg-Stern et al[12] (68 mg· kg^{-1}· d^{-1}, 14.2 years old) and Mandelbaum et al[13] (70.9 mg· kg^{-1}· d^{-1}, 11 years old) used higher LEV dosage as well as the average age of the participants was more than the current study (60 mg· kg^{-1}· d^{-1}, 3.16 years). Thus, a relatively lower drug concentration was used in this study, which might be one of the factors resulting in the lower complete rate as well as the lower efficacy rate. Therefore, it is relatively safe to say that the epilepsy is easier to control, given an older patient and when a higher LEV dosage is prescribed. But this research does not verify a direct correlation between the patient's age and the therapeutic efficacy, which is likely due to the limited number of research subjects. Coppola et a[14] found that LEV showed a higher efficacy for generalized seizures than the partial seizures. The current research detected a statistical difference between the therapeutic efficacies of LEV on these two kinds of seizures. One of the two child patients with epileptic spasms showed an improvement a month later after taking LEV. Their symptoms were reduced more than 50% after a 6-month therapy and 80% after a 12-month therapy, which indicates that the LEV is effective in children suffering from epileptic spasms, as attested by previous reports. Therefore, when monotherapy proves dissatisfying to epileptic syndromes, the add-on LEV can be an option with good reason.

LEV possesses a quick efficacy for child refractory epilepsy[15-18]. The control rate and the efficacy rate calculated after a 3-month phase and a 6-month phase are apparently higher than the rates calculated after a 12-month phase as well as a decrease in epileptiform discharges was also noted (65.5%). The in-depth analysis discovered that the control rate of epilepsy bears positive correlation with the improvement of the EEG ($p < 0.01$), which suggests that the LEV is a broad spectrum anti-epilepsy drug and can diminish the epileptic seizures as well as the epileptiform discharges.

In the early stage of the add-on LEV therapy, children with refractory epilepsy may show signs of mental disorder (agitation, fatigue), which be eased via slowing down the medication process[19-23]. Periodic examinations of blood parameters, hepato-renal function and electrolytes show no abnormality, suggesting that the LEV and the traditional anti-epilepsy drugs act differently. Our results are in parallel to Coppola et al[14] findings that agitation and mental disorders are detected within 4 months. The untoward reactions of LEV increments are eased remarkably by a decreased LEV increment. The retention rate of LEV becomes close to 90% which is much higher than that of Goldberg-Stern's results (69%). This indicates that the LEV add-on therapy features good tolerance and safety.

Conclusions

We showed that the add-on LEV therapy of child refractory epilepsy displays a quick efficacy and fewer untoward reactions. It can control and reduce the epileptic seizures as well as decrease the neurocyte epileptiform discharges[24-26]. Therefore, LEV stands as the optimal drug to treat child refractory epilepsy.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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