ORIGINAL ARTICLE

Comparison of the effect of oral levetiracetam solution and intermittent oral diazepam tablets in reducing the recurrence of febrile seizures in children 6-60 months

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ABSTRACT

Introduction & Objective: One of the major problems of children is a febrile seizure that induces many complications for them. The aim of this study was to evaluate the effect of oral levetiracetam solution and intermittent oral diazepam tablets in reducing the recurrence of febrile seizures in children aged 6-60 months.

Method: This clinical trial was performed on 46 children aged 6-60 months who referred to the hospital with febrile seizures in the years 2019 and 2020. Children were randomly divided into two groups of oral levetiracetam and oral diazepam and the effectiveness of these medications in reducing the recurrence of febrile seizures was compared between the two groups and the findings were analyzed using statistical software.

Results: The mean age of children was 24.1 months. The duration of seizures, number of seizures, recurrence of seizures, and the mean time interval to the recurrence of seizures were similar in the two groups of oral levetiracetam and oral diazepam, and no significant difference was observed (P> 0.05). Recurrence was observed in 13% of patients in the levetiracetam group and 8.7% in the diazepam group (P = 0.22). The most common type of seizure in patients in both groups was focal seizure (P = 0.07).

Conclusion: Based on the results obtained in the study, it was concluded that the effect of oral levetiracetam and intermittent oral diazepam in reducing the recurrence of febrile seizures in children aged 6-60 months are similar, and therefore, each of these two drugs can be used according to the condition of children and the discretion of the physician.

Keywords: Levetiracetam, Diazepam, Febrile seizures, Pediatrics, Recurrence of seizures

INTRODUCTION

Seizures are sudden and transient manifestations of symptoms and/or signs of excessive or simultaneous abnormal nerve activity in the brain. Febrile seizures (FS) are the most common seizure disorder in pediatrics and the most common neurological problem in childhood, affecting 2% to 5% of children between 6 and 60 months of age. (2 and 5). FS is more common in boys than girls and slightly more common in black children than in white children. The overall prevalence of this disorder is higher in Asia (6). In addition, FS is more common in children from lower social classes due to inadequate access to medical care (7). Seizures are also associated with acute seasonal illnesses (8).

Children with developmental disorders and nervous system damage are more susceptible to FS (9). Nervous system growth and health conditions before the first febrile seizure are the most important indicator for the prognosis of the disease. These patients often have a family history of febrile seizures or epilepsy. FS usually occurs between 6 and 60 months of age and the highest incidence is between 12 and 18 months of age (10). The cause of febrile seizures is multifactorial. It is generally believed that febrile seizures are caused because of the vulnerability of the developing central nervous system (CNS) in children to the effects of fever, in combination with a predisposing genetic background and environmental factors. Therefore, genetic and environmental factors play an important role in inducing febrile seizures (11). Febrile seizures are divided into two categories: simple and complex. Simple febrile seizures are generalized (without a focal component), occur once in a 24-hour period, last less than 15 minutes, and are not associated with an increased risk of epilepsy, whereas complex febrile seizures are long-lasting (≥15 minutes) and focal, occur more than once in 24 hours, and have a 2-5% risk of developing epilepsy (12). Children with FS are at risk for recurrence of the disease and, consequently, developing epilepsy (13, 14). Although febrile seizures in children are often benign and self-limiting (15), childhood seizures are a frightening experience for parents and affect the quality of life of children in cases of recurrence (16).

In acute cases, selective drugs such as lorazepam or diazepam are used to prevent continuous seizures (17). Intermittent diazepam in oral or anal form is effective in preventing the recurrence of febrile seizures (3, 18); however, the side effects associated with intermittent use of diazepam in the prevention of febrile seizures outweigh its potential benefits (3). Another drug that has recently been considered is levetiracetam, which has shown good results in improving and reducing seizure recurrence in adults and children. However, the effectiveness of this drug in children has been less studied (19, 20). As mentioned, febrile seizures are common in infancy and early childhood. Research has shown that levetiracetam is effective in

reducing the recurrence of febrile seizures, and on the other hand, new FS treatments are needed due to the side effects of current drugs such as benzodiazepines. Considering the importance of choosing the appropriate drug to control the recurrence of febrile seizures in children, with maximum effectiveness and the least side effects, this study aimed to compare the therapeutic effect of oral levetiracetam and intermittent diazepam in reducing the recurrence of febrile seizures in children aged 6-60 months.

MATERIALS AND METHODS

Methods and Design: This single-blind randomized controlled trial was performed on 46 children aged 6 to 60 months with a history of febrile seizures. The cases were selected from patients with fever and seizures who were admitted to Children's Hospital in Qazvin, Iran, in 2019-2020. After a full explanation of the treatment method and study procedure, written consent was obtained from the families of all patients.

Inclusion and Exclusion Criteria: Inclusion criteria included children 6 months to 60 months, at least one recurrence of seizures in the past two weeks or one episode of febrile seizures in the last month or a history of two or more episodes of febrile seizures in the past six months, and Axillary T≥ 38 ° C with no CNS infections.

Exclusion criteria included non-febrile seizures during follow-up, intolerable complications such as anxiety and insomnia during follow-up, lack of parental cooperation, history of previous non-febrile seizures, intracranial infections or head trauma, and use of antiepileptic drugs (AEDs).

Sample Size: Considering the findings of previous studies on patients with seizures (18) and the following assumptions, the sample size was calculated using G * Power 3.1.9.2 software, and 46 people (23 patients in each group) were finally elected.

$\alpha = 0.05$, $\beta = 0.20$, $P_1 = 50.00\%$, $P_2 = 10.14\%$

Due to severe side effects during treatment, abandonment of treatment, and thus the reduction of the statistical population, a 20% drop in the sample size was considered. Sampling was performed by non-probability convenience sampling method among the patients who met the inclusion criteria. The first person to enter the study was considered number one and was placed in the designated group for number one, and sampling continued until the sample size was completed.

Intervention description: Patients who entered the study were randomly divided into two groups using WinPepi software. After entering the study, each patient was included in a group that was unknown and the drug was given to the parents. When the parents observed symptoms of sickness or fever in the child (runny or stuffy nose, hot flashes, sore throat, cough), the baby's body temperature should be measured immediately. If the child's temperature indicated fever (T> 37.5), the child was given the drug. Diazepam at a dose of 0.3 mg/kg/dose was given every eight hours for 2 days and levetiracetam (prepared by Abidi Company) at a dose of 15-20 mg/kg was given daily for two days. The patients' condition was followed up for 52 weeks. In case of severe side effects (severe weakness, vomiting, or dizziness), the patient was removed from the study and given standard treatment. Patients were unaware of the medication they received (single-blind).

Collection of Data and Variables: At six-month intervals, the researcher contacted the family of cases and followed up on medication, fever, and seizures. After measuring the variables, the data were collected in the patient evaluation checklist. The criteria for diagnosing complex FS were febrile seizures lasting longer than 15 min, recurrent seizures on the same day, focal seizure activity, or focal findings during the post-seizure period. Variables included age, gender, family history of seizures, duration of seizures, body temperature at the time of admission, number of seizures before hospitalization, recurrence of febrile seizures after starting the drug, type of seizures, the cause of fever and seizures, pre-seizure developmental disorders, sodium excretion disorders, and findings of electroencephalogram (EEG).

Data Analysis: After completing the checklists, the information was entered into SPSS software version 25 and the frequencies were calculated using descriptive statistical tests. Quantitative data were expressed as mean ± standard deviation and qualitative data were expressed as frequency and frequency percentage. Chi-square and t-test were used for the comparison of the groups. For all findings, a significance level of $p < 0.05$ was considered.

Ethical Considerations: The present study was approved by the dissertation council of Qazvin University of Medical Sciences and the researchers adhered to all the principles of protocols and guidelines recommended by the declaration of Helsinki on ethics in research. Before entering the study, written consent was obtained from the children's parents for participation in the study. The children's parents were assured that the plan was confidential and that there was no medical charge.

RESULTS

In this study, 46 children aged 6-60 months were examined. The mean age of children was 24.1 months. According to Table 1, the mean age of the patients was equal in both groups (P = 0.15). Also, the frequency distribution of gender of the patients was similar in the two groups (P = 0.09). Family history of the disease had the same frequency in both groups (P = 0.12).

Table 1- Demographic variables of the two study groups

Parameters		Group		p
		Levetiracetam	Diazepam	
Age(months)	N	23	23	0.15
	mean	24.00	24.61	
sex	male	56.5%	47.8%	0.09
	female	43.5%	52.2%	
Family	Pos	20.7%h	23.8%	0.12
	Neg	79.3%	76.2%	
Age (years; mean ± SD)	24.1 ± 6.21			

According to Table 2, 87% of cases in the oral levetiracetam group and 81% of cases in the diazepam group experienced seizures of less than 15 minutes, which was not statistically significant in both groups (P = 0.19). More than 47% of patients in the oral levetiracetam group and more than 47% of patients in the diazepam group

experienced one seizure, and 43% of children in both groups experienced two seizures, but the number of seizures was not statistically significant (P = 0.25). Recurrence was observed in 13% of patients in the levetiracetam group and 8.7% in the diazepam group, which demonstrated no statistically significant difference (P = 0.22). The most common type of seizure was focal epilepsy in both groups (P = 0.07). The cause of fever and seizures in the patients was similar in the two groups and did not show a statistically significant difference (P = 0.08). Electrolyte disorders did not show a statistically significant difference between the two groups (P = 0.32). Developmental diseases were rarely observed in both groups (P = 0.12). The frequency of EEG findings in the studied patients did not show a significant difference between the two groups (P = 0.09).

Table 2- Comparison of the groups in terms of the parameters of seizure

parameters		Group		p
		Levetiracetam	Diazepam	
Seizure Length	<15	87.0%	81.0%	0.19
	>15	13.0%	19.0%	
Before Intervention Seizure count	1	47.8%	45.3%	0.25
	2	43.5%	44.9%	
	3	8.7%	9.8%	
Recurrence	Pos	13.0%	8.7%	0.22
	Neg	87.0%	91.3%	
FS type	Focal	74.6%	56%	0.07
	Generalized	25.4%	44%	
Cause of FS	GI	66.7%	56.5%	0.08
	Respiratory	33.3%	20.1%	
	urinary	0.0%	23.4%	
Developmental Disease	Pos	8.7%	4.3%	0.12
	Neg	91.3%	95.7%	
Electrolyte Disease	Pos	4.3%	2.2%	0.32
	Neg	95.7%	97.8%	
EEG	NL	32.8%	41.4%	0.09
	ANL	67.2%	58.6%	

NL:Normal
ANL:Abnormal

DISCUSSION

Seizures are the most common sign of any neurological disorder for various reasons in childhood. There are concerns about the effects of the drugs used on the growing brain. Levetiracetam is a new antiepileptic drug with neuroprotective properties that has been used in adults and pediatrics, but there is limited research on its use in children (21). In the present study, the effectiveness of levetiracetam and diazepam in children aged 6 to 60 months was compared and evaluated. Our findings showed that the duration of seizures, number of seizures, seizure recurrence, and the mean time interval to seizure recurrence were similar in the two groups of oral levetiracetam and oral diazepam, and no significant difference was observed. Recurrence was observed in 13% of patients in the levetiracetam group and 8.7% in the diazepam group.

In a 2014 study by Lin-Yan Hu et al., conducted on 115 children with FS with a history of two or more febrile seizures (89 boys and 29 girls), 78 children (61 boys and 17 girls) received oral levetiracetam with a dose of 15-30 mg/kg twice daily (body temperature > 37.5° C) for 1 week and then received a dose reduction of 50% every 2 days until complete discontinuation of the drug in the second week, while 37 children (25 boys and 12 girls) received no medications. In the levetiracetam group, 78 children experienced a total of 148 episodes of fever; Of these 78 children, 11 experienced 15 cases of FS. In the control group, 64 episodes of fever were experienced among 37 children; Of these 37 children, 19 had 32 cases of FS during the 48-week follow-up. The recurrence rate of febrile seizure was 14.10% (11 patients out of 78) in the group of patients treated with levetiracetam and in the control group, this rate was 51.35% (19 out of 37) (P <0.001). No significant difference was observed between the two groups in terms of the recurrence rate of FS. No side effects (only one case of drowsiness) were observed during the follow-up period (18).

In another study in 2018 by the same research group, Lin-Yan Hu et al., patients with recurrent FS underwent electroencephalogram (EEG) 2 weeks after the last febrile seizure. With the onset of fever (T> 37.5 ° C), patients with epileptiform waves were treated with oral levetiracetam at a dose of 15-30 mg/kg twice daily for 1 week, and then the dosage was gradually reduced (50% reduction every two days) until the complete discontinuation in the second week. The frequency of febrile seizures and the recurrence rate of FS were analyzed during a 48-week follow-up. All EEGs were read by a pediatric neurologist and an electroencephalograph specialist, and only focal spikes, sharp or clustered waves, and generalized slow spike-and-waves were considered epileptic waves. Among the 19 patients with epileptic waves on the EEG, 13 of 19 patients (68.42%) had simple FS and 6 of 19 (31.58%) had complex FS. Up to 57.89% (11 of 19) had a family history of seizure disorders and 36.84% (7 of 19) had a family history of FS in first-degree relatives. In 8 of 19 patients (42.11%), the first FS occurred at <18 months of age. Seven out of 19 patients (36.84%) had generalized spike, 63.16% (12 of 19)

had focal spike in the electroencephalogram, and during the 48-week follow-up period, patients had 26 episodes of fever, but none of them showed recurrence of seizure. In general, the results of this study suggest that the use of intermittent oral LEV can prevent the recurrence of FS and epilepsy in patients with recurrent FS and abnormal EEG (22).

In 2016, Salehi Omran et al. conducted a study in Iran and evaluated the effectiveness of phenobarbital in comparison with diazepam in preventing recurrence of FS in children; the recurrence rate in the phenobarbital group was 23% and in the diazepam group was 15.5%, and the difference was not statistically significant (23). The obtained results from the phenobarbital treatment group in this study were similar to the findings of the Levetiracetam group in the present study.

In our study, levetiracetam was very effective and no major side effects were observed. Studies have shown that levetiracetam is not associated with serious systemic side effects (24). Also, allergic rashes due to levetiracetam are very rare, which is significantly different compared to other anticonvulsant drugs (25). A systematic review has shown that the side effects of levetiracetam are acceptable and the therapeutic efficacy of this medication in preventing seizures appears to be similar to phenytoin (26).

In the present study, 21.7% of the patients in both groups had a family history of the disease and the most common type of seizure in the patients in both groups was focal epilepsy. Similar studies have shown that levetiracetam has been shown to be effective in the treatment of focal, myoclonic, and tonic-clonic epilepsies (27). Levetiracetam prevents the consecutive action potentials of neurons (28). Levetiracetam could not be extensively metabolized in humans and is excreted by the kidneys, and in children, it is rapidly and almost completely absorbed after oral administration. Due to the lack of hepatic metabolism and low protein binding, its side effects are very low and do not require control tests (29). Another study reported that the risk of recurrent febrile seizures was about 30-40%, which can be related to genetic and environmental factors. In addition, the onset of febrile seizures in younger ages and family history of the disease can increase the risk of recurrent FS (30).

Based on the results of our study, levetiracetam was observed as an effective therapeutic agent to prevent recurrence and reduce the frequency of seizures. A cohort study by Li et al. in 2017, found that children treated with levetiracetam had a recurrence rate of 15.5% after 50 weeks of treatment and follow-up, and the frequency of febrile seizures was 12.4%. They also concluded that levetiracetam could be an effective drug to prevent recurrence and reduce the frequency of febrile seizures (31). Another study showed that levetiracetam at a dose of 2500-1000 mg daily provided adequate control of seizures in juvenile myoclonic epilepsy and none of the patients had any side effects (32). Histopathological studies by Mustafa Kumar et al. (2014) showed that levetiracetam reduced the number of apoptotic neurons, its neuroprotective effects prevented hypoxic-ischemic encephalopathy in neonatal mice, and significantly improved behavioral performance in the future (33); the potential of these long-term effects can be explored in future research in different parts of the world. In a study by Specchio et al., patients that were resistant to antiepileptic therapy were treated with levetiracetam. In 37.5% of cases with myoclonic epilepsy and 73% of cases with generalized tonic-clonic seizures, the disease was completely controlled (34,35), which confirms the good efficacy observed in our study

In total, together with two studies in China (20, 22) and our study, a total of three studies have been performed on the effect of levetiracetam on febrile seizures. In previous studies, the effect of levetiracetam was not compared with any other drug. In the other two studies, the consumption of this drug was continued for 2 weeks after the onset of fever, whereas in our study the use of levetiracetam continued for 2 days after the onset of fever.

One of the limitations of the present study was the lack of cooperation and communication of some parents during the follow-up period. In this regard, periodic contacts were made during the patient's treatment process and families were encouraged by reminding them of the treatment goals.

Finally, it is suggested that more studies with greater sample size and longer follow-up period be performed, and other treatment and prophylaxis methods be considered in children with fever and seizures to identify the best treatment method. In addition, conducting studies in several centers can increase the generalizability of the results.

CONCLUSION

Based on the results obtained in the study, it was concluded that the effect of oral levetiracetam and intermittent oral diazepam in reducing the recurrence of febrile seizures in children aged 6-60 months are similar, and therefore, each of these two drugs can be used according to the condition of children and the discretion of the physician. Also, in order to further evaluate the role of levetiracetam in the management of febrile seizures in children less than 60 months of age, further randomized controlled trials with larger sample sizes and longer follow-up periods are required.

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