Original Article

J Adv Med Biomed Res. 2024; 32(152): 168-173

The Effect of Intermittent Oral Anticonvulsant Levetiracetam in Prevention of Recurrence of Febrile Seizure in Children: A Randomized Clinical Trial Study

Javad Shabani [1], Mitra Hemmati [1], Mostafa Sedighi [1*]

1. *Department. of Pediatrics, School of Medicine , Dr. Kermanshahi Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran*

Article Info

10.61186/jambr.32.152.168

Received: 2023/03/29;
Accepted: 2024/10/02;
Published Online: 27 Sep 2024;

Corresponding Information:
Mostafa Sedighi,
Dept.of Pediatrics,School of Medicine,Dr. Kermanshahi Hospital,Kermanshah University of Medical Sciences,Kermanshah,Iran
E-Mail:
sedighimostafa2000@gmail.com

ABSTRACT

Background & Objective: Febrile seizure (FS) is the most common childhood seizure disorder that occurs in 3-4% of children .The aim of this study was to determine the effect of intermittent oral anticonvulsant Levetiracetam in prevention of the recurrence of febrile seizure (FS) in children.

Materials & Methods: This a randomized clinical trial study was conducted on 108 children with FS referred to the pediatric department of Mohammad Kermanshahi Hospital in Kermanshah in 2020. Then, eligible patients were divided into intervention (Levetiracetam; n= 72) and control (Acetaminophen; n= 36) groups using balanced block randomization. The intervention group received a dose of 30-60 mg/kg Levetiracetam during the febrile illness for prophylaxis for 9 months. In contrast, in the control group, only acetaminophen was prescribed just to reduce fever. Finally, the number of FS recurrences were studied in two groups. The data were analyzed using SPSS 26.

Results: The mean (±S.D) age were 2.37 (±1.01) vs. 2.30 (±0.95) years in the intervention and control groups; respectively. The number (%) of boys in the two groups under study was 39 (54.1) and 19 (52.7), respectively. The mean time to first seizure recurrence after the intervention was significantly longer in the intervention group (5.70 ± 0.82 months) than in the control group (2.32 ± 0.75 months) (*P-Value<0.05*). Also, the mean number of recurrences of FS in the intervention group (2.25 ± 0.80) was significantly lower than the control group (4.13 ± 0.79) (*P-Value<0.05*).

Conclusion: The administration of oral anticonvulsant Levetiracetam may be effective in the reduction of the recurrences of FS, however, detailed studies in this field is recommended.

Keywords: Levetiracetam, Recurrence, Febrile seizure, Children, Clinical trial study

Copyright © 2023, This is an original open-access article distributed under the terms of the Creative Commons Attribution-noncommercial 4.0 International License which permits copy and redistribution of the material just in noncommercial usages with proper citation.

Introduction

Febrile seizure (FS) is the most common childhood seizure disorder that occurs in 3-4% of children, although this figure has been reported as high as 11% in some regions **(1)**. According to the definition of the international league against epilepsy (ILAE), convulsions accompanied by a temperature of more than 38°C in neurologically healthy children aged 1 month to 7 years are considered as FS. Usually, these children do not have infection, acute electrolyte disorder, and history of seizures without previous fever **(2, 3)**. FS is divided into two types of simple and complex febrile convulsion. Complex FS includes cases where the seizure was localized or lasted more than 10-15 minutes or repeated within 24 hours, or there is a focal neurological finding in the post-seizure phase **(4)**. There is another type of FS called recurrent

febrile convulsion, which is said to occur again after 20 hours of the initial seizure. Almost one third of children with FS experience relapse **(5)**. FS does not have a clear cause or pathogenesis, and its mechanisms are still not well understood. However, positive family history, fever above 38°C, smoking or alcohol consumption by the mother during pregnancy and hospitalization in the intensive care unit during infancy have been introduced as risk factors for this disease. Although FS has apparently worrisome clinical signs, the prognosis is generally benign **(6, 7)**.

The use of antipyretics such as acetaminophen and ibuprofen can also lead to the reduction of secondary symptoms caused by the increase in body temperature and discomfort, although the use of antipyretic drugs cannot lead to the prevention of FS **(8)**. Oral benzodiazepines such as Diazepam or Clobazam are usually prescribed in children with a high risk of recurrence of FS. Both drugs have a similar effect in terms of preventing recurrence and are used orally, rectally or sublingually as prophylaxis, alternately **(9)**. Although diazepam is the most common drug used to prevent FS, it has side effects such as drowsiness and ataxia **(10)**. Other first-line drugs such as Clobazam and sodium valproate, although effective, but due to side effects and recurrence of fever and seizures, are less often prescribed by specialists today **(11)**.

Levetiracetam is another anticonvulsant drug whose performance is not well known, however, it is used together with other drugs in the treatment of paroxysmal, myoclonic, or generalized tonic-clonic epilepsy. Its usual side effects include dizziness, sleepiness, irritability, sore throat, fatigue and weakness. Its severe side effects include severe allergic reactions (rash, hives, itching, breathing problems, etc.), unusual thoughts, dark urine color, drowsiness, extreme weakness, fever and mood changes **(12)**. However, its rapid onset of action, lack of drug interactions, and its availability as an intravenous solution make it an optimal drug for the treatment of seizures **(13)**. In previous studies, Levetiracetam has been introduced as a well-tolerated drug, but different results have been obtained regarding its effectiveness in the preventive treatment of FS **(14)**. According to the above explanations and the lack of consistency in the results of the studies obtained regarding the comprehensive decision for preventive treatment in children with FS, the present study was designed with the aim of investigating the effect of intermittent oral anticonvulsant Levetiracetam in prevention of the recurrence of FS in children.

Materials and Methods

I. Study Design and Subjects

This is a randomized clinical trial study conducted on 108 children with febrile seizure referred to the pediatric department of Mohammad Kermanshahi Hospital in Kermanshah in 2020. The sampling method was convenience. The inclusion criteria were 6 to 60 month aged children having simple FS. Exclusion criteria consisted of history of underlying cardio respiratory disease, moderate and severe malnutrition, immune deficiency, neurological disorder, central nervous system infection, developmental disorder or progressive neurological disorder and complex FS. The above patients were excluded from the study because of higher risk of seizure recurrences and basically they are are candidates for continuous daily use of anticonvulsant than intermittent prophylaxis which makes them at the risk of recurrent complicated febrile seizures. Also, since the studied patients and control group with positive family history of febrile seizure and epilepsy need to take daily prophylactic antiepileptics, they were excluded at the onset of study.

II. The intervention

The research objectives were explained for the parents of the patients and the informed consent was obtained. They asked to record the fever episodes in a 9 months period. Eligible patients were divided into the intervention (levetiracetam; n= 72) and control (acetaminophen only; n= 36) groups using balanced block randomization. The intervention group received 60 mg/kg/day of levetiracetam in two dividend doses during the febrile illness. This intervention was ordered for 9 months. In control group, acetaminophen was prescribed for fever control. Parents/caregivers were trained to handle seizure attacks and to use the rescue medication (rectal diazepam). They were asked to record the number of fever episodes and or seizure attacks.

III. Statistical Analysis

In descriptive analysis, mean (S.D) and number (%) were used for quantitative variables. In analytical analysis, the independent-samples T-test and Chi square test to compare the quantitative and qualitative variables in two group; respectively. The data were analyzed using SPSS26 software and *p-value <0.05* was considered as a significant level.

IV. Ethical Considerations

The protocol study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the Deputy of Research and Ethics Committee of Kermanshah University of Medical Sciences (ID-number: IR.KUMS.REC.1400.075). Additionally, this clinical trial study was registered in Iranian Registry of Clinical Trials (registration ID: IRCT20130812014333N170).

Results

This clinical trial study was conducted on 108 children with febrile seizures referred to the pediatric department of Mohammad Kermanshahi Hospital in Kermanshah in 2020. These patients were randomly divided into intervention (levetiracetam; n= 72) and control (acetaminophen; n= 36) groups using balanced

block randomization. The mean (±S.D) age were 2.37 (±1.01) vs. 2.30 (±0.95) years in the intervention and control groups; respectively. The number (%) of boys in the two groups was 39 (54.1) and 19 (52.7), respectively. Generally, there were no significant statistical difference between the two groups in terms of sex and age before intervention (P-Value>0.05), which can be a reason that randomization process has occurred correctly (Table 1).

Table 1. Comparison of baseline variables in intervention and control groups

Qualitative Variables		Intervention group	Control group	P-Value*
		Number (%)	Number (%)	
Sex	Boy	39 (54.1)	19 (52.7)	0.361
	Girl	33 (45.9)	17 (47.3)	
	Total	72 (100)	36 (100)	
Quantitative variable	Group	Number	Mean	S.D	P-Value**
Age (year)	Interventional	72	2.37	1.01	0.733
	Control	36	2.30	0.95	

*: Chi square test

**: Independent sample t-test

Table 2. The results of the Kolmogorov-Smirnov test to check the normality of the primary outcomes

Variable	Test Statistic	Mean	P-Value
The number of repetitions of fever and seizures	0.195	2.87	0.533
Time to first seizure recurrence (Month)	0.228	4.47	0.651

The results of the Kolmogorov-Smirnov test to check the normality of the primary outcomes showed that the number of FS recurrences and time to first seizure recurrence variables have a normal distribution, therefore, independent-Samples T-Test is used to compare two intervention and control groups (Table 2).

The independent t-test results showed that the mean time to first FS recurrence in the levetiracetam group (5.70 ± 0.82) was significantly longer than acetaminophen group (2.32 ± 0.75), in other words, the mean time to first FS recurrence after the intervention was longer in the intervention group than in the control group (*p-value <0.05*). Also, the mean number of FS recurrences in the levetiracetam group (2.25 ± 0.80) was significantly lower than the acetaminophen group (4.13 ± 0.79) (*p-value <0.05*) (Table 3).

In addition, there was no significant observed side effects in the children tacking levetiracetam.

Table 3. Comparison of primary outcomes in intervention and control groups

Primary outcomes	Group	Number	Mean	S.D	P-Value*
Time to first seizure recurrence (Months)	Intervention	72	5.70	0.82	0.027
	Control	36	2.32	0.75	
The number of repetitions of fever and seizures	Intervention	72	2.25	0.80	0.013
	Control	36	4.13	0.79	

*Independent-Samples T-Test

Discussion

The results of this study showed the mean (±S.D) age were 2.37 (±1.01) vs. 2.30 (±0.95) years in the intervention and control groups; respectively. The number (%) of boys in the two groups were 39 (54.1) and 19 (52.7), respectively. The mean time to first seizure recurrence after the intervention was significantly longer in the intervention group (5.70 ± 0.82) than in the control group (2.32 ± 0.75) (P-Value<0.05). Also, the mean number of FS recurrences in the intervention group (2.25 ± 0.80) was significantly lower than the control group (4.13 ± 0.79) (P-Value<0.05).

In line with the results of this study, in a clinical trial study conducted by Lin-Yan Hu et al. with the aim of investigating the efficacy of intermittent oral levetiracetam (LEV) in the prevention of febrile seizure, LEV with a dose of 15–30 mg/kg per day twice daily for 1 week was prescribed, then, the dose was gradually reduced and stopped at the end of the second week. Finally, it was observed that LEV can prevent the recurrence of febrile seizures and epileptic discharges up to 48 weeks **(15)**. In the study of Nalin Chaudhary et al., which investigated the efficacy of LEV compared to Clobazam (CLB) in reducing the recurrence of febrile seizures in children, 50 children received 15-30 mg/kg per day twice daily at the onset of fever for one week, then the dose was gradually reduced and stopped in the second week. The second group received 2.5 to 5 mg CLB once daily at bedtime for two weeks. The results showed that although the febrile seizure recurrence rate in the CLB group was significantly lower than the LEV group, both drugs were effective in preventing the recurrence of febrile seizures **(16).** In another study conducted by Farzaneh et al. in Iran with the aim of the effect of oral levetiracetam solution and intermittent oral diazepam tablets on the recurrence of febrile seizures in children aged 6-60 months, the results indicated that the duration of seizures, the number of seizures, the recurrence of seizures and the average time interval until the recurrence of seizures were similar in the two groups **(17)**. In a cohort study conducted by Offringa et al., the recurrence rate and frequency of seizures in children treated with levetiracetam after 50 weeks of treatment were 15.5% and 12.4%, respectively. Finally, they concluded that the levetiracetam can be effective in preventing seizure recurrence and reducing its frequency **(18).** Other similar studies have also suggested that levetiracetam can be effective in the treatment of focal, myoclonic, and tonic-clonic epilepsies and prevent consecutive action potentials of neurons **(19, 20)**.

As seen, the majority of studies were consistent with the results of our study regarding the efficacy of anticonvulsant Levetiracetam in preventing the occurrence of FC. However, the antiepileptic mechanism of levetiracetam is still not fully understood. It is possible that levetiracetam inhibits N-type voltage-gated calcium channels. Levetiracetam may also bind to synaptic proteins that modulate neurotransmitter release, and through displacement of negative modulators may facilitate Gamma-aminobutyric acid (GABA) inhibitory transmission. Some other studies on the mechanism of levetiracetam say that this drug binds to the synaptic vesicle glycoprotein 2A (SV2A) protein, which is a synaptic vesicle glycoprotein, and inhibits presynaptic calcium channels, thereby reducing the exocytosis of neurotransmitters. It seems that this drug prevents the transmission of electrical impulses from the nerves **(21-23)**.

It should be mentioned that Levetiracetam like most antiepileptics is easily available in most drug stores. The price of uncovered insurance of levetiracetam syrup is roughly 1.5 $ (90,000 Tomans) and 1 $ with insurance coverage and this can be one of the main advantages of this drug compared to It is diazepam.

Conclusion

The results of our study show that the administration of oral anticonvulsant levetiracetam may be effective in reducing the recurrence of febrile seizure without significant side effects, however, detailed studies in this field are recommended.

Acknowledgments

The authors are grateful for the sincere cooperation of the staff of Mohammad Kermanshahi Hospital and the families of the children who participated in this study.

Authors' Contribution

SM: Study design,MH:Assisting for the patients refered . SM , JSH :Data Collection and patients follow up

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

This study was funded by Kermanshah University of Medical Sciences, Kermanshah, Iran.

Ethics Approval and consent to participate

The study was approved by the Deputy of Research and Ethics Committee of Kermanshah University of Medical Sciences (ID-number: IR.KUMS.REC.1400.075).

References

1. Kavanagh FA, Heaton PA, Cannon A, Paul SP. Recognition and management of febrile convulsions in children. Br J Nurs. 2018;27(20):1156-62. https://doi.org/10.12968/bjon.2018.27.20.1156 PMid:30418862

2. Smith DK, Sadler KP, Benedum M. Febrile seizures: risks, evaluation, and prognosis. Am Family Physic. 2019;99(7):445-50.

3. Eilbert W, Chan C. Febrile seizures: A review. J Am College Emerg Physic Open. 2022;3(4):e12769. https://doi.org/10.1002/emp2.12769 PMid:36016968 PMCid:PMC9396974

4. Whelan H, Harmelink M, Chou E, Sallowm D, Khan N, Patil R, et al. Complex febrile seizures-A systematic review. Dis Mon. 2017;63(1):5-23. https://doi.org/10.1016/j.disamonth.2016.12.001 PMid:28089358

5. Kumar N, Midha T, Rao YK. Risk factors of recurrence of febrile seizures in children in a tertiary care hospital in Kanpur: A one year follow up study. Ann Indian Acad Neurol. 2019;22(1):31. https://doi.org/10.4103/aian.AIAN_472_17 PMid:30692757 PMCid:PMC6327698

6. Minardi C, Minacapelli R, Valastro P, Vasile F, Pitino S, Pavone P, et al. Epilepsy in children: from diagnosis to treatment with focus on emergency. J Clin Med. 2019;8(1):39. https://doi.org/10.3390/jcm8010039 PMid:30609770 PMCid:PMC6352402

7. Sawires R, Buttery J, Fahey M. A review of febrile seizures: recent advances in understanding of febrile seizure pathophysiology and commonly implicated viral triggers. Front Pediatr. 2022;9:801321. https://doi.org/10.3389/fped.2021.801321 PMid:35096712 PMCid:PMC8793886

8. Gontko-Romanowska K, Żaba Z, Panieński P, Steinborn B, Szemień M, Łukasik-Głębocka M, et al. The assessment of laboratory parameters in children with fever and febrile seizures. Brain Behav. 2017;7(7):e00720. https://doi.org/10.1002/brb3.720 PMid:28729928 PMCid:PMC5516596

9. Pavlidou E, Tzitiridou M, Panteliadis C. Effectiveness of intermittent diazepam prophylaxis in febrile seizures: long-term prospective controlled study. J Child Neurol. 2006;21(12):1036-40. https://doi.org/10.1177/7010.2006.00221 PMid:17156694

10. Gavgani LF, Laghousi D, Sarbakhsh P, Jahangiri L, Vahed N, Hajebrahimi S. Comparing the effect of intermittent diazepam and continuous phenobarbital in preventing recurrent febrile seizures among children under 6 years old: A systematic review and meta-analysis. J Isfahan Univ Med Sci. 2023;28. https://doi.org/10.4103/jrms.jrms_1114_21 PMid:37213451 PMCid:PMC10199379

11. Khosroshahi N, Faramarzi F, Salamati P, Haghighi SMO, Kamrani K. Diazepam versus clobazam for intermittent prophylaxis of febrile seizures. Indian J Pediatr. 2011;78:38-40. https://doi.org/10.1007/s12098-010-0220-0 PMid:20890683

12. Pizza V, Busillo V, Agresta A, Bisogno A, Capasso A. Elderly patients with migraine: an open-label study on prophylaxis therapy with levetiracetam. Cent Nerv Syst Agents Med Chem. 2011;11(1):31-4. https://doi.org/10.2174/187152411794961086 PMid:21250937

13. Mruk AL, Garlitz KL, Leung NR. Levetiracetam in neonatal seizures: a review. J Pediatr Pharmacol Therapeut. 2015;20(2):76-89. https://doi.org/10.5863/1551-6776-20.2.76 PMid:25964725 PMCid:PMC4418685

14. Hu LY, Zou LP, Zhong JM, Gao L, Zhao JB, Xiao N, et al. Febrile seizure recurrence reduced by intermittent oral levetiracetam. Ann Clin Translat Neurol. 2014;1(3):171-9. https://doi.org/10.1002/acn3.34 PMid:25356397 PMCid:PMC4184546

15. Hu LY, Shi XY, Li H, Zhang MN, Ma SF, Zou LP. Intermittent oral levetiracetam reduced recurrence of febrile seizure accompanied with epileptiform discharge: a pilot study. Italian J Pediatr. 2018;44:1-7. https://doi.org/10.1186/s13052-018-0507-8 PMid:29907116 PMCid:PMC6003147

16. Chaudhary N, Narayana R, Chaudhary S. Reduction of febrile seizure recurrence comparative efficacy of intermittent oral levetiracetam vs clobazam.Am Acad Neurol. 2016; (P3. 239) https://doi.org/10.1212/WNL.86.16_supplement.P3.239

17. Farzaneh Bajestani S , Pirzadeh Z, Farshadmoghadam H. 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. Pakistan J Med Health Sci. 2021;15(4).

18. Offringa M, Newton R, Nevitt SJ, Vraka K. Prophylactic drug management for febrile seizures in children. Coch Database System Rev. 2021(6). https://doi.org/10.1002/14651858.CD003031.pub4 PMid:34131913 PMCid:PMC8207248

19. Xu JC, Shen J, Shao WZ, Tang LJ, Sun YZ, Zhai XF, et al. The safety and efficacy of levetiracetam versus phenytoin for seizure prophylaxis after traumatic brain injury: A systematic review and meta-analysis. Brain Injury. 2016;30(9):1054-61. https://doi.org/10.3109/02699052.2016.1170882 PMid:27295203

20. Abou-Khalil B. Levetiracetam in the treatment of epilepsy. Neuropsychiatr Dis Treat. 2008;4(3):507-23. https://doi.org/10.2147/NDT.S2937 PMid:18830435 PMCid:PMC2526377

21. Lynch BA, Lambeng N, Nocka K, Kensel-Hammes P, Bajjalieh SM, Matagne A, et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. Proceed Nat Acad Sci. 2004;101(26):9861-6. https://doi.org/10.1073/pnas.0308208101 PMid:15210974 PMCid:PMC470764

22. Vogl C, Mochida S, Wolff C, Whalley BJ, Stephens GJ. The synaptic vesicle glycoprotein 2A ligand levetiracetam inhibits presynaptic Ca2+ channels through an intracellular pathway. Molec Pharmacol. 2012;82(2):199-208. https://doi.org/10.1124/mol.111.076687 PMid:22554805

23. Rogawski MA. Diverse mechanisms of antiepileptic drugs in the development pipeline. Epilepsy Res. 2006;69(3):273-94. https://doi.org/10.1016/j.eplepsyres.2006.02.004 PMid:16621450 PMCid:PMC1562526

How to Cite This Article:

Javad Shabani, Mitra Hemmati, Mostafa Sedighi. The Effect of Intermittent Oral Anticonvulsant Levetiracetam in Prevention of Recurrence of Febrile Seizure in Children: A Randomized Clinical Trial Study J Adv Med Biomed Res. 2024; 32(152): 168-173.

Download citation:
BibTeX | RIS | EndNote | Medlars | ProCite | Reference Manager | RefWorks

Send citation to:
Mendeley Zotero RefWorks