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Prophylactic Oral Diazepam for Pediatric Epilepsy Patients with Fever-Triggered Episodes

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Abstract

Introduction: Epilepsy is a long-standing brain disorder struck by a persistent propensity to have seizures that are not caused by any instant injury to the central nervous system. It also involves numerous consequences on cognition, the brain's biology, psychology, and social aspects due to periodic seizures. Epilepsy can affect individuals of all ages and genders worldwide. In patients diagnosed with epilepsy based on clinical symptoms, EEG results, age over 60 months, and frequency of unprovoked seizures, the occurrence of seizures during a fever can be triggered. This is because changes in body temperature can impact the electrical activity of neurons and other cellular processes. This study aimed to investigate the effect of oral diazepam on the number of attacks of seizures in epilepsy patients during febrile illness.

Methods: from 2020 to 2023, patients were collected during the consultations to private clinics, and outpatient (pediatric & neuro-medicine clinic). 430 patients were collected all those patients diagnosed as epilepsy according to clinical findings and EEG. All patients on antiepileptic drugs either monotherapy or 2 types of drugs aged more than 5 years. 96 patients involved in the study half of them given prophylactic oral diazepam and the 2nd group placebo.

Results: The number of assaults per year during febrile illness is significantly reduced with therapy; there is no significant correlation was seen between treatment and age or sex.

Conclusion: Oral diazepam can reduce the number of attacks of seizures in epilepsy patients during febrile illness.

Keywords: Epilepsy, Oral diazepam, Fever, Febrile seizure (FS), Central nervous system (CNS).

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INTRODUCTION

Epilepsy is a disease that causes a persistent affinity to have seizures devoid of any abrupt cause in the CNS. It also leads to various consequences on neurobiology, cognition, psychology, and social aspects due to recurring seizures. This condition can affect individuals of all ages and genders and is prevalent worldwide.¹

Epilepsy is a prevalent neurological disorder that impacts individuals from various demographics, including age, race, social status, and location². The seizures associated with epilepsy are repetitive episodes marked by consistent changes in behavior that indicate the neural processes at play. The diagnosis of epilepsy involves distinguishing it from other conditions that cause temporary changes in awareness or behavior. Typically, a thorough medical history or witnessing a seizure is enough to confirm the presence of the disorder. While the cause of epilepsy can often be determined, approximately half of cases remain without a known origin³.

While everyone with epilepsy experiences seizures, not everyone with epilepsy suffers seizures. Epileptic seizures can also be brought on by an abrupt insult to the central nervous system (CNS), such as a systemic, toxic, metabolic, or structural issue⁴. Known as acute symptomatic or provoked seizures, they may not return until the acute phase has passed or the underlying cause has been treated. These seizures are believed to be acute reactions to the underlying cause.⁵ The following conditions are linked to seizures, according to the International League Against seizures (ILAE): Experiencing one unprovoked (or reflex) seizure with a chance of more seizures; (2) experiencing two or more unprovoked (or reflex) seizures occurring more than twenty-four hours apart, equivalent to the total likelihood of recurrence (at least 60%) after two unprovoked seizures in the ten years that follow; or (3) being diagnosed with epileptic syndrome⁶. To simplify population-based investigations, the ILAE Epidemiology Commission proposes to define epilepsy as the occurrence of two or more unprovoked seizures that occur at least 24 hours apart⁷. Any seizure that occurs in the absence of a known trigger is known as an unprovoked seizure. These seizures can be classified as idiopathic or cryptogenic (having no known cause or risk factors), remote symptomatic (occurring after prior stable brain injury), or progressive (occurring after progressive brain abnormalities, such as tumors or de-

generative conditions). One hemisphere of the brain can have focal seizures, both hemispheres can experience generalized seizures or the source of the seizures is uncertain⁸.

Fever can trigger seizures in epilepsy patients who have been diagnosed based on clinical symptoms, EEG results, age over 60 months, and the occurrence of unprovoked attacks. This is because temperature variations can have an impact on several biological functions, including neuronal electrical activity. Temperature significantly impacts how certain ion channels in neurons operate, particularly in the normal and fever ranges of around 36-42 °C. One such ion channel is TRPV4 (transient receptor potential vanilloid 4). Important ionic currents are also influenced by temperature in terms of their strength and speed. These results imply that a rise in the temperature of the neural tissue may enhance the frequency, amplitude, or synchronization of neuronal activity, which in turn may cause seizures⁹.

Generalized seizures referred to as febrile seizures typically impact kids in the six-month to five-year age range. They are characterized by a fever exceeding 100.4 °F (38 °C), which is not linked to an infection of the (CNS), a history of afebrile seizures, or a known cause of seizures (e.g., electrolyte imbalance, hypoglycemia, or substance abuse)¹⁰.

The convulsive temperature threshold varies for each patient; therefore, a specific fever threshold is not necessary to trigger febrile seizures.^{11,12} Primary risk factors for febrile seizures are neurological impairment, viral infection, developmental delay, low blood levels of iron and zinc, maternal stress and smoking, and a family history of seizures.¹⁰

The updated guideline outlined the criteria for using prophylactic diazepam suppositories as follows: 1. Children with a history of recurrent febrile seizures and at least two of the six risk factors – existing neurological abnormalities or developmental delays, focal or recurrent seizures within 24 hours, family history of febrile seizures or epilepsy, age less than 12 months, seizure occurring within 1 hour of fever onset, and seizure with a body temperature below 38.0°C, 2. the children who have experienced a prolonged febrile seizure lasting 15 minutes or longer.¹³ Except for two risk factors – seizures within an hour of the commencement of a fever and seizures with a body temperature below 38.0°C – the amended guideline's criteria for the preventive use of diazepam suppository were nearly comparable to the

previous one.

However, the new guideline specifies that the routine use of diazepam suppository upon arrival at the emergency department is unnecessary if seizures have ceased.¹³ Upon arrival, the previous guideline did not provide instructions on the usage of diazepam suppository¹⁴ and the decision on how to use diazepam suppositories upon arrival for children in whom FS has stopped was left to the pediatrician's judgment. Therefore, there are differences between the previous and current guidelines regarding their usage.

Children who had previously experienced febrile seizures were given oral diazepam for 48 hours at a rate of 0.33 mg/kg every 8 hours. The risk of febrile seizures per person-year was reduced by 44% when diazepam was used¹⁵. To stop seizure episodes in epilepsy patients who experienced seizures during a feverish sickness, we will employ oral diazepam in our trial according to the same protocol.

PATIENTS AND METHOD

From 2020 to 2023, patients were collected during consultations with private clinics, and outpatient (pediatric & neuro-medicine clinics). 430 patients were collected all those patients diagnosed as epilepsy according to clinical findings and EEG. All patients on antiepileptic drugs either monotherapy or 2 types of drugs and aged more than 5 years.

96 of the patients have a provocative factor for seizure which is fever, patients were divided into two groups 48 patients in each group, the 1st group was given oral diazepam in prophylactic dose 0.1-0.3mg/kg/dose for 3 days and the 2nd group did not give oral diazepam (placebo). Patients with poor compliance to treatment and those who had epilepsy due to trauma or neurological insults were excluded from the study from the start.

Data was collected in the form of age, sex, trigger factor, number of attacks during febrile illness [before and after prophylactic therapy, and compliance either to chronic treatment or prophylactic therapy.

Ethical approval: The study was accepted by the approval committee of the College of Medicine, Al-Qadisiyah University. The verbal consensus was obtained from all participants following the full design of the study goal and ways.

Statistical analysis: Data were transformed into SPSS software (version 22) for purpose of statistical descrip-

tion and analysis. Categorical variables were expressed as percentages and number. A comparison of means was done using a student t-test. Comparison of proportions was done using the chi-square test or Fischer exact test according to justified statistical assumptions. The level of significance was set at $p \leq 0.05$.

RESULTS

To calculate the p-value for the data, we will use a chi-square test of independence (The program used to calculate the p-value in this context is a Python script utilizing the scipy library, specifically the stats.chi2_contingency function) then the p-values from the chi-square tests are extracted This test will help us determine if there is a significant association between treatment (on treatment vs. placebo) and the categorical variables provided (sex, age, and the number of attacks per year before and after the treatment). as shown in Table 1.

Table 1. Total patients (sex, age, no. of attacks, compliance)

		Treatment	Placebo	Total
Sex				
Male		28	22	50
Female		20	26	46
Age				
	5-10 years	32	27	59
	11-16 years	16	21	37
No of attacks / Year(during febrile illness)				
Before		28	26	54
After		2	24	26
Compliance				
Compliance to treatment		Fair	Fair	-
Compliance to prophylaxis		Fair	Fair	-

Here are the p-values for each category based on the chi-square tests:

- Sex (male vs. female)
 - p-value: 0.307
 - Interpretation: There is no significant association between treatment and sex at the 0.05 significance level.
- Age (5-10 years vs. 11-16 years)
 - p-value: 0.402
 - Interpretation: At the 0.05 significance level, there is no discernible relationship between age and therapy.
- Number of attacks per year (before vs. after)
 - p-value: 0.00035
 - Interpretation: At the 0.05 significance level, there is a significant correlation between the number of assaults annually and the type of therapy received. This implies that the number of assaults was significantly decreased as a result of the therapy.

In summary, the number of attacks per year during febrile illness is significantly reduced with therapy, although there is no significant correlation seen between treatment and age or sex. As shown in table-2.

Table 2. P-value (sex, age, no. of attacks)

	Treatment	Placebo	p-value	
Sex				
Male	28	22	0.307	
Female	20	26		
Age				
	5-10 years	32	27	0.402
	11-16 years	16	21	
No of attacks / Year(during febrile illness)				
	Before	28	26	0.00035
	After	2	24	

Also, number of attacks and its decrement can be simply shown in Figure 1 where the patients on treatment had good responses to therapy while the placebo group decreased by 2 attacks only.

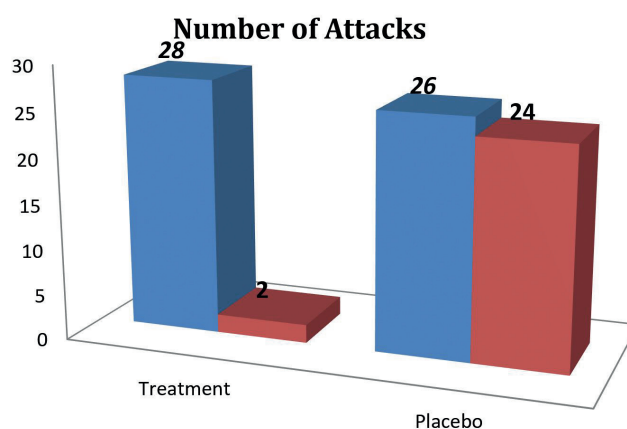


Figure 1. Number of Attacks before and after treatment.

DISCUSSION

Diazepam was administered as a preventive measure to avoid seizure episodes in cases of febrile seizures. A study conducted on patients with a history of febrile seizures showed that giving oral diazepam during fever episodes could lower the chances of recurrence. Children who had experienced febrile seizures in the past were either given while they had a fever, oral diazepam (0.33 mg/kg, every 8 hours for 48 hours) or a placebo. According to the study, using diazepam reduced the probability of febrile seizures per person-year by 44%¹⁵.

According to recent research, kids who had previously experienced febrile seizures been administered oral diazepam during fever episodes and later compared to children in a control group who did not receive any treatment. The study found that the recurrence rate of febrile seizures in the group treated with oral diazepam was 11%, while the control group had a recurrence rate of 30%.¹⁶ It is important to mention that all children who were deemed unsuccessful with diazepam treatment were not following the prescribed drug regimen, mainly due to experiencing negative side effects from the medication.

In the same manner, we give oral diazepam to epilepsy patients during febrile illness (those who develop seizures while they are febrile) and we find the total number of attacks reduced by 92% while in placebo decreased by 7% only.

That means the effective role of oral diazepam in reducing the number of attacks in epilepsy patients during febrile illness as in febrile seizure, higher per cent in our study because we exclude patients with poor compliance at the beginning of collecting data to

give more precise per cent to a decrement in the number of attacks.

Children who had a fever or just when they had a seizure were given rectal or oral diazepam in a study by Knudsen et al.¹⁷ Whether treatment targeted at treating or preventing seizures did not affect the overall prognosis of the children in either group, according to a twelve-year follow-up. So we can expect no known negative feedback on using intermittent doses of diazepam on our patients in the study.

One potential disadvantage of taking medicine intermittently is that a seizure might happen before a fever is noticed. Indeed, in a number of these research, it was more probable that recurrent seizures were caused by a failure in the method rather than a failure of the medication that can interpret occurring of seizures while using oral therapy in our study (8%).

CONCLUSION

We can use oral prophylactic diazepam in epilepsy patients who develop attacks during febrile illness and follow up the response before we decide to add another antiepileptic drug to control several attacks, or at least it will be useful in decreasing the number of attacks.

Ethical approval: the current study was permitted by the Ethical Committee approval of the College of Medicine, University of Al-Qadisiyah.

"The author declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law."

Informed Consent: verbal consent was obtained from every participant

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Conflict of interest: no conflict of interest was declared by the author

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