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# Association between seizure susceptibility with type and optimal dose of antihistamine in patients with a febrile seizure; A retrospective cohort study in Gorgan, Iran

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## Abstract

**Introduction:** Febrile seizures (FSs) are caused by the simultaneous consumption of first- and second-generation antihistamines, which prolong the process in some cases.

**Objectives:** The present study aimed to evaluate the relationship between seizure susceptibility and type of antihistamines in patients with FS.

**Patients and Methods:** This retrospective cohort study was conducted on 364 children with FS admitted to Taleghani Hospital in Gorgan, Iran in 2020. The subjects were selected via convenience sampling and divided into two groups of antihistamine and non-users based on their medical files. Data analysis was performed in SPSS16 using descriptive statistics and chi-square, independent t-test, Mann-Whitney U test, and relative risk.

**Results:** The mean age of the patients was  $22.77 \pm 14.91$  months (6-60 months). 56.1% of the patients were male. Antihistamine was prescribed for 15.6% of the subjects, and the mean interval between fever onset and seizure was shorter in the antihistamine group ( $P=0.37$ ). On the other hand, the mean seizure duration was significantly longer in the antihistamine group ( $P=0.049$ ). The risk of a seizure lasting more than five minutes was 1.14 times higher in the first-generation antihistamine group compared to the second-generation group ( $P=0.078$ ).

**Conclusion:** According to the results, the patients with a history of antihistamine use during the febrile period experienced a significantly longer period of seizure, and a significant relationship was observed between the severity of seizures and antihistamine use. In addition, the mean seizure duration was longer in the first-generation antihistamine group. Therefore, the use of this class of drugs in this age range should be limited to the prescription of a specialist.

## Introduction

Advancement in medical sciences has changed the mortality and morbidity pattern of societies, and the control of non-communicable diseases has become a major priority in the field of health care. Although febrile seizures (FSs) are often self-limiting and benign, they are among the most horrifying experiences of parents (1). FS is the most common type of childhood seizure disorder, occurring in approximately 3-4 % of children aged less than five years (2). The incidence rate of FS in countries such as India, Japan, and Ghana has been reported to be 5-10%, 8.8%, and 14%, respectively (3,4). The International League against Epilepsy defines FS as the seizures occurring with a fever of higher than 38°C in children aged one month to seven years with no infection of the central nervous system, acute electrolyte

## Key point

According to the results, the risk of seizure was higher in the users of first-generation histamines compared to the users of second-generation histamines. Therefore, children in this age range must consume this type of drug only with the prescription of a specialist and should avoid taking medications without a specialist's prescription.

imbalance, or a history of afebrile seizures (5). The risk factors for FS remain unknown although genetic and environmental factors are known to be involved (6). To date, three classes of genes with an autosomal dominant mode of inheritance have been considered in this area. Other contributing factors to the emergence of FSs include a family history of seizure and epilepsy, plasma ferritin and zinc deficiency, maternal smoking habits, and alcohol consumption during pregnancy (7).

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Age is considered to be the most significant risk factor for recurrent FSs as the recurrence risk has been estimated at 28% and 50% in children aged more and less than one year, respectively (8). According to the literature, increased histamine levels elevate the seizure threshold and reduce the severity and duration of seizures (9). Among the four histamine receptors, H<sub>1</sub> and H<sub>3</sub> receptors are suggested to be of paramount importance in decreasing seizure activity. Furthermore, the first generation of H<sub>1</sub> receptor antagonists (e.g., diphenhydramine and chlorpheniramine) elicits epileptiform activity (10). The H<sub>3</sub> receptor antagonists block the action of histamine at the H<sub>3</sub> receptor, thereby reducing seizure activity by releasing histamine (11). On the other hand, histamine receptors are often classified into two categories of first-generation antihistamines and second-generation antihistamines (11).

Some of the findings in this regard have indicated the association of FSs with some first-generation antihistamines (e.g., diphenhydramine, pheniramine, and pyrimethamine) and second-generation antihistamines (e.g., cetirizine, loratadine, and terfenadine) (11,12). Since sedative antihistamines prolong FS duration, the Japanese Society of Child Neurology released a set of guidelines in 2015, which contraindicated the use of sedative antihistamines in patients with FS. However, Daida et al (13) observed no significant difference between the antihistamine and non-user groups in terms of the mean duration of FS. Therefore, their findings could not support the correlation between sedative antihistamine use and the prolonged duration of FS (14,15). According to Sugitate et al (16) FS duration was shorter in the antihistamine group, and the risk of FS duration of fewer than 10 minutes was 1.2 times higher in first-generation antihistamine users compared to non-users.

## Objectives

Given the limited evidence and contradictory results in this regard, the present study aimed to evaluate the correlation between seizure susceptibility and type of antihistamine in the patients with FS who were referred to Taleghani Hospital in Gorgan, Iran during 2019-2020.

## Patients and Methods

### Study design

The present retrospective cohort study was conducted in Gorgan city, northeast of Iran. 364 the records and information related to children with FS based on the research by Haruyama et al (15). The subjects were selected via convenience sampling at the Taleghani children teaching hospital in Gorgan, Iran in the 2020 year and divided into two groups of antihistamine and non-user based on their medical files.

### Data collection

The clinical data of the patients included the type of antihistamine (first- or second-generation), seizure

susceptibility, and antibiotic use. Demographic characteristics were age, gender, and place of residence, which were collected using a researcher-made checklist. Seizure susceptibility was defined as the length of fever and seizure, the interval between fever and seizure, and the severity of seizure and fever. In addition, the interval between seizure and fever was classified as less than five minutes and more than five minutes based on research by Miyata et al (17).

The inclusion criteria of the study were an age range of six months to five years and a fever above 38°C. The exclusion criteria were using unknown antihistamine drugs 24 hours before the seizure and diagnosis of epilepsy before the onset of a recent seizure.

### Statistical analysis

Data analysis was performed using mean and standard deviation for the qualitative data, in addition to frequency distribution tables for quantitative data were used. The Shapiro-Wilk test assesses the normality of the variables. Chi-square and relative risk [RR] with 95% confidence interval (CI), independent *t* test, and Mann-Whitney U test were also applied to compare the response variables in SPSS. In all the statistical analyses, the *P* value of 0.05 was considered significant.

## Results

In total, 364 subjects with a mean age of 22.77 ± 14.91 months (age range: 6-60 months) were enrolled in the study. In terms of gender, 56.1% of the patients were male (mean age: 22.16 ± 12.94 months), and 43.9% were female (mean age: 23.58 ± 16.98 months). Regarding the place of residence, 49.2% and 50.8% of the patients lived in rural and urban areas, respectively. According to the obtained results, 83.9% and 83.2% of the children in the antihistamine and non-user groups had no history of antibiotic use, respectively. In addition, no significant differences were observed between the study groups in terms of gender, place of residence, and antibiotic use (Table 1).

According to the findings, 56 children (15.4%) used antihistamines, 11% of which were first-generation and 4.4% were second-generation. The mean seizure duration in the users of first- and second-generation antihistamines was 1.09 ± 1.77 and 1 ± 1.85 minutes, respectively. No significant differences were observed between the first- and second-generation groups regarding seizure duration (*P*=0.55) and the interval between fever and seizure (*P*=0.79). On the other hand, the risk of a seizure lasting more than five minutes was 1.14 times higher in the first-generation antihistamine group compared to the second-generation antihistamine group. No significant relationship between the type of antihistamine (first- and second-generation) and the severity of seizure (*P*=0.078).

In addition, prolonged severity (more than five minutes) was reported in 30.8% and 69.2% of the subjects

**Table 1.** Demographic characteristics of patients

Variable	Variable levels	Antihistamine	Non-user	P value
		No. (%)	No. (%)	
Gender	Male	25 (12.3)	179 (87.7)	0.062
	Female	31 (19.4)	129 (80.6)	
Place of residence	Rural	25 (14)	154 (86)	0.461
	Urban	31 (16.8)	154 (83.2)	
Antibiotic use	Yes	9 (14.8)	52 (85.2)	0.88
	No	47 (15.5)	256 (84.5)	

in the antihistamine and non-user groups, respectively. A significant relationship between seizure severity and antihistamine use (Table 2). The risk of a seizure lasting more than five minutes was also 2.68 times higher in the antihistamine group compared to the non-user group (RR = 2.68; 95% CI: 1.11-6.52).

Fever was higher than 38 °C in 38.3% of the subjects, and fever above 38 °C was reported in 61.7% and 61.8% of the patients in the antihistamine and non-user groups, respectively. However, no significant association was denoted between fever and antihistamine use (Table 2).

The mean interval between fever and seizure was 5.87±15.41 and 4.54±11.6 hours in the non-user and antihistamine groups, respectively. However, no significant difference was observed between the study groups regarding the mean interval between fever and seizure ( $P=0.374$ ). The mean seizure duration was estimated at 0.79±1.71 and 1.06±1.78 minutes in the non-user and antihistamine groups, respectively. Furthermore, the mean duration of seizure was significantly higher in the antihistamine group compared to the non-user group ( $P=0.049$ ). While the mean seizure duration in the female patients of the two groups was higher than the male patients, the difference was not considered statistically significant (Table 3). The

mean rank of FS duration was lower in the patients living in rural areas in the antihistamine group compared to those living in urban areas in the non-user group; however, the difference in this regard was not considered significant (Table 3).

### Discussion

In general, antihistamines are divided into two categories of first-generation and second-generation drugs. In the present study, first-generation antihistamines were most commonly used, and seizure duration was slightly longer in this group. Moreover, the risk of a seizure lasting more than five minutes was 1.23 times higher in the users of first-generation antihistamines compared to the second-generation users (RR=1.23; 95% CI: 0.22-6.88). The risk of a seizure lasting more than five minutes was 2.68 times higher in the antihistamine group compared to the non-user group (RR=2.68; 95% CI: 1.11-6.52). In a systematic review and meta-analysis, the risk of severe seizure (more than five minutes) was reported to be slightly higher in antihistamine users compared to non-users (RR=1.14; 95% CI: 0.87-1.49) (17).

Our findings indicated a reduction of the interval between fever and seizure, as well as a significant increase

**Table 2.** Correlations between antihistamine use with fever and seizure severity

Variable	Variable levels	Antihistamine Use		P value
		Yes No. (%)	No No. (%)	
Seizure severity	Less than 5 minutes	48 (14.2)	290 (85.8)	0.024
	More than 5 minutes	8 (30.8)	18 (69.2)	
Fever severity	<38 °C	34 (39.3)	188 (38.2)	0.87
	>38 °C	22 (61.7)	116 (61.8)	

**Table 3.** Correlations between seizure duration and demographic variables of patients in study groups

Variable	Variable levels	History of antihistamine use		No history of antihistamine use	
		Mean rank	P value	Mean rank	P value
Gender	Male	24.24	0.058	149.15	0.33
	Female	31.94		157.17	
Place of residence	Rural	24.24	0.058	154.30	0.66
	Urban	31.94		150.7	

in the seizure duration of the antihistamine group compared to the non-user group, which is consistent with the previous studies in this regard (16-23). Furthermore, fever severity was lower in the antihistamine group compared to the non-user group, which is consistent with previous findings (22). However, no relationship was observed between fever severity and seizure incidence in the two groups. Therefore, the incidence of high-degree fevers could not predict the severity and increase of seizure duration.

Non-generalized seizure requires the differentiation of focal lesions. Therefore, unusual seizures should be considered an unpleasant medical condition requiring further intervention (18). Decreased antihistamine-induced hypothalamic histamine neurons may increase neuronal excitability. In addition, interleukin-1 beta is associated with seizures as a seizure agent and increases seizure susceptibility in patients with FS (23). While the new-generation H<sub>1</sub>A has fewer side effects due to not passing the blood-brain barrier, it should be used with caution in younger children since this agent may disrupt the central anticonvulsant histaminergic system (21). Some studies have supported the use of optimal doses of H<sub>1</sub> antagonists in feverish children with allergic symptoms (13,18,24). Nevertheless, Daida et al (13) reported no significant association between antihistamine use and seizure duration, recommending the use of antihistamines for patients with a history of FS.

### Conclusion

According to the results, the use of H<sub>1</sub> histamine antagonists (especially old-generation drugs) could increase seizure duration and decrease seizure threshold in children aged 6-60 months through sedative properties. The risk of seizure was higher in the users of first-generation histamines compared to the users of second-generation histamines. Therefore, children in this age range must consume this type of drug only with the prescription of a specialist and should avoid taking medications without a specialist's prescription.

### Limitations of the study

In the present study, using the new generation of antihistamines was associated with a shorter mean seizure duration and lower seizure severity compared to old-generation antihistamines. Given the limited evidence and highly heterogeneous results in this regard, the subject remains controversial.

### Authors' contribution

**Conceptualization:** Seyed Ali Aghapour.

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**Formal analysis:** Mousa Ghelichi-Ghojogh.

**Funding acquisition:** Seyed Ali Aghapour.

**Investigation:** Hossein Gorzin.

**Methodology:** Mousa Ghelichi-Ghojogh.

**Project administration:** Seyed Ali Aghapour.

**Resources:** Seyed Ali Aghapour.

**Supervision:** Seyed Ali Aghapour.

**Validation:** Mousa Ghelichi-Ghojogh.

**Visualization:** Seyed Ahmad Hosseini.

**Writing—original draft :** EG, Mousa Ghelichi-Ghojogh.

**Writing—review and editing:** Seyed Ahmad Hosseini, Hossein Gorzin.

### Conflicts of interest

The authors decline any kind of conflict of interest.

### Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Golestan University of Medical Sciences approved this study (Ethical code# IR.GOUMS.REC.2020.332). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from Hossein Gorzin thesis (Thesis #111126) of a pediatric resident at this university. Additionally, ethical issues (including plagiarism, data fabrication, and double publication) were completely observed by the authors.

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