

## Oral Diazepam in Febrile Seizures Following Acellular Pertussis Vaccination

### Abstract

**Background:** Febrile seizure is the most common type of seizures among children, which is a terrible and frightening experience for parents who are concerned about its recurrence. The aim of this study was to evaluate the effect of diazepam on preventing the recurrence of febrile seizure following acellular pertussis vaccination. **Materials and Methods:** In this clinical trial, 121 children with a history of febrile seizure that required the pertussis vaccination were enrolled and divided into two groups; the first group was treated with oral diazepam for 48 h after vaccine injection and the control group received antipyretics only if fever occurred after the vaccination and used rectal diazepam for controlling seizure if a seizure occurred. The incidence of fever and seizure after the injection of the vaccine and incidence of febrile seizure were compared. **Results:** Nearly, 85.7% in the oral diazepam group and 87.9% in the rectal diazepam group had fever after receiving the pertussis vaccine, but the incidence of fever was not significantly different between the groups. Seven children (12.06%) in the rectal diazepam group had a seizure after pertussis vaccination, and none of the children in the oral diazepam group had a seizure after receiving the vaccine at 18 months of age. This difference was significant. **Conclusion:** Prophylaxis with diazepam administration in children with a history of febrile seizure can prevent recurrence of febrile seizure after pertussis vaccination.

**Keywords:** *Diazepam, seizure, vaccine*

### Introduction

The febrile seizure is the most common type of seizure in children and occurs in 2%–5% of children, generally affecting children between the ages of 3 months and 5 years, and the peak of occurrence is at 18 months of age.<sup>[1]</sup> The febrile seizure is one of the most common causes of hospitalization and referral to pediatric emergencies globally.<sup>[2]</sup> Although febrile seizures are benign and self-limiting in most cases, they remain as terrible and frightening experiences for parents.<sup>[1]</sup> Febrile seizures include seizures in children after the age of 6 months accompanying a febrile malady, which the fever has not been caused by central nervous system infection, and no history of unprovoked seizures exists, and has no criteria for acute symptomatic seizure.<sup>[3]</sup> Any viral or bacterial disease can lead to febrile seizures, and febrile seizures can also occur after vaccine injection.<sup>[4]</sup>

An important concern with these patients is the risk of recurrence, that is, about 29%–35%.<sup>[5]</sup> Despite using antipyretic

drugs when fever is present in children with febrile seizures, limited evidence exists to demonstrate if antipyretics reduce the risk of this disorder.<sup>[6]</sup> According to the studies, fever reduction is not an effective way to prevent recurrence of febrile seizures.<sup>[7]</sup> There is some evidence about the diazepam prophylaxis effect on preventing recurrence of febrile seizures and most of the comments suggest that this treatment seems to be effective.<sup>[8]</sup> The main complications of using diazepam in children are drowsiness and ataxia and may overshadow the clinical judgment of the physicians for identifying more serious febrile illnesses such as meningitis and encephalitis.<sup>[9]</sup> Studies in children with febrile seizures have shown that oral diazepam is well tolerated by children and using oral diazepam reduces the risk of recurrence of febrile seizure by up to 50%, and using this medication in febrile illnesses reduced the risk of febrile seizures.<sup>[9]</sup> There are three management methods for febrile seizures' recurrence: using rectal diazepam if seizures last longer than 5 min, using oral diazepam for

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### Access this article online

**Website:** [www.advbiores.net](http://www.advbiores.net)

**DOI:** 10.4103/abr.abr\_96\_18

### Quick Response Code:



**How to cite this article:** Ghazavi M, Nasiri J, Yaghini O, Soltani R. Oral diazepam in febrile seizures following acellular pertussis vaccination. *Adv Biomed Res* 2019;8:29.

**Received:** May, 2018. **Accepted:** February, 2019.

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48 h after the initiation of fever, and using phenobarbital and sodium valproate; of these three methods, using oral diazepam for 48 h after the initiation of fever is usually more used than other methods.<sup>[10,11]</sup>

One of the causes of fever in children is the injection of vaccine, which is commonly seen following pertussis vaccination, and the vaccination process in Iran includes receiving the pertussis vaccine as a acellular vaccine as DTP (diphtheria, tetanus toxoids and pertussis) at the age of 18 months and at the age of 6 years and also as DTP-HH at 2, 4, and 6 months of ages. The concern of the physicians and parents who have experienced febrile seizures in their children is the recurrence of febrile seizures after the injection of the vaccine.<sup>[12,13]</sup> Evaluations of postvaccination complications in some studies have shown that two of the side effects of this vaccine were the pain at the injection site (86.9%) and postvaccination fever (48.4%).<sup>[14]</sup> There are also other studies that reported 54.5% rate of fever incidence after pertussis vaccination and most of these complications occurred after the 1<sup>st</sup> or 2<sup>nd</sup> day after vaccination.<sup>[15]</sup> There are also studies which showed that the pertussis vaccine was associated with higher incidence of febrile seizures in the first 3 days after vaccination and did not accompany nonfebrile seizures.<sup>[16]</sup> One of the side effects of pertussis vaccination is the febrile seizure, and one of the main concerns of the parents is the onset of fever after pertussis vaccination. The possibility of seizure incidence following a pertussis vaccination might occur following a fever and also studies have shown that this type of acellular vaccine is neurotoxic and cause of seizure might be this fact.<sup>[17]</sup> Seizures have been reported to occur with more incidences following the acellular pertussis vaccination. Patients with a history of febrile seizure are prone to recurrence of the seizure following a vaccine injection.<sup>[17]</sup> In this study, we aimed to investigate whether diazepam prophylaxis is able to prevent the recurrence of febrile seizure following acellular vaccination or not.

## Materials and Methods

This is a randomized clinical trial conducted on children with a history of febrile seizure requiring the injection of pertussis vaccine in ages of 18 months and 6 years.

The sample size of this study was calculated as 130 individuals based on previous studies with a 95% confidence interval, 1.96 and coefficient of statistical test power of 0.84. Participants of the study were selected based on the inclusion and exclusion criteria; initially, the study was fully explained for the parents, and if satisfied, the informed consent form was completed. The inclusion criteria of the study involved: (1) age more than 1 year and (2) history of febrile seizures. Exclusion criteria consisted: (1) having contraindications for the pertussis vaccine, including the occurrence of seizures following vaccine injecting, (2) continuous usage of anticonvulsants in the child, and (3) the parents' disinclination to continue

participation in this study. The cases were randomly divided into two groups of 65 using random allocation software. The first group was treated with diazepam tablets (Kharazmi Pharmacy Factory, Iran) at a dose of 1 mg/kg daily as TID, with a maximum daily dose of 15 mg. The medication was given to the children for 48 h after vaccine injection. Furthermore, if fever occurred in this group, antipyretics were used. After the injection of the vaccine, the control group used antipyretics only if fever occurred, and in case of seizure, rectal diazepam was used for controlling seizure at a dose of 0.5 mg/kg.

Before the vaccine was injected, a special form was completed for each child, including the name, date of birth, age, gender, address, telephone number, number of febrile seizures, age at the first febrile seizure, age at the last febrile seizure, type of the seizure, evolutionary process, history of prematurity, neonatal jaundice history, neonatal seizure history, history of neonatal hospitalization, and the history of febrile seizure and epilepsy in first-, second-, and third-degree relatives. On the third and 7<sup>th</sup> days after the injection of the vaccine, patients' parents were contacted and were asked about the incidence of fever and also seizure at the time after the injection of the pertussis vaccine. In cases of the occurrence of fever or seizure, a special form was reported for each patient.

Participants' information was entered into SPSS version 22 (SPSS corp. the USA)<sup>[18]</sup> and analyzed. Mean and the standard deviation were used for reporting the quantitative data, and for reporting the qualitative information, number and percentages were used. To compare the data, sample *t*-test and Chi-square tests were used. In this study,  $P < 0.05$  is considered as statistically significant. This study was approved by the Ethics Committee of Isfahan University of Medical Sciences (396064). Furthermore, this study was registered in the Iranian Registry of Clinical Trials (IRCT20130311012782N24) (<https://irct.ir/trial/33542>).

## Results

In this study, 130 children with the previous history of febrile seizure were selected and divided into two groups of 65 individuals. Two participants in the first group and 7 individuals in the second group did not cooperate at the time of follow-up and were excluded from the study [Figure 1], and information was collected from 121 patients (63 in the first group and 58 in the second group). In the oral diazepam group, 68.3% (43 patients) and 44.8% (26 children) of the rectal diazepam group were male ( $P = 0.16$ ) [Tables 1 and 2]. Among the children examined, 2 individuals in the oral diazepam group and 1 participant in the rectal diazepam group had received the pertussis vaccine at the age of 6 years and were followed up, and the rest of the participants were followed up after receiving the vaccine at the age of 18 months.

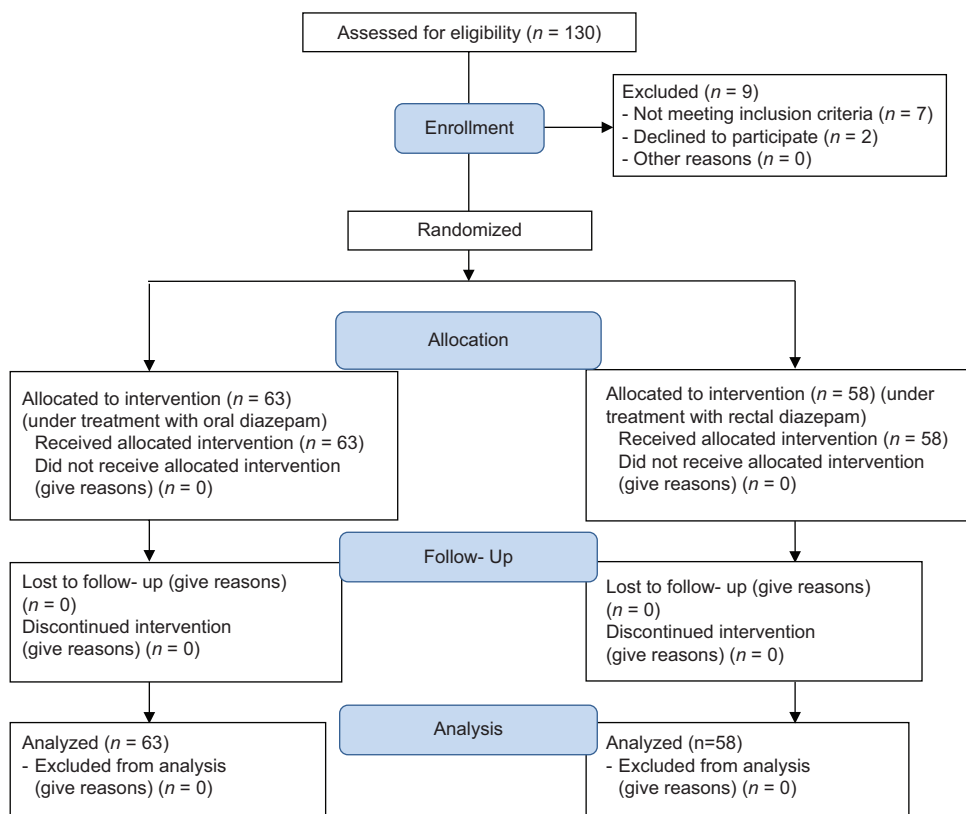


Figure 1: Consort flow diagram

Table 1: Mean and standard deviation of quantitative variables in study groups

Variable	Mean±SD		P
	Oral diazepam group	Rectal diazepam group	
Age	18.47±2.07	18.32±10.6	0.34
Number of seizures	1.47±0.69	1.77±0.7	0.52
Age at the first seizure	10.46±11.94	11.86±1.47	0.07
Age at the last seizure	15.03±12.35	18.43±7.68	0.16

SD: Standard deviation

The number of seizures experienced before the intervention was  $1.47 \pm 0.69$  times in the oral diazepam group and was  $1.77 \pm 0.70$  in the rectal diazepam group ( $P = 0.52$ ). The age at the first seizure was  $10.46 \pm 11.94$  months in the diazepam group and  $11.86 \pm 1.47$  months in the rectal diazepam group ( $P = 0.07$ ), and the age at the last seizure was  $15.03 \pm 12.35$  months in the oral diazepam group and was  $18.43 \pm 7.68$  months in the rectal diazepam group ( $P = 0.16$ ). The type of seizure was “simple” in 49.2% (31 cases) of the children in the oral diazepam group and 58.6% (34 cases) of the children in the rectal diazepam group ( $P = 0.1$ ). Developmental milestone was normal in both groups, and there was no child with any abnormal evolution. The history of prematurity was found in only 7.9% (5 cases) of the children in the diazepam group. History of neonatal jaundice was present in 82.5% (52 cases) of the children in the oral diazepam

group and 41.3% (50 cases) of the children in the rectal diazepam group ( $P = 0.62$ ). None of the children in neither of the groups had a history of neonatal seizure. The history of neonatal hospitalization was present in 19% (12 cases) of the children in the oral diazepam group and 20.7% (12 cases) of the children in the rectal diazepam group ( $P = 0.82$ ). Distribution of the history of febrile seizure and epilepsy in first-, second-, and third-degree relatives did not differ significantly between the groups ( $P < 0.05$ ) [Tables 1 and 2].

Nearly, 85.7% of the children (54 patients) in the oral diazepam group and 87.9% of the children (51 patients) in the rectal diazepam group had fever after the injection of the pertussis vaccine, but there was no significant difference in regard to the incidence of fever between the groups ( $P = 0.79$ ). Seven (12.06%) of the children in the rectal diazepam group had seizure after receiving the vaccine, and all of them had used rectal diazepam during seizure and then had been transferred to a hospital or clinic, and none of the children in the oral diazepam group demonstrated seizure after the vaccine injection at the age of 18 months ( $P = 0.006$ ). In this study, 95% of the patients were at the age of 18 months.

## Discussion

This study evaluated the prophylactic effect of oral diazepam in the recurrence of febrile seizure following an injection of pertussis vaccine and concluded that oral

**Table 2: Frequency distribution of qualitative variables in the study groups**

Variable	Oral diazepam group, n (%)	Rectal diazepam group, n (%)	P
Gender			
Boy	43 (68.3)	26 (44.8)	0.16
Girl	20 (31.7)	32 (55.2)	
Type of the seizure			
Simple	31 (49.2)	34 (58.6)	0.1
Complex	32 (50.8)	24 (41.4)	
Prematurity	5 (7.9)	0	0.06
Neonatal jaundice	52 (82.5)	50 (41.3)	0.62
History of febrile seizure in first-degree relatives	13 (20.6)	12 (20.7)	0.58
History of febrile seizure in second-degree relatives	11 (17.5)	12 (20.7)	0.81
History of febrile seizure in third-degree relatives	10 (15.9)	7 (12.1)	0.61
History of epilepsy in first-degree relatives	4 (6.3)	6 (10.3)	0.51
History of epilepsy in second-degree relatives	4 (6.3)	7 (12.1)	0.35
History of epilepsy in third-degree relatives	4 (6.3)	0	0.12

administration of this medication can significantly prevent seizure attacks following postvaccination fever but does not make any difference in the incidence of the fever.

Febrile seizures in children are the seizures after the age of 6 months accompanying a febrile illness which the fever was not due to central nervous system infections and the patient had no history of neonatal seizures or unprovoked seizures and did not have criteria for symptomatic acute seizures.<sup>[3]</sup> One of the fears of the parents of children who have experienced a febrile seizure for once is the recurrence of seizure attacks. The risk of the recurrence of febrile seizure depends on the genetic and environmental factors. In previous studies, some risk factors for the recurrence and febrile seizures have been reported: (1) age <1 year, (2) history of febrile seizure in first-degree relatives, (3) occurrence of seizure after fever <40 degrees, (4) incidence of seizure less than an hour from the onset of fever, (5) complex seizures, (6) history of epilepsy in first-degree relatives, (7) male gender, (8) parental familial relativity, (9) going to kindergarten and frequent attacks of fever, and (10) several attacks of febrile seizure, the first five of which are more important.<sup>[19]</sup> In this study, risk factors such as family history, age, type of seizure, and gender were studied in two groups; no significant differences were seen between the groups in terms of these risk factors. In this regard, patients in these two groups were rather homogeneous.

In this study, a high percentage of patients in both groups experienced fever after the injection of pertussis vaccine, and only a small group of patients did not report fever. The

pertussis vaccine has been recommended by international vaccination committees and is injected at 18 months of age and at 6 years of age in children, and studies have shown that this vaccine increases the risk of fever and also febrile seizures.<sup>[20,21]</sup> There is evidence that this vaccine develops a high fever between the ages of 12 and 23 months.<sup>[22]</sup> A study of 459,000 children between the ages of 12 and 23 months has shown that the injection of the pertussis vaccine has been associated with an increase in febrile seizure 7–10 days after vaccination.<sup>[23]</sup>

In this study, children who received oral diazepam 48 h after receiving the pertussis vaccine did not demonstrate any febrile seizure episodes, while 7 patients in the group who received antipyretics only if fever occurred after the vaccination were reported with febrile seizure. Of the patients who experienced the seizure, 5 cases (71.42%) experienced the seizure on the 2<sup>nd</sup> day and 2 (28.58%) experienced the seizure on the 3<sup>rd</sup> day after receiving the vaccine. Previous studies on children with febrile seizure show the effects of diazepam prophylaxis to prevent recurrence of febrile seizure.<sup>[8,24]</sup> A study on children with febrile seizure has examined the effects of rectal and oral diazepam in preventing recurrence of this disorder in febrile illnesses and has shown that relapse rate in the group receiving oral diazepam was 0%–16% and the rate in the rectal diazepam group was 10%–36%.<sup>[25]</sup> Another study on 406 children with febrile seizure has been evaluated using oral diazepam at a dose of 1 mg/day in children with febrile illnesses and has stated that the medication, as divided into three doses (every 8 h), has been tolerated well by children and also reduced the risk of the recurrence of febrile seizures by up to 50%.<sup>[9]</sup> Another study on 85 children with febrile seizure compared the effects of two medications, diazepam, and phenobarbital and has demonstrated that administration of these medications is beneficial in patients with febrile conditions, and there is no difference between the two groups. In this study, the risk of recurrence of febrile seizure was 18.2% in the diazepam group and 32.3% in the phenobarbital group.<sup>[26]</sup> The results of this study correlate with the results of previous studies and indicate the desirable effects of oral diazepam in reducing the recurrence of febrile seizure, especially after receiving the pertussis vaccine. In previous studies, diazepam has generally been administered in the febrile processes and did not investigate the fever caused by the pertussis vaccine, while our study evaluated the effects of this medication after the administration of the pertussis vaccine, which is one of the vaccines that after its injection, children experiences fever and parents are worried about it.

This study has many strengths and weaknesses. One of the strengths of this study was the similarity of the two groups in terms of risk factors for recurrence of febrile seizure, which did not have any significant differences between the groups and probably did not have any significant

effects on the results of this study. The other strong point of this study is the evaluation of the effects of diazepam on reducing the recurrence of febrile seizure following the injection pertussis vaccine, which is one of the vaccines that mothers are concerned about the fever they cause and may even refuse the vaccine for fear of the recurrence of febrile seizure. One of the limitations of this study is the sample size used which is small for generalizing to the entire community, and for evaluating the exact and definite effects of diazepam in reducing the febrile seizures after receiving the vaccine at the age of 18 months, it is necessary that further larger studies need to be conducted with higher sample sizes.

## Conclusion

Overall, this study has demonstrated that prescribing diazepam for prophylaxis in children with a history of febrile seizure can prevent recurrence of febrile seizure following a pertussis vaccination.

## Acknowledgments

This study was approved by the Research Deputy at the Faculty of Medicine of Isfahan University of Medical Sciences.

## Financial support and sponsorship

The current study was supported by Isfahan University of Medical Sciences.

## Conflicts of interest

There are no conflicts of interest.

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