FEBRILE SEIZURE AND THE EFFICACY OF DIAZEPAM IN CONTROLLING RECURRENCE OF FEBRILE SEIZURES IN CHILDREN: A LITERATURE REVIEW

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ABSTRACT
Febrile seizures are a benign condition classically associated with high fever in children during their early lives. It occurs between 6 months to 6 years of age, in the setting of an acute febrile illness, without previous afebrile seizures, significant prior neurological abnormality and no CNS infection. Febrile seizures can be classified as simple and complex febrile seizures. The prognosis of febrile seizure is good for most of the patients though it can be tiresome for children as well as for parents. The prevention of febrile seizure is highly desirable. Diazepam is a benzodiazepine that has been used widely in the management of epilepsy and other convulsive disorders for the past four decades and controls seizures in 60–80% of the cases. An overview of febrile seizures and the efficacy of diazepam in controlling recurrent febrile seizures, and its adverse effects has been overviewed in this article by comparing various literature studies. Conclusion: Though febrile seizure is a benign condition, it is highly desirable to prevent recurrent episodes inorder to prevent consequences associated with it. Diazepam is safe and effective in controlling acute febrile seizure recurrences in children with minimal side effects.

KEYWORDS: Febrile seizure, diazepam, children, benzodiazepines, recurrence, epilepsy.

1. INTRODUCTION
Febrile seizure is defined as a seizure occurring in febrile children between the ages of 6 and 60 months who do not have an intracranial infection, metabolic disturbance, or history of febrile seizures (AAP).[1] Febrile seizures can be considered as a syndrome due to its similar characteristics among various affected children such as, 1) Febrile seizures are commonly limited to a certain age groups, 2) Most of the children with febrile seizures shows normal neurological and structural development after the seizure episodes, 3) Febrile seizure is not associated with developmental or structural anomalies in the brain, although the vulnerability to febrile seizure is increased with the existence of such pathology.[2] Febrile seizures can be classified as simple and complex febrile seizures.[3] The differentiating features among the two types are mentioned in Table1. Simple febrile seizures are generalized, tonic clonic seizures which lasts less than 15 minutes and do not recur within the same febrile illness where as complex febrile seizures lasts more than 15 minutes, presents with focal features at the onset or during the seizure and reoccur within the same febrile illness. Febrile status epilepticus (FSE) is a subgroup of complex febrile seizures. Most febrile seizures are simple; however, up to 30% might present as complex febrile seizures.[12] The peak age of onset in developing febrile seizure is 14-18 months of age and the incidence rate is about 3-4% in normal young children.[3] It is mostly associated with simple viral infections and are benign. The overall recurrence rate after the first episode is about 30-37% but in child less than one year of age, it could be about 50%.[4] Febrile seizures occur more commonly in Asian population.[5] Gender predominance has also been studied. There are studies that conclude a higher incidence of febrile seizures in male children than in female children.[6] Some studies have shown no significant gender differences.[7] It is found that simple febrile seizures do not carry a risk of death, but there is a very small risk of death after complex febrile seizures (CFSs), particularly febrile status epilepticus.[8]
Table 1: The differentiating features of simple febrile seizures and complex Febrile seizures.

<table>
<thead>
<tr>
<th>Features</th>
<th>Simple febrile seizures</th>
<th>Complex febrile seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>Short (&lt;15 minutes)</td>
<td>Longer (&gt;15 minutes)</td>
</tr>
<tr>
<td>Focal features</td>
<td>Generalized tonic-clonic features</td>
<td>Focal seizures with or without secondary generalization.</td>
</tr>
<tr>
<td>Recurrence</td>
<td>No recurrence within the next 24 hours</td>
<td>May present with repetitive seizures during the next 24 hours</td>
</tr>
<tr>
<td>Postictal features</td>
<td>No postictal pathology</td>
<td>Todd’s paresis may be present (a period of paresis of affected limbs)</td>
</tr>
</tbody>
</table>

2. OBJECTIVES
This review is an overview of febrile seizures and safety, efficacy, mechanism of action and adverse effects of diazepam in controlling febrile seizure recurrences by comparing various studies.

3. METHODS
An electronic search was carried out at PubMed, Embase, Cochrane library, Nelson book of pediatrics and Google search engine to realize this review. Search was limited to literature and studies published in English language. The keywords used were febrile seizure, diazepam, children, benzodiazepines, recurrence, and epilepsy.

3.1 Definition
Febrile seizures are defined differently by the National Institutes of Health (NIH), the International League against Epilepsy (ILAE), and the American Academy of Pediatrics (AAP). NIH (1980) defined FS as an abnormal, sudden, excessive electrical discharge of neurons (gray matter) that propagates down the neuronal processes (white matter) to affect an end organ in a clinically measurable fashion, occurring in infancy or childhood, usually between 3 months and 5 years of age, and is associated with fever but lacks evidence of intracranial infection or defined cause. [13] The ILAE (1993) defined FS as a seizure occurring in childhood after age 1 month, associated with a febrile illness not caused by infection of the CNS, without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria of other acute symptomatic seizures. [34] Most recently, the AAP (2008) defined febrile seizure as a seizure occurring in febrile children between the ages of 6 and 60 months who do not have an intracranial infection, metabolic disturbance, or history of afebrile seizure. [1] Febrile seizures are commonly classified as simple and complex febrile seizures.

3.2 Risk factors
The risk factors for developing first febrile seizures includes, genetic factors, age, gender, fever, type and duration of seizure, a first or second degree relative with a positive family history of febrile seizures, a neonatal nursery stay of more than 30 days, developmental delay, premature birth, fetal growth retardation, environmental factors such as exposure to nicotine in utero, alcohol consumption during pregnancy, perinatal exposure to antiretroviral drugs or antihistamine use. [9,10,12] The children with more than two or more risk factors have a chance of developing febrile seizures around 28%. [11] The factors associated with greater risk of recurrent febrile seizure is a family history of FS and onset of first FS at less than 18 months of age. The other two definite risk factors are peak temperature and the duration of fever prior to seizure. [12] The shorter the duration of fever, the higher the chance of recurrences. Gastroenteritis is the underlying illness appeared to have a significant protective association with febrile seizure. [12] The studies have also shown significant relationship between recurrence of febrile seizures and influenza A, [13] Iron deficiency anemia [14] and vaccination with measles containing vaccine. [15]

3.3 Pathophysiology
The mechanism of febrile seizure remains unclear but it is thought to be multifactorial. Both genetic and environmental factors are suspected to be responsible for the febrile seizure episodes. Many neuronal functions such as several temperature-sensitive ion channels are altered by elevated brain temperatures. The fever-promoting pyrogen interleukin-1β contributes to development of fever generation and fever leads to the synthesis of this cytokine in the hippocampus. [36] Interleukin-1β, acting via both glutamate and GABA, has been shown to increase neuronal excitability. Fever of specific infectious etiologies, specifically human herpes virus 6 (HHV6), might influence the possibility of generation of FS. [36] The genetic composition has likely resulted in neurodevelopmental vulnerability, with alterations in sodium channel expression, hypothalamic dysregulation, and both cortical and hippocampal excitability.

3.4 Clinical Presentation
The classical scenario of simple FS is a seizure developing in the setting of acute febrile illness other than central nervous system infection. It affects children between 6 months and 5 years of age. The seizure is described as generalized, lasting less than 15 minutes, either generalized clonic or generalized tonic-clonic, which do not recur within the same febrile illness. The child is otherwise neurologically healthy, with no concerning focal neurological deficits. Motor and social development is usually normal. History and physical examination are crucial to conclude the cause of the fever. Complex febrile seizures occurs in age group outside the usual range, focal onset seizures, prolonged seizures lasting more than 15 minutes, recurrent seizures within the same day, and patients with an unexpected
prolonged recovery period. Simple FS are more common than complex FS. Febrile status epilepticus a subgroup of complex FS are associated with very small risk of death.\[8\]

3.5 Diagnosis and Management
There are no routine laboratory tests required, but to check electrolytes and blood sugar levels might be beneficial, especially with a gastroenteritis illness. A simple febrile seizure does not usually require further evaluation such as electroencephalography, neuroimaging, or other investigations. However, meningitis should be ruled out in any febrile child. In infants younger than 1 year, performance of an lumbar puncture is strongly advised, because the clinical signs and symptoms associated with meningitis may be minimal or absent in this age group.\[21\] The AAP recommends not to perform following investigations routinely for identifying the cause of a simple FS: measurement of serum electrolytes (calcium, phosphorus, or magnesium), blood glucose, or complete blood count. However, some children seen with FS are dehydrated initially and have low serum sodium concentration; therefore, they should be treated with hydration therapy with hypotonic fluid. In young children, evaluation of complete blood count may be useful to rule out bacteremia. Neuroimaging studies are indicated for patients with a history of trauma or unusual residual neurological manifestations. The prognosis of febrile seizure is good for most of the patients though it can be tiresome for children as well as for parents. The prevention of next seizure episode is important to prevent hypoxic brain damage and sudden fall related injuries. Thus, prevention of febrile seizure is highly desirable. The mainstay of managing febrile seizure is to rule out the cause of fever and exclude any intracranial pathology or infection. Reassurance and education of the parents regarding the disease and management would be beneficial. Although antipyretics have shown uncertain to prevent febrile seizure and recurrences, antipyretics can be initiated to control the fever and for reassurance. Prophylactic anticonvulsants may not be beneficial unless for recurrence cases. Over the past decades various regimens of benzodiazepines have been tried with various degree of success. Diazepam is a benzodiazepine that has been extensively used in the management of epileptic seizures for four decades.\[16\] Acute medications such as rectal diazepam (0.5 mg/kg) or buccal (0.4-0.5 mg/kg) or intranasal (0.2 mg/kg) midazolam administration are effective in controlling an ongoing seizure when intravenous access is not accessible, and can also be provided for home use in patients with initial prolonged febrile seizure and a high risk of recurrences.\[15\] Diazepam given orally or rectally has been demonstrated statistically to be effective in reducing the recurrence of simple and complex FS; however, prior to the detection of fever seizure could begin, resulting in “failure” of the preventive therapy.\[23,24,30\]

3.6 Role of diazepam
Diazepam is a classical benzodiazepine which has been used extensively to treat seizures for decades. Diazepam has anticonvulsant properties. It has no effect on GABA levels and no effect on glutamate decarboxylase activity, but has a slight effect on gamma-aminobutyric acid transaminase activity. It has a rapid onset and a short duration of action. Intravenous and rectal diazepam plays a major role in preventing acute febrile seizures. Intermittent prophylaxis with oral diazepam during first 3 days of febrile illness is associated with fewer complications such as lethargy and ataxia.\[17\] Rectal diazepam is generally regarded as gold standard for prehospital management of acute seizures in children.

3.7 Mechanism of action
Benzodiazepines are positive allosteric modulators of the GABA type A receptors (GABA A). The GABA A receptors are ligand-gated chloride-selective ion channels that are activated by GABA, the major inhibitory neurotransmitter in the brain. Binding of diazepam to this receptor complex promotes binding of GABA, which in turn increases the total conduction of chloride ions across the neuronal cell membrane. Increased chloride ion influx causes hyperpolarization of the neuronal membrane. As a result, the difference between resting potential and threshold potential is increased and firing is less likely. The arousal of the cortical and limbic systems in the central nervous system is reduced.\[18\] Diazepam appears to act on areas of the limbic system, thalamus, and hypothalamus, inducing anxiolytic effects. Benzodiazepine drugs including diazepam increase the inhibitory processes in the cerebral cortex.\[19\]

3.8 Pharmacokinetics of diazepam
Diazepam has a rapid onset of action (3-5 minutes for IV and 15-30 minutes for IM) and a short duration of action (20-30minutes). Diazepam can be administered orally, parental, rectal (gel, suppository, solution), intramuscularly. It has rapid absorption and fast onset of action when administered orally where as in IM route it has a slow absorption. The bioavailability after oral administration is 100% and 90% after rectal administration. The half-life of diazepam is 30-56 hours in general.\[18\] The distribution half life is about 2 to 13 minutes.\[20\] Peak plasma levels occur between 30 and 90 minutes after oral administration and between 30 and 60 minutes after intramuscular administration. After rectal administration, peak plasma levels occur after 10 to 45 minutes. Diazepam is highly protein bound and lipidsoluble, and is widely distributed throughout the body after administration. It easily crosses both the blood–brain barrier and the placenta, and is excreted into breast milk. After absorption, diazepam is redistributed into muscle and adipose tissue.\[20\] Diazepam undergoes oxidative metabolism by demethylation (CYP 2C9, 2C19, 2B6, 3A4, and 3A5), hydroxylation (CYP 3A4 and 2C19) and glucuronidation in the liver as part of the cytochrome P450 enzyme system. It has several pharmacologically active metabolites. The main active
metabolite of diazepam is desmethyldiazepam. These metabolites are excreted primarily in the urine.[20]

3.9 Side effects of diazepam
In children, diazepam can cause side effects such as lethargy, nervousness, irritability, excitement, insomnia, muscle cramps, amnesia, ataxia, trembling, unusual restlessness, confusion, nightmares, or mental depression, difficult or frequent urination, blurred vision, dry mouth, upset stomach including diarrhea.

4. DISCUSSION
Febrile seizures are seizures occurring between 6 months to 6 years of age, in the setting of an acute febrile illness, without previous afebrile seizures, significant prior neurological abnormality and no CNS infection. Diazepam has been used in the management of epilepsy and other convulsive syndromes for the past four decades and controls seizures in 60–80% of the cases.[21] An ideal anticonvulsant should be safe, effective, rapidly acting, easy to administer and cost effective. In acute seizures, intravenous or rectal preparations of diazepam are usually preferred. The efficacy of diazepam in controlling febrile seizure, its recurrences and the adverse effects has been overviewed in this article by comparing various literature studies. This review includes trials using randomized or quasi randomized study that compared diazepam with placebo or no treatment. Children aged between 6 months to 7 years with the history of febrile seizure are included in their studies.

Various studies
There are around ten trials that compared oral or rectal diazepam with placebo or no treatment. The interventions compared against placebo or no treatment included intermittent oral diazepam in four studies (Autret 1990, Ramakrishnan 1989, Rosman 1993, Verrotti 2004), or rectal diazepam in six studies (Knudsen 1985, Mosquera 1987, Pavlidou 2006, Taghdiri 2011, Uhari 1995, Hirabayashi 2008). In three trials (Autret 1990; Rosman 1993; Uhari 1995) the control group received placebos and in the remaining six the controls received no treatment. Most trials assessed recurrence at 6, 12 and 24 months, recurrence at 18, 36, 48 and 60 to 72 was only assessed by one trial each. All trials included participants with a first febrile seizure (FS), except Rosman 1993 (≥1 FS) and Taghdiri 2011 (all FSs), and some included only participants with simple febrile seizures (Autret 1990; Verrotti 2004).

Rosman et al 1993 studied 406 children aged six to 60 months who had at least one febrile seizure. The interventions were intermittent oral diazepam 0.33 mg/kg 8th hourly or placebo. Outcomes were recurrent seizures and adverse effects during 24 months of treatment. Out of 153 children who were treated with diazepam, 39% had lethargy, ataxia, irritability and other moderate side effects that were reversed after dose reduction. The study concludes that oral diazepam, given during febrile illness, is safe and reduces the risk of recurrent febrile seizures.[22] A major criticism for this study, however, was that the number of patients to treat to prevent one FS was 14.[22] Verrotti et al 2004 studied 110 children aged six months to five years with one simple febrile seizure; 45 children were randomly assigned as group A to treat with intermittent oral diazepam (0.35 mg/kg every 8th hourly) during each episode of fever higher than 38.8°C, continuing until the child had been afebrile for 24 hours; and 65 children were assigned to group B with no treatment. They were followed for assessment of recurrent seizures at 48 months after randomization and adverse medication effects during the 48 months of treatment. The study was statistically significant, P value <0.05. The most common side effects observed were ataxia, lethargy and irritability. In particular, 14 children (31.1%) had ataxia, 13 (28.8%) presented lethargy and 11 children (24.4%) had irritability. In all cases, these side effects lasted less than 36 hours. No deaths or persisting hemiplegia occurred in the study. All children were followed for at least 48 months after the first febrile seizure; more than half of first recurrences occurred within 6 months, three quarters within 12 months, and 96% of first recurrence took place within 24 months of the onset. This study concluded, oral diazepam, given only when fever is present, is an effective means of controlling the risk of recurrent febrile seizures.[23] Knudsen et al 1985 reported a study of 289 children following their first febrile seizure, allocated either to intermittent rectal diazepam 0.5mg/kg every 12 hours (5 mg for children less than 3 years or 7.5 mg for children aged over three years) until the temperature falls below 38°C compared to no treatment. They were followed for assessment of recurrent seizures at 6, 12, and 18 months after randomization and adverse effects during 18 months of treatment. His study reached the conclusion that diazepam management during a fever is ineffective in very low-risk children (no risk factors), has medium efficacy in intermediate-risk children, and is highly efficacious in high-risk patients. In the high-risk group, the recurrence rate is reduced from 75% to 100% by means of prophylaxis.[24]

Mosquera et al 1987 studied 69 children following a first febrile seizure and administered intermittent rectal diazepam 0.5 mg/kg/dose, continuous oral valproate 30 mg/kg/day or no treatment. Children were followed for assessment of recurrent seizures at 6, 12, and 24 months after randomization; adverse medication effects were not addressed.[25] Pavlidou et al 2006 studied 139 children aged six to 36 months that were randomly assigned in a prospective controlled trial to receive either intermittent prophylaxis with rectal diazepam (group A= 68) or no prophylaxis (group B= 71). The children were followed for assessment of recurrent seizures at 6, 12, and 36 months after randomization and adverse medication effects during 36 months of treatment. They have observed 38 febrile seizure recurrences in diazepam group (Group A) and 103 recurrences in control group
Taghdiri et al 2011 studied 80 children, aged nine months to five years after their first febrile seizure, and treated them with either rectal diazepam (0.5 mg/kg) combined with acetaminophen or acetaminophen only. Children were followed for 12 months for assessment of recurrence. The study concluded rectal diazepam at the time of fever may reduce the risk of recurrence of seizures in simple febrile convulsions.[20]

Uhari et al 1995 studied 180 children following a first febrile seizure and allocated to intermittent rectal followed by intermittent oral diazepam 0.2 mg/kg or placebo. Both groups were treated with antipyretics for the duration of the fever. They were followed for assessment of recurrent seizures and adverse medication effects for 24 months. The combination of acetaminophen and low dose diazepam did not reduce the recurrent febrile seizure.[21] Ramakrishnan et al 1986 studied 120 children aged two to 72 months following a first febrile seizure. These children were allocated to continuous phenobarbionate 3 to 5 mg/kg/day, intermittent phenobarbionate in the same dosage, intermittent oral diazepam 0.6 mg/kg/day or no treatment. They were followed for assessment of recurrent seizures at 60 to 72 months after randomization and adverse medication effects for 24 months. The combination of acetaminophen and low dose diazepam did not reduce the recurrent febrile seizure.[22] Uhari et al 1995 started with a rectal dose (2.5 mg for < 7 kg, 5 mg for 15 kg and 10 mg for > 15 kg children) and after six hours they were followed by oral diazepam 0.2 mg/kg every eight hours during fever with a maximum of two days.[23] There were significant overall findings at 6, 12, 18, 24, 36 and 48 months, not at 60 to 72 months. In hirayabashi 2008 studies, 16 children had recurrence in 5 hours after the first onset in control group and 2 recurrences out of 95 treated cases (diazepam suppository 0.5mg/kg). There was a significant reduction of recurrent febrile seizure risk with intermittent diazepam versus placebo or no treatment at all time points, except for 60 to 72 months.

The adverse reactions associated with following studies are mentioned in Table 2. Most of the adverse effects were mild with the diazepam and did not exist after 36 hours. Many studies are concerned that the side effects of diazepam can delay the diagnosis of an underlying illness such as meningitis or encephalitis. Infection of the central nervous system must always be measured in case of a seizure with fever, especially in infants of age less than 18 months. When in doubt, a lumbar puncture is always preferable to rule out the exact cause. Intermittent diazepam therapy for the prevention of recurrence of febrile seizures has been well studied and proven to be effective.[22,24] However Cllobazam, a 1.5 benzodiazepine is effective in controlling recurrence of febrile seizures with less side effect of ataxia as compared to diazepam.[32]
or normal alertness or lethargy. One sudden unexpected death in placebo
neurologic Fact Sheet

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CONCLUSION

Though febrile seizures are a benign condition, the prevention is highly desirable in order to prevent recurrent seizure episodes associated with it. The mainstay of managing febrile seizure is to rule out the cause of fever and exclude any intracranial pathology or infection. Reassurance and a detailed parental education regarding the disease and management would be beneficial. This review concludes with the fact that diazepam is safe and effective in controlling febrile seizure recurrences with minimal side effects.

REFERENCES


