

## ORIGINAL ARTICLE:

**COMPARISON OF INTRAVENOUS DIAZEPAM AND INTRAVENOUS MIDAZOLAM FOR TREATMENT OF RECURRENT FEBRILE SEIZURES**

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**Background:** Recurrent febrile seizures are seizures in children less than 5 years of age which reoccur within 24 hours. Benzodiazepines such as midazolam and diazepam are used to stop and decrease the recurrent rate of febrile seizures. The objective of study was to compare the efficacy of intravenous midazolam with intravenous diazepam for treatment of recurrent febrile seizures in paediatric patients.

**Methods:** This observational cross-sectional study observed 60 children aged 6 to 59 months with recurrent febrile seizures who presented at paediatric clinic in Combined Military Hospital Kharian and THQ Hospital, Kharian from Sep to Nov 2023. The response time was noted for children who received intravenous midazolam 0.2 mg/Kg only and IV diazepam 0.2 mg/Kg only. The children were randomly allocated into group A (midazolam group) and Group B (diazepam group.) Study was done after taking informed consent from the parents. Both drugs were given during the fits. **Results:** The time interval from drug administration to cessation of febrile seizures was 2.50±0.94 minutes in the midazolam group and 2.4±1.12 minutes in the diazepam group. There was no significant difference between the two groups ( $p=0.567$ ). Minor dizziness and sedation were the only main effects reported. **Conclusion:** Both diazepam and midazolam have same efficacy in the treatment of recurrent febrile seizures.

**Keywords:** Midazolam, Diazepam, Febrile seizures, Efficacy

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**INTRODUCTION**

A seizure episode in a child six months to fifty-nine months of age plus low-grade fever, without central nervous system infection or metabolic imbalance, is called a febrile seizure.<sup>1</sup> It is generalized tonic-clonic type of seizure lasting usually for 15 minutes. It stops itself after some time. Simple febrile seizures are common in children, occurring in 3-6% of children. Simple febrile seizures patients do not require hospital admission. Common risk factors of simple febrile seizure are viral illness and vaccinations.<sup>2</sup>

On the other hand a complex recurrent febrile seizure lasts more than 15 minutes, is focal and reoccurs within 24 hours. They are not likely to stop themselves, and a benzodiazepine should be injected to stop the complex recurrent seizure. If seizures are not stopped, it can lead to brain damage. Rapid control of seizures reduces future adverse outcomes.<sup>3</sup> Complex recurrent febrile seizure paediatric patients require hospital admission sometimes, but children of younger age and unreliable follow-up must be admitted.<sup>4</sup> Risk factors of recurrent febrile seizures include genetics, age less than 17 months, fever duration less than 24 hours, low grade fever, first degree relative, children in day care centre, dehydrated children and male gender.<sup>5</sup> Only 2% children with this type of seizures might have an attack of epilepsy in future.<sup>6</sup> Seizures cause emotional and mental stress for parents and treating doctors. Parents are very terrified when their children get recurrent

seizures. There is risk of injury with a seizure lasting more than 15 minutes.<sup>7</sup>

Many medicines have been used including diazepam, phenobarbitone, midazolam, zinc, paracetamol have been used to reduce the recurrence of febrile seizures.<sup>8</sup> Phenobarbitone is an antiepileptic drug and has side effects and routine use is not recommended. Intramuscular approach (IM) for diazepam and midazolam causes persistent pain at injections site which makes children uncomfortable. Per Rectal (PR) administration of diazepam is unpleasant for paediatric patients. Disrobing children makes them more uncomfortable. Buccal route is also difficult in patients with seizures because of risk of finger biting. IV route is the preferred route. IV diazepam is the most commonly used benzodiazepine; however, it has rare side effects of respiratory depression, bradycardia and respiratory arrest.<sup>9</sup> Midazolam is water soluble, fast acting, slightly expensive, not widely used in Pakistan yet. Its ring structure closes at physiological pH, becomes lipophilic and passes blood-brain-barrier rapidly. It has fast clinical effects on the central nervous system. No respiratory side effects are reported with midazolam. Intranasal midazolam is becoming very popular for the treatment of febrile seizures.<sup>10</sup>

Antipyretics can decrease the discomfort of the child but do not reduce the frequency of recurrent seizures.<sup>11</sup> A study found no benefit of zinc supplementation for prevention of recurrent febrile seizures.<sup>8</sup>

Our study aims to compare intravenous midazolam with diazepam in paediatric patients of Kharian for management of recurrent febrile seizures.

## MATERIAL AND METHODS

This observational cross-sectional study was carried out at CMH Kharian and THQ Hospital Kharian from September to November 2023, after getting ethical approval from CMH Kharian Medical College Ethical Committee (File No. 2000/Gen/ECA/2023/01). Sample size was calculated using WHO Sample Size Calculator at confidence level of 95%, alpha error of 5%, and study power of 80%.<sup>12</sup> Total 60 children of either gender were enrolled through non-probability sampling technique. Inclusion criteria was children between ages of 6 months to 59 months presenting with recurrent febrile seizures. Exclusion criteria was presence of trauma to CNS, hypoglycaemic children, hypocalcemic fits, and known epileptic children. The response time for seizure cessation was noted for children who received IV midazolam 0.2 mg/dL only and IV diazepam 0.2 mg/dL only. Group A (midazolam group) had 32 children. Group B (diazepam group) had 28 children. Informed consent from the parents were obtained. Both drugs were given only during the fits.

Data was analysed using SPSS-20. Variables such as age and time were presented as mean with standard deviations. Independent sample *t*-test was used to compare the mean of both groups, and  $p \leq 0.05$  was considered significant.

## RESULTS

Among 60 enrolled patients there were 32 males and 28 females. The mean age of patients in Group A was  $3.27 \pm 1.31$  years and in Group B it was  $3.77 \pm 1.09$  years. There was no significant difference between age of both groups. The time interval between drug administration and cessation of seizure was similar for both IV midazolam and IV diazepam. No significant side effects were reported in either group.

**Table-1: Clinical characteristics of study groups**

	IV Midazolam	IV Diazepam
Male	16	16
Female	15	13
Mean age (years)	$3.27 \pm 1.31$	$3.77 \pm 1.09$
<b>Cause of febrile seizures</b>		
URTI	6	7
Acute otitis media	8	9
Bronchopneumonia	6	6
Dysentery	4	3
Other	5	6

**Table-2: Drug effect time interval among study groups**

Time interval (min)	IV Midazolam Mean $\pm$ SD	IV Diazepam Mean $\pm$ SD	P
Drug administration to cessation of seizure	$2.50 \pm 0.94$	$2.4 \pm 1.12$	0.567

## DISCUSSION

In our study URTI was the most common cause of febrile seizure, followed by acute otitis media, bronchopneumonia and dysentery. The underlying patho-physiological causes of recurrent febrile seizures are diverse. Any pathology that can disrupt the normal neuronal function and connectivity can make the brain epileptic. Gene mutations in voltage gated channels of sodium, calcium, potassium and chloride can lead to increased excitability in neurons. There is loss of functions of inhibitory GABA interneurons.<sup>12</sup> However, a clear aetiology is still lacking.

We found that intravenous midazolam was just as effective at reducing seizure activity of febrile seizures as intravenous diazepam. Hence intravenous midazolam can be used as an alternate remedy to diazepam.

Similarly, study done by Batool *et al*<sup>13</sup> in Fauji Foundation Hospital Pakistan showed that intranasal midazolam and intravenous diazepam had same efficacy. They had 62 patients from age 3 months to 12 years and used intranasal midazolam. We used intravenous midazolam in patients aged 6 months to 5 years. However, Kazmi *et al*<sup>14</sup> study in neurology unit of Children Hospital, Lahore Pakistan on 164 paediatric patients showed that intravenous midazolam was better than intravenous diazepam in managing status epilepticus. In Kazmi study patients were suffering from status epilepticus, and our study patients had recurrent febrile seizures. A Swiss study<sup>15</sup> reported that IV diazepam is better in adults and intranasal midazolam is better in children for termination of seizures.<sup>15</sup>

## CONCLUSION

Intravenous midazolam can be used as a rescue medication for the treatment of recurrent febrile seizures in children in the absence or shortage of diazepam. Both midazolam and diazepam have same efficacy.

## LIMITATIONS

This study did not study neonates. Further studies on larger children population with other types of seizures are recommended.

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**WP:** Concept and design of study, Getting ethical approval, Data collection, Drafting of article, Critical review

**AA:** Concept and design of study, Data collection, Drafting of article, Critical review

**IA:** Data collection, Drafting of article, Critical review, Statistical analysis

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**MUS:** Data collection, Drafting of article, Critical review, Statistical analysis

**MUA:** Drafting of article, Critical review

**SH:** Concept of study, Data collection, Critical review

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