

## **Midazolam versus Diazepam in Resolving Seizure Activity in Pediatric Patients**

Paramedic Mini CAT – Fanshawe College

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### **Background**

Seizures are bursts of uncontrolled electrical activity between brain cells that cause abnormalities in movement, behaviour, sensation, and state of awareness. Benzodiazepines are a class of drug used to help with seizure activity and aid in its cessation as they work by slowing down the central nervous system and impacting neurotransmitters. Medications such as diazepam and midazolam, two examples of benzodiazepines, are used in the pre-hospital setting by paramedics, as well as in the emergency department. In the pre-hospital setting, paramedics must think quickly and make fast decisions when it comes to administering medications to their patients. However, with all the options of medications, is one medication better than the other in seizure cessation?

### **Review question**

Patient/Problem: seizure activity pediatric patients

Intervention: midazolam

Comparison/Control: diazepam

Outcome: if midazolam is a more effective medication than diazepam in resolving seizure activity

**Search strategy 1 for PubMed:** ((diazepam) AND (midazolam)) AND (seizures OR seizure OR seizure activity)

**Limits:** Free full text, Full text, In the last 5 years, Humans, Child: birth-18 years

**Search strategy 2 for PubMed:** ((cessation OR termination) AND (diazepam AND midazolam)) AND (seizure OR seizures OR seizure activity)

**Limits:** Free full text, Full text, In the last 5 years, Child: birth-18 years

**Search strategy for Academic Search Ultimate:** (intranasal midazolam OR intravenous midazolam) AND (intranasal diazepam OR intravenous diazepam) AND (seizures or epilepsy or seizure activity or seizure disorder)

**Limits:** Full text, 2017-2022

**Databases searched:** PubMed, Academic Search Ultimate

Search results: 23 (PubMed 1: 9, PubMed 2: 1, Academic Search Ultimate: 13)

Included for review: 3 studies reviewed as relevant for this CAT

Title, author, year	Study Design and Population	Intervention	Outcomes	Results	Weaknesses & Strengths
<p><b><u>Title</u></b> Comparison of intranasal midazolam with intravenous diazepam for treatment of acute seizures in children: A randomized controlled trial</p> <p><b><u>Author(s)</u></b> Batool, I., Mujtaba, H., Gul, F., Savul, S., Khan, H., &amp; Ather, U.</p> <p><b><u>Year</u></b> 2020</p>	<p>A randomized control trial</p> <p><math>n=62</math> pediatric patients</p> <p>Randomized into two groups (Group A and B)</p> <p><b><u>Inclusion</u></b></p> <ul style="list-style-type: none"> <li>- All children aged 3 months to 12 years presenting during a seizure episode within the study duration in the Fauji Foundation Hospital</li> </ul> <p><b><u>Exclusion</u></b></p> <ul style="list-style-type: none"> <li>- Neonates</li> <li>- Children with concomitant upper respiratory tract infections</li> </ul>	<p><b><u>Group A:</u></b> patients were given 0.2mg/kg intranasal midazolam administered as drops in both nostrils</p> <p><b><u>Group B:</u></b> patients were given 0.3mg/kg diazepam intravenously</p>	<p>Intranasal midazolam is an effective non-invasive method for control of acute seizures in children.</p> <p>Though the efficacy of control of seizures of intranasal midazolam and intravenous diazepam was the same, the time from arrival to start of treatment was significantly shorter in intranasal midazolam. Through this, the administration of midazolam</p>	<ul style="list-style-type: none"> <li>- The mean time from arrival at hospital to start of treatment was significantly shorter (<math>p &lt; 0.05</math>) in the group that was administered midazolam compared to the group that was administered diazepam (2.07 + 0.27 vs. 5.06 + 0.81 minutes)</li> <li>- The mean time to control seizures after arrival in hospital was significantly shorter (<math>&lt; 0.05</math>) in IN midazolam administration in comparison to IV diazepam administration</li> <li>- At 10 minutes in group A, 87.5% of patients showed a good response, 3.1% exhibited a delayed response, and 9.4% had a poor response</li> <li>- At 10 minutes in group B, 87.5% of patients showed a good response, 6.3% showed</li> </ul>	<ul style="list-style-type: none"> <li>+ Population included pediatrics as young as 3 months</li> <li>+ Monitored select vitals at 5-minute intervals</li> <li>- Both medications were administered through different routes and dosages</li> </ul>

	<ul style="list-style-type: none"> <li>- Patients admitted in pediatric ward with refractory status epilepticus taking multiple drugs</li> <li>- Children presenting during seizure episode with an IV line already in place</li> </ul>		<p>resulted in controlling the seizure earlier in comparison to diazepam.</p>	<p>a delayed response, and 7.2% had a poor response</p>	
<p><b><u>Title</u></b> A comparison of intravenous midazolam and diazepam in management of status epilepticus in children</p> <p><b><u>Author(s)</u></b> Kazmi, A., Abbas, G., Khurshid, A., Shah, S., Mallhi, T., Hanif, M., Saleem, U., Shah, A., &amp; Riaz, N.</p> <p><b><u>Year</u></b> 2021</p>	<p>A comparative study <i>n</i>=164 pediatric patients</p> <p>Divided into two groups of 82 (50%) patients conducted in the pediatrics neurological emergency unit of The Children's Hospital and the Institute of Child Health</p> <p><b><u>Inclusion</u></b></p> <ul style="list-style-type: none"> <li>- Either gender</li> <li>- Aged 1 to 14 years</li> <li>- Having status epilepticus of duration &gt;5 minutes</li> </ul> <p><b><u>Exclusion</u></b></p> <ul style="list-style-type: none"> <li>- Received prior anticonvulsant</li> </ul>	<p>Patients were randomly allocated using the lottery method into two equal groups, with the former receiving IV diazepam 0.3mg/kg and the latter receiving IV midazolam 0.15mg/kg</p>	<p>IV midazolam was more effective and safer in managing pediatric status epilepticus patients in ED than IV diazepam.</p> <p>IV midazolam was quick in action and less likely to cause adverse reactions.</p>	<ul style="list-style-type: none"> <li>- Midazolam had a 93.90% success in treatment while diazepam had a 78.05% success in treatment</li> <li>- The mean time from drug administration to stoppage seizures: midazolam was approximately 2.58 minutes <math>\pm</math> 1.6, diazepam was approximately 4 minutes <math>\pm</math> 2.1</li> <li>- Midazolam acts rapidly in comparison to diazepam</li> </ul>	<ul style="list-style-type: none"> <li>+ Parameters were specific</li> <li>+ Both medications were administered intravenously</li> <li>+ Relatively up to date</li> <li>- Weak size of study</li> <li>- Did not use all pediatric ages</li> </ul>

	<p>treatment other than benzodiazepine</p> <ul style="list-style-type: none"> <li>- patients on assisted ventilation</li> <li>- patients diagnosed with metabolic fits due to hypoglycaemia treated in emergency with glucose</li> <li>- chronic liver disease assessed through history and medical record</li> <li>- known patients of chronic renal disease</li> </ul> <p>Those with hypertensive encephalopathy detected on blood pressure reading done in ED</p> <ul style="list-style-type: none"> <li>- those with history of head injury</li> </ul>				
<p><b><u>Title</u></b> Drug management for acute tonic-clonic convulsions including convulsive status</p>	<p>18 randomised and quasi-randomised trials</p> <p><i>n</i>=2199 participants (children)</p>	<p>Medications: lorazepam, diazepam, and midazolam</p> <p>Route: rectal, buccal, nasal, intramuscular, and intravenous</p>	<p>- IV administration for anticonvulsants led to more rapid seizure cessation – however, usually compromised by the time taken to</p>	<p>- Low to very low-quality evidence comparing buccal midazolam with rectal diazepam for the treatment of acute tonic-clonic convulsions (RR for seizure cessation 1.25, 95% CI 1.13 to 1.38; 4 trials; 690 children) -Buccal and IN anticonvulsants shown to</p>	<p>+ Compares all possible routes with multiple drugs + Routes that were similar were compared to one another as</p>

<p>epilepticus in children</p> <p><b><u>Author(s)</u></b> McTague, A., Martland, T., Appleton, R.</p> <p><b><u>Year</u></b> 2018</p>			<p>establish IV access</p> <ul style="list-style-type: none"> <li>- Buccal midazolam or rectal diazepam are acceptable first-line anticonvulsants for the treatment of acute tonic-clonic convulsion that lasted at least 5 minutes if IV access is absent</li> </ul>	<p>lead similar rates of seizure cessation as IV anticonvulsants – IN midazolam was equivalent to IV diazepam (RR 0.98, 95% CI 0.91 to 1.06; 2 trials; 122 children; moderate-quality evidence)</p> <ul style="list-style-type: none"> <li>- IM midazolam showed similar rate of seizure cessation to IV. Diazepam</li> <li>- IV routes of administration: no statistically significant or clinically important differences between midazolam and diazepam (RR for seizure cessation 1.08, 95% CI 0.97 to 1.21; 1 trial; 80 children; moderate-quality evidence)</li> </ul>	<p>well with other routes</p> <ul style="list-style-type: none"> <li>+ Good population size</li> <li>+ Summary findings provided were divided into tables comparing each route with one another</li> <li>- No ages were specified</li> <li>- Quality of evidence for some important outcomes were noted as low to very low</li> <li>- Trials included involve information from the years 1995 to 2015</li> </ul>
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**Comments:**

The final paper contained multiple articles from various countries and years. The study designs differed from each article provided allowing for information to be obtained in several ways obtaining a concise conclusion. The results provided from the articles above conclude that midazolam is not superior to diazepam in resolving seizure activity in pediatric patients. Although these articles did not specify whether they pertain specifically to the hospital or the pre-hospital setting, the results that were found may be implicated in both circumstances.

**Considerations:**

Based on the outcome outlined above, more research must be obtained in order to reach an accurate conclusion. The articles provided use evidence of varying quality and are obtained from multiple timelines concerning the same medications. As demonstrated from other research, medication administration and protocols are constantly evolving, therefore, the information provided above may no longer be valid in present time.

**Clinical bottom line:**

Although multiple studies demonstrate an interest in comparing the different medications that can be administered during seizure activity in pediatric patients, there was no significant evidence provided supporting the use of midazolam over the use of diazepam. Rather than the medication being used, these trials have demonstrated that the intravenous route for administering anticonvulsants result in a more rapid cessation of seizures than other routes examined. It was also noted that the intravenous route may not always be optimal as the time taken to establish intravenous access may be prolonged in some situations. With this observation, buccal and intranasal administration were provided as an alternate route.

**References**

- Batool, I., Mujtaba, H., GUL, F., Savul, S., Khan, H. S., & Ather, U. (2020). Comparison of intranasal midazolam with intravenous diazepam for treatment of acute seizures in children: A randomized controlled trail. *Isra Medical Journal*, 12(1), 7-11.
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- McTague, A., Martland, T., & Appleton, R. (2018, January 10). *Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children*. The Cochrane database of systematic reviews. Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6491279/>