

A comparison of intravenous midazolam and diazepam in management of status epilepticus in children

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Abstract

Objective: To compare the efficacy of intravenous midazolam and diazepam in the management of status epilepticus seizures in children.

Method: The comparative study was conducted in the paediatric neurological emergency unit of The Children's Hospital and the Institute of Child Health, Multan, Pakistan, from December 15, 2018, to May 14, 2019, and comprised paediatric patients of status epilepticus seizures which were divided into Diazepam and Midazolam groups. Data was analysed using Graph-Pad Prism 5.

Results: Of the 164 patients, 82(50%) were in each of the two groups. There was no significant difference between the groups in terms of weight, age, residence area of patients and mean duration of seizures ($p>0.05$). Status epilepticus seizures subsided after intravenous midazolam administration in 77(93.90%) cases, while success in the diazepam group 64(78.05%) ($p<0.05$). Mean time taken by midazolam to halt seizures was significantly shorter than diazepam ($p<0.05$) and less cases of treatment failure were observed with intravenous midazolam ($p<0.05$). Somnolence was observed after diazepam administration in 47(57.3%) cases ($p=0.0001$).

Conclusion: Intravenous midazolam was found to be superior in efficacy than intravenous diazepam in controlling status epilepticus seizures.

Keywords: Diazepam, Midazolam, Status epilepticus, Seizures. (JPMA 71: 640; 2021)

DOI: <https://doi.org/10.47391/JPMA.843>

Introduction

The word epilepsy is derived from a Greek word meaning "to take court, to grab or to seize".¹ It is a chronic non-communicable disease that affects people of all ages, and seizures can be acute in nature.² Epilepsy may be generalised or focal. If electroencephalogram (EEG) abnormalities and seizures are generalised, it is generalised epilepsy. It may be partial, or focal, if EEG and clinical presentation suggest focal onset. But this classification is not always clear.³ Sudden excessive electrical discharge in brain cells cause seizure episodes.⁴ Depending on clinical presentation, guidelines of the International League against Epilepsy classify seizures as generalised convulsive or non-convulsive or as focal.^{5,6} Generalised seizures occur if abnormal electrical activity affect both cerebral hemispheres.⁷ Generalised seizures affects most or all parts of brain. Generalised seizures are of many types, including atonic, tonic, clonic, absence, myoclonic and tonic-clonic. Most violent type of seizures are tonic-clonic because they commonly involve the whole body.⁸ Partial seizures affect a

portion of one cerebral hemisphere of the brain.⁹ Status epilepticus is a central nervous system (CNS) emergency that comprises one or a series of seizures persisting for more than 30min without complete retrieval of consciousness.^{10,11} If a seizure extends beyond 5min, it will often last at least 30min unless anticonvulsants are given. Patients who have seizures continuing for 5min or longer are expected to be in the initial stages of convulsive status epilepticus and must be treated rapidly.¹² Globally, every year about 2.4 million individuals are diagnosed with epilepsy.¹³ Worldwide, about 10.5 million children below 15 years have active epilepsy. It is about 25% of the worldwide epilepsy population. Every year about 3.5 million individuals are developing epilepsy. From these, more than 80% are living in developing countries and 40% are <15 years.³

Status epilepticus is a frequently encountered neurological disorder in the emergency of paediatric neurology department of hospitals. Intravenous (IV) anticonvulsant drugs are suitable in the initial stage treatment used for the management of this disorder.¹⁴ Immediate management of recurrent seizures follow the fundamental principles of emergency care that a drug should terminate the seizures safely and promptly. Ideally, the given drug should be safe and effective. It must be easy to administer and have a prolonged anti-seizure action.³ To control convulsive seizure quickly, the drug should reach the brain rapidly

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without serious untoward effects. IV injection of anticonvulsants might be the route of choice for this purpose.^{15,16} Benzodiazepines are used as first-line treatment of recurrent seizures via IV or rectal route.^{3,16}

Midazolam is an effective water-soluble anticonvulsant drug which belongs to the benzodiazepine class.^{17,18} It can be given through rectal, intramuscular (IM), IV and nasal routes of drug administration.¹⁹ Midazolam, like diazepam, is lipophilic in nature at physiological potential of hydrogen (pH) 2.8-3.6. Lipophilic nature aids in quick diffusion into the CNS.²⁰ On the other hand, diazepam can be administered rectally, orally, or via IM and IV.²¹ IV diazepam is used as the standard acute treatment for status epilepticus.^{16,22} Accumulation of diazepam can cause prolonged sedation in newborn.²³ Both drugs produce anticonvulsant action by enhancing inhibitory activity of gamma-aminobutyric acid receptor.²⁰

The current study was planned to compare the efficacy of IV midazolam and diazepam.

Patients and Methods

1) The comparative study was conducted in the paediatric neurological emergency unit of The Children's Hospital (TCH) and the Institute Of Child Health (ICH), Multan, Pakistan, from December 15, 2018, to May 14, 2019. After approval from the ICH ethics review board, the sample size was determined using Open-Epi calculator.²⁴ The sample was raised using non-probability sampling technique, approaching all paediatric patients with status epilepticus visiting the emergency department (ED). Those included were patients of either gender aged 1-14 years having status epilepticus of duration >5min. Those excluded were patients who had received prior anticonvulsant treatment other than benzodiazepine; patients on assisted

ventilation; patients diagnosed with metabolic fits due to hypoglycaemia treated in emergency with glucose; chronic liver disease assessed through history and medical record; known patients of chronic renal disease; those with hypertensive encephalopathy detected on blood pressure reading done in ED; and those with history of head injury.

Data was collected after permission for the respective hospital managements and written informed consent from parents/guardians of the subjects enrolled. Baseline demographic characteristics, including age and gender as well as type and duration of seizure were noted.

The patients were randomly allocated using the lottery method into two equal groups A and B, with the former receiving IV diazepam 0.3mg/kg and the latter receiving IV midazolam 0.15mg/kg. All patients were monitored and timing of cessation of seizures was recorded. Treatment was considered successful if seizures stopped within 10 minutes of dose dispensation. If seizures did not stop within 10 minutes, second-line drug was administered as per the institutional protocol.

Supportive treatment was provided according to the hospital emergency protocol. Emergency resuscitation equipment was available to manage any untoward reaction, like respiratory depression, hypotension and cardiac arrhythmia. Data was collected on pre-designed proforma.

Data was analyzed using Graph-Pad Prism version 5. Descriptive statistics were used for quantitative Variables, while frequencies and percentages were calculated for qualitative variables. Fisher's exact test was used to compare the efficacy of the two drugs. $P \leq 0.05$ was taken as significant.

Results

Of the 164 patients, 82(50%) were in each of the two

Table-1: Baseline characteristics.

Sr. No.	Parameters	Midazolam	Diazepam	p-value	Odd ratio (Diazepam=0)
1	No. of patients	82	82		
2	Male	47 (57.32 %)	38 (46.34 %)	0.211	1.55/0.643
3	Female	35 (42.68 %)	44 (53.66 %)		
4	Mean weight (kg)	14.14	14.84	0.41	0.976
5	Mean age (years)	3.94±2.8	4.5±2.9	0.22	0.932
6	Residence	Rural 51.39 % Urban 48.61 %	Rural 51.21 % Urban 48.78 %	0.619	0.808
7	Types of status epilepticus	Convulsive 80 (97.56 %) Non-Convulsive 2 (2.44 %)	Convulsive 80 (97.56 %) Non-Convulsive 2 (2.44 %)	1	1
8	Family history of seizures	Yes 15 (18.29 %) No 67 (81.71 %)	Yes 10 (12.20 %) No 72 (87.80 %)	0.385	1.612
9	Types of seizures	Tonic seizures 4(4.88 %)	Tonic seizures 6(7.32 %)		-
	Clonic seizures 5(6.09 %)	Clonic seizures 7(8.53 %)			1.071
	Focal seizures 9(10.98 %)	Focal seizures 8(9.76 %)		0.376	1.687
	Myoclonic seizures 14(17.07%)	Myoclonic seizures 6(7.32 %)			3.5
	Tonic clonic seizures 50(60.98 %)	Tonic clonic seizures 55(67.07 %)			1.364

Table-2: Treatment response.

Sr. No.	Parameter	Midazolam	Diazepam	p- value	Odd ratio
1	Duration of seizures (min)	36.52 ±22.18	38.81±26.27	0.5	0.996
2	Dose (mg)	2.16 ±0.862	4.42 ±1.656	0.0001	0.113
3	Treatment success	77 (93.90 %)	64 (78.05 %)	0.006	0.309
5	Mean time from drug administration to stoppage of seizures (min)	2.58±1.6	4±2.1	0.0001	0.699
6	Adverse effect (Somnolence)	Yes 5 (6.10 %) No 77 (93.90 %)	Yes 47 (57.32 %) No 35 (42.68 %)	0.0001	2.025
7	Either fits are controlled within 10 min	Yes 77 No 5	Yes 64 No 18	0.006	0.309

Table-3: Vital signs before and after administration of drug.

Sign	Diazepam		Midazolam	
	Before administration of drug	After administration of drug	Before administration of drug	After administration of drug
Systolic blood pressure (mmHg)	94.09±9.848	93.54±8.069	92.75±10.25	90.06±9.179
Diastolic blood pressure (mmHg)	61.83±9.112	61.89±7.724	60.63±9.486	60.18±7.874
Heart rate (beats/min.)	93.37±10.73	89.83±10.38	95.04±9.092	92.28±9.318
Oxygen saturation (%)	94.8±7.73	96.51±2.038	95.18±4.327	95.93±2.985
Respiration rate (Exhale/min.)	26.67±5.93	26.28±9.58	28.03±6.045	25.63±5.65
Temperature (Fahrenheit)	98.92±1.368	98.87±1.28	98.83±1.322	98.66±1.146

groups. Tonic-clonic seizure was the most common type 105(64%). There was no no significant differences in baseline characteristics (Table-1).

The seizures subsided after IV midazolam administration in 77(93.90%) cases, while success in the diazepam group was 64(78.05%) ($p<0.05$). In the diazepam group, 1(1.2%) patient expired due to respiratory depression Mean time from drug administration to stoppage of seizures was significantly lower for midazolam compared to diazepam group ($p<0.05$). Somnolence was observed after diazepam administration in 47(57.3%) cases ($p=0.0001$) (Table-2).

There was no significant difference in the vital signs between the groups (Table-3).

Discussion

The current study is novel in comparing intravenous benzodiazepines in children. Treatment with benzodiazepines have potential risks, like cardiovascular events and respiratory depression, as well as benefits, like prevention from life-threatening convulsive seizures.²⁵ Buccal and nasal spray of midazolam is safe and effective in seizure control, but these routes are not of choice. When patient is in a state of seizure, it is difficult to open the mouth of the patient or nasal congestion may render these routes ineffective.^{16,26,27} Midazolam acts rapidly than

diazepam.²⁸ Generally, IV diazepam is given for cessation of acute life-threatening seizures.²⁹ Convulsive status epilepticus seizures can be managed by rectal diazepam efficiently, but plasma concentration of rectally-administered diazepam varies and it also fails in controlling seizures in 30% patients.^{30,31} Moreover, the rectal route is not convenient, and parents are reluctant to have medication administered by this route.¹²

The current study demonstrated that IV midazolam was more efficacious in controlling status epilepticus seizures. Mean time from IV injection to stoppage of seizures was shorter for midazolam group and there were fewer cases of treatment failure. The results are in line with previous findings, like studies in Western countries have led to guidelines suggesting use of midazolam in cases of status epilepticus seizures.^{32,33} An investigational study reported 85.7% efficacy of continuous midazolam comparable with diazepam infusion.³⁴ Midazolam may be a drug of choice in the management of refractory status epilepticus.³⁵ IV midazolam is quick in its action compared with IV diazepam. It took 2.58min to stop epileptic seizures while IV diazepam took 4min in the current study. Midazolam is very efficacious if administered shortly after the onset of seizures.¹⁴

The current study found that IV midazolam was less like to cause somnolence in children. Midazolam is safe to

be administered to children. It caused no significant side effect; similar to observations in studies comparing IV diazepam versus buccal midazolam, rectal diazepam versus buccal midazolam, rectal diazepam versus buccal midazolam and buccal midazolam alone.^{12,36-38} Studies in Japan have reported less incidences of cardiovascular events and respiratory depression with midazolam.¹⁴ One study reported 5% incidence of adverse effects due to midazolam which is almost similar to the finding of the current study.³⁹

The sample size of the current study is one of its limitations. Besides, the patients were monitored for 6h in ED which is not long enough to monitor adverse drug events and interactions effectively.

Conclusion

IV midazolam was more effective and safe in managing paediatric status epilepticus patients in ED than IV diazepam. It was quick in action and less likely to cause adverse reactions.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

References

- Amudhan S, Gururaj G, Satishchandra P. Epilepsy in India II: Impact, burden, and need for a multisectoral public health response. *Ann Indian Acad Neurol*. 2015; 18:369-81.
- Christensen J, Vestergaard M, Pedersen MG, Pedersen CB, Olsen J, Sidenius P. Incidence and prevalence of epilepsy in Denmark. *Epilepsy Res*. 2007; 76:60-5.
- Guerrini R. Epilepsy in children. *Lancet*. 2006; 367:499-524.
- WHO. Report on epilepsy. World Health Organization, 2018.
- Brodie MJ. Diagnosing and predicting refractory epilepsy. *Acta Neurol Scand Suppl*. 2005; 181:36-9.
- Engel J, Pedley TA, Aicardi J. Epilepsy. In: Engel J, Pedley TA, Aicardi J, eds. *A Comprehensive Textbook: Vol 3*. UK: Lippincott-Raven, 1998; pp 74-7.
- Angalakuditi M, Angalakuditi N. A comprehensive review of the literature on epilepsy in selected countries in emerging markets. *Neuropsychiatr Dis Treat*. 2011; 7:585-97.
- Ganaie S, Bashir A. Epilepsy in Kashmir, J&K: Childhood Seizures & Epilepsy, Types, Causes, Diagnosis, Intervention, Prevalence and Action. *Int J Translation Community Dis*. 2014; 2:13-20.
- Schachter SC. Seizure disorders. *Vet Clin North Am Small Anim Pract*. 1980; 10:3-29.
- Blume WT, Lüders HO, Mizrahi E, Tassinari C, van Emde Boas W, Engel J Jr. et al. Glossary of descriptive terminology for ictal semiology: report of the ILAE task force on classification and terminology. *Epilepsia*. 2001; 42:1212-8.
- Sillanpää M, Shinnar S. Status epilepticus in a population-based cohort with childhood-onset epilepsy in Finland. *Ann Neurol*. 2002; 52:303-10.
- Scott RC, Besag FM, Neville BG. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. *Lancet*. 1999; 353:623-6.
- Uthara S, Basheer M, Babu A. A review on cost effective analysis of antiepileptic drugs. *Int J Bioassays*. 2017; 6:5507-12.
- Hayashi K, Osawa M, Aihara M, Izumi T, Ohtsuka Y, Haginoya K. et al. Efficacy of intravenous midazolam for status epilepticus in childhood. *Pediatr Neurol*. 2007; 36:366-72.
- Momen AA, Malamiri RA, Nikkhah A, Jafari M, Fayezi A, Riahi K. et al. Efficacy and safety of intramuscular midazolam versus rectal diazepam in controlling status epilepticus in children. *Eur J Paediatr Neurol*. 2015; 19:149-154.
- Ashrafi MR, Khosroshahi N, Karimi P, Malamiri RA, Bavarian B, Zarch AV. et al. Efficacy and usability of buccal midazolam in controlling acute prolonged convulsive seizures in children. *Eur J Paediatr Neurol*. 2010; 14:434-8.
- Lahat E, Goldman M, Barr J, Eshel G, Berkovitch M. Intranasal midazolam for childhood seizures. *Lancet*. 1998; 352:620.
- Mary ER, Brown JK, Clarke M. Nasal rather than rectal benzodiazepines in the management of acute childhood seizures? *Dev Med Child Neurol*. 1996; 38:1037-45.
- Mahmoudian T, Zadeh MM. Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children. *Epilepsy Behav*. 2004; 5:253-5.
- Rainbow J, Browne GJ, Lam LT. Controlling seizures in the prehospital setting: diazepam or midazolam? *J Paediatr Child Health*. 2002; 38:582-6.
- Hillestad L, Hansen T, Melsom H, Drivenes A. Diazepam metabolism in normal man. II. Serum concentration and clinical effect after oral administration and cumulation. *Clin Pharmacol Ther*. 1974; 16:479-84.
- Chamberlain JM, Altieri MA, Futterman C, Young GM, Ochenschlager DW, Waisman Y. A prospective, randomized study comparing intramuscular midazolam with intravenous diazepam for the treatment of seizures in children. *Pediatr Emerg Care*. 1997; 13:92-4.
- Mandelli M, Tognoni G, Garattini S. Clinical pharmacokinetics of diazepam. *Clin Pharmacokinet*. 1978; 3:72-91.
- Dean A, Sullivan KM, Soe MM. OpenEpi: Version 2013. Open source epidemiologic statistics for public health. [Online] [Cited 2018 June 11]. Available from: URL: <https://www.neuroaro.gov.ng/main/index.php/resources/article-blog/210-the-sample-size-determination-gibberish-and-way-out>
- Lowenstein DH, Alldredge BK. Status epilepticus. *New Eng J Med*. 1998; 338:970-6.
- Anderson M. Buccal midazolam for pediatric convulsive seizures: efficacy, safety, and patient acceptability. *Patient Prefer Adherence*. 2013; 7:27-34.
- McMullan J, Sasson C, Pancioli A, Silbergleit R. Midazolam versus diazepam for the treatment of status epilepticus in children and young adults: a meta-analysis. *Acad Emerg Med*. 2010; 17:575-82.
- Wallace SJ. Nasal benzodiazepines for management of acute childhood seizures? *Lancet*. 1997; 349:222.
- Bhattacharyya M, Kalra V, Gulati S. Intranasal midazolam vs rectal diazepam in acute childhood seizures. *Pediatr Neurol*. 2006; 34:355-9.
- Mpimbaza A, Ndeezee G, Staedke S, Rosenthal PJ, Byarugaba J. Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial. *Pediatrics*. 2008; 121:e58-e64.
- Ogutu B, Newton C, Crawley J, Muchohi S, Otieno G, Edwards G. et al. Pharmacokinetics and anticonvulsant effects of diazepam in children with severe falciparum malaria and convulsions. *Br J Clin Pharmacol*. 2002; 53:49-57.
- Stoll B, Kliegman R. The fetus and the neonatal infant. In: *Dalam Behrman RE, Kliegman RM, Jenson HB, eds. Nelson*

- textbook of pediatrics. Philadelphia: Saunders, 2000.
33. Menkes J. Perinatal asphyxia and trauma In: Menkes JH, Sarnat HB, eds. Child Neurology 7th edition. London: Lippincott Williams & Wilkins, 2000; pp 427-36.
 34. Singhi S, Murthy A, Singhi P, Jayashree M. Continuous midazolam versus diazepam infusion for refractory convulsive status epilepticus. J Child Neurol. 2002; 17:106-10.
 35. Gilbert DL, Gartside PS, Glauser TA. Efficacy and mortality in treatment of refractory generalized convulsive status epilepticus in children: a meta-analysis. J Child Neurol. 1999; 14:602-9.
 36. Talukdar B, Chakrabarty B. Efficacy of buccal midazolam compared to intravenous diazepam in controlling convulsions in children: a randomized controlled trial. Brain Dev. 2009; 31:744-9.
 37. Baysun Ş, Aydın ÖF, Atmaca E, Güner YY. A comparison of buccal midazolam and rectal diazepam for the acute treatment of seizures. Clin Pediatr (Phila). 2005; 44:771-6.
 38. Kutlu NO, Dogrul M, Yakinci C, Soylu H. Buccal midazolam for treatment of prolonged seizures in children. Brain Dev. 2003; 25:275-8.
 39. Neville B, Chin R, Scott R. Childhood convulsive status epilepticus: epidemiology, management and outcome. Acta Neurol Scand Suppl. 2007; 186:21-4.
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