



Original Article

Efficacy of Midazolam Vs Diazepam in The Treatment of Status Epilepticus

Afzal Khan¹, Salma Aziz², Khowla Anis³, Muhammad Qasim Khan^{4*}, Taimoor Jamil⁵ and Muhammad Salman⁶¹Pediatric Unit, MTI Lady Reading Hospital, Peshawar, Pakistan²Pakistan Air Force Base, Risalpur, Pakistan³THQ Shakargarh, Lahore, Pakistan⁴Pediatric Unit, Bacha Khan Medical College, Mardan, Pakistan⁵NCHD, Services Hospital, Lahore, Pakistan⁶Pediatric B Unit, MTI Lady Reading Hospital, Peshawar, Pakistan

ARTICLE INFO

Key Words:

Status Epilepticus, Midazolam, Diazepam, Efficacy

How to Cite:

Khan, A., Aziz, S., Anis, K., Khan, M. Q., Jamil, T., & Salman, M. . (2023). Efficacy of Midazolam Vs Diazepam in The Treatment of Status Epilepticus: Efficacy of Midazolam Vs Diazepam. Pakistan Journal of Health Sciences, 4(06).
<https://doi.org/10.54393/pjhs.v4i06.842>

*Corresponding Author:

Muhammad Qasim Khan
 Pediatric Unit, Bacha Khan Medical College, Mardan,
 Pakistan
qasimkhan.dr.02@gmail.com

Received Date: 6th June, 2023Acceptance Date: 27th June, 2023Published Date: 30th June, 2023

ABSTRACT

Managing status epilepticus remains a formidable task in contemporary epilepsy care. This persistent and self-perpetuating epileptic activity presents with various manifestations with generalized convulsions being the prevailing form. **Objective:** To compare the efficacy of intravenous Midazolam with intravenous Diazepam in the treatment of status epilepticus.

Methods: It was a Randomized controlled trial conducted at Pediatric Department, Lady Reading Hospital Peshawar. All new cases of SE were enrolled in study in OPD. Patients in group A were subjected to intravenous midazolam (0.2 mg/kg body weight infused in normal saline over 10 mins) and patients in group B were subjected to DZP (0.15mg/kg body weight infused in normal saline over 10 mins). All children were carefully monitored for the cessation of SE.

Results: Out of the 120 cases included in the study, 72 (60.0%) were male patients, and 48 (40.0%) were female patients. The average age of the study participants was 3.67 ± 1.81 years. Among these 120 cases, 77 (64.2%) resided in rural areas, while 43 (35.8%) lived in urban areas. Efficacy was noted in 97 (80.8%) of our study cases, efficacy in group A was noted to be in 56 (93.3%) while in group B efficacy was noted to be in 41 (68.3%) ($p = 0.001$). **Conclusions:** Our study results support the use of Midazolam as it was found to be safe, effective and reliable as compared with Diazepam, as efficacy was significantly more common in Midazolam group.

INTRODUCTION

Seizures are frequently encountered emergency, representing approximately 1-2% of all visits to the emergency department. Among these cases status epilepticus occurs in around 6% of the cases [1]. However, there is still uncertainty regarding the optimum management of status epilepticus. It is estimated that nearly one in ten individuals will experience a seizure activity in lifetime [2]. While the majority of seizures are of short span and self-limited, a significant number of individuals suffer from seizure activity that is prolonged

and recurring without gaining consciousness, which constitute a medical emergency status epilepticus is a condition with significant morbidity and mortality, contributing to approximately 55000 deaths per in the US [3, 4]. The most complications associated with SE are gastric aspiration, ischemic brain damage, cardiac instability and damage to neurons [5]. While clinical studies have established a correlation between the duration of seizure activity with increased rates of mortality and poor neurological outcome, these findings do

not prove causality. However, research conducted on animal models shows that neuronal damage increases with increase in the duration of seizure activity [6]. Experimental models of status epilepticus also reveal that the efficacy of anticonvulsants in rapidly terminating seizures diminishes as the time between the onset of convulsions and a delay in appropriate anticonvulsants therapy [7]. If seizures are not promptly halted, increasing the dose of benzodiazepines become necessary to achieve seizure cessation, and ultimately, seizures become refractory to anticonvulsant therapy [8]. For the past three decades, benzodiazepines have been the primary treatment choice for status epilepticus (SE). However, there is uncertainty about the optimum anticonvulsants and their route of administration in outside of the hospitals particularly in cases where intravenous (IV) access is not readily available [9]. Diazepam is commonly used in management of seizure activity as it can be administered both intravenously and rectally [10]. Nonetheless, diazepam is believed to be less effective in terminating seizures compared to other benzodiazepines, especially when given rectally. Furthermore, diazepam is associated with a higher likelihood of complications such as prolonged sedation and respiratory depression [11]. On the other hand, midazolam (MDZ) is rapidly absorbed following intramuscular (IM) injection, does not require refrigeration, and is more cost-effective [12]. Requiring IV access before administering benzodiazepines can potentially lead to unnecessary delays in treating SE, putting the patient at risk even within the emergency department (ED) setting. The idea of non-IV administration of midazolam for SE treatment is an appealing alternative, but the efficacy is yet to be established [13]. In one study, 72.1% of children with status epilepticus had seizure free period for more than 30 minutes after cessation with diazepam [10]. In another study, 95% of children on continuous infusion of midazolam recovered from status epilepticus [14]. In another study, 92.3% of children subjected to midazolam recovered from status epilepticus compared to 90.1% patients in the diazepam group [15]. In another study, the mean time between active treatment start and cessation of seizures was 4.4 ± 0.5 mins in midazolam group compared to 3.3 ± 0.8 mins in diazepam group. The overall efficacy in terms of persistent seizure absence was 87.5% each for midazolam and diazepam groups [16]. SE is not uncommon in any population and if not treated aggressively in time, it can lead to severe complications and even life threatening. Moreover, the published literature has suggested a variety of benzodiazepines are available in the market with no proven or established efficacy of any. The choice and route of administration of these drugs vary from one population to another. This

study was an attempt to compare the intravenous MDZ with DZP in the treatment of SE as to our knowledge, we couldn't find any recent literature comparing these two drugs. Since no recent studies has been conducted in the past five years in our population, this study aims to fill the gap by providing the latest up to date information regarding the comparative effectiveness of intravenous midazolam and intravenous diazepam in treating status epilepticus in children. The findings of this study will not only contribute to our understanding of the topic but also be shared with other healthcare professionals, potentially serving as a valuable resource for future research endeavors and clinical decision-making.

METHODS

It was a Randomized Controlled Trial conducted at the Department of Pediatrics, Lady Reading Hospital Peshawar from 10-12-2019 to 09-06-2020. The total sample size was 120, equally divided among two groups. Sample size was calculated using the WHO formula keeping 92.3% efficacy of MDZ and 72.1% efficacy of DZP, 95% confidence interval and 90% power of test [15]. The sampling technique was non-probability sampling. After approval from the hospital ethical committee, a written informed consent was taken from the patients. All children, aged 6 months to 15 years of both genders presenting with status epilepticus with duration > 15 mins were enrolled in the study. All children diagnosed with muscular dystrophies, history of anticonvulsants prior to admission, any other chronic illness was excluded from the study. All patients were assessed by researcher by detailed history from parents followed by detailed clinical examination and complete set of baseline investigations was done. All children were randomly allocated in two groups by lottery method. Patients in group A were subjected to intravenous midazolam (0.2 mg/kg body weight infused with normal saline over 10 minutes) and patients in group B were subjected to DZP (0.15mg/kg body weight infused with normal saline over 10 minutes). All children in both the groups were carefully monitored for the cessation of SE. Among patients who recover from SE, were monitored for next 30 minutes to determine the intervention efficacy. For children who fail to recover after 10 minutes of therapy, a repeat dose was given as per international SE treatment protocols. Weight was measure according to a formula {weight = age (years) X 2+ 8}. All observations were done under supervision of an expert pediatrician fellow of CPSP and having minimum of five years of experience. All the above-mentioned information including age, gender, residence, cousin marriage, employment status, education of patients, socioeconomic status was recorded in a pre-designed proforma (Annexure I). Data were analyzed using SPSS version 20.0. Quantitative variables like age were

described in terms of means \pm standard deviation. Categorical data like gender, residence, and cousin marriage, and employment status, education of patients, socioeconomic status and efficacy were described in the terms of frequency and percentages. Efficacy in both the groups was compared with chi square test. Efficacy in both the groups was stratified with regards to age, gender, residence, cousin marriage, employment status, education of patients, socioeconomic status to see effect modification using chi square test. P-value of < 0.05 was kept significant. All results were presented as tables and diagrams.

RESULTS

A total of 120 participants were enrolled following strict inclusion criteria. Out of the total 120 study cases, male patients were 73(60%) whereas female patients were 48 (40%). The mean age was 3.67 ± 1.81 years, the minimum age was 01 year whereas the maximum age noted was 08 years. The mean age for male participants was 3.58 ± 1.65 whereas for female patients it was noted to be 3.79 ± 2.03 years. The major junk of patients i.e., 109(90.8%) were aged up to 6 years (Table 1). Out of the total 120 cases, 77(64.2%) were resident of rural areas whereas 43(35.8%) belongs to urban population. 79(65.8%) of the study participants belong to a poor socioeconomic class whereas 41(34.2%) belongs to middle income class, ninety-eight (81.7%) were employed. 58(48.3%) of parents had cousin marriages and 70 (58.3%) were illiterate (Table1).

Table 1: Socio-demographic characteristics

Variables	Group 1	Group 2
Gender (n=120)	Frequency (%)	Frequency (%)
Male	37(61.7)	35(58.3)
female	23(38.3)	25(41.7)
Total	60(100)	60(100)
Age groups (in Years) (n=120)		
Up to 6 n=109 (90.8 %)	54(90)	55(91.7)
More than 6 n= 11 (9.2 %)	06(10)	05(8.3)
Residential status (n=120)		
Rural n = 77 (64.2 %)	39(65)	38(63.3)
Urban n= 43 (35.8 %)	21(35)	22(36.7)
Total	60(100)	60(100)
Socioeconomic status (n=120)		
Poor n = 79 (65.8 %)	41(68.3)	38(63.3)
Middle Income n= 41 (34.2 %)	19(31.7)	22(36.7)
Total	60(100)	60(100)
Cousin Marriage (n=120)		
Yes n = 58 (48.3 %)	28(46.7)	30(50)
No n = 62 (51.7 %)	32(53.3)	30(50)
Total	60(100)	60(100)

Literacy (n=120)		
Illiterate n = 70 (58.3 %)	37(61.7)	33
Literate n = 50 (41.7 %)	23(38.3)	27(45)
Total	60(100)	60(100)

Out of the total study cases efficacy was noted in 97(80.8%) of cases, in group A it was 56(93.3%) whereas in group B the efficacy was noted in 41(68.3%)($p = 0.001$)(Table 2).

Table 2: Distribution of study cases by Efficacy

Gender with regards to efficacy in both groups				
Gender	Efficacy	Groups		p-value
		GROUP A	GROUP B	
Male (n=72)	Yes(n=60)	35	25	0.011
	No(n=12)	02	10	
Female (n=48)	Yes(n=37)	21	16	0.039
	No (n=11)	02	09	
Age with regards to efficacy in both groups (n = 120)				
Age	Efficacy	Groups		p-value
		GROUP A	GROUP B	
Up to 6 Years (n=109)	Yes(n=91)	52	39	0.001
	No(n=18)	02	16	
More than 6 Years (n=11)	Yes(n=06)	04	02	0.567
	No(n=05)	02	03	
Residential status with regards to efficacy in both groups.				
Residential status	Efficacy	Groups		p-value
		GROUP A	GROUP B	
Rural (n=77)	Yes(n=65)	37	28	0.013
	No(n=12)	02	10	
Urban (n=43)	Yes(n=32)	19	13	0.034
	No(n=11)	02	09	
Socioeconomic status with regards to efficacy in both groups				
Socioeconomic status	Efficacy	Groups		p-value
		GROUP A	GROUP B	
Poor (n=79)	Yes(n=66)	39	27	0.005
	No(n=13)	02	11	
Middle Income (n=41)	Yes(n=31)	17	14	0.075
	No(n=10)	02	08	
Cousin marriage with regards to efficacy in both groups.				
Cousin Marriage	Efficacy	Groups		p-value
		GROUP A	GROUP B	
Yes(n=58)	Yes(n=47)	26	21	0.043
	No(n=11)	02	09	
No (n=62)	Yes(n=50)	30	20	0.010
	No(n=12)	02	10	
Literacy with regards to efficacy in both groups.				
Literacy	Efficacy	Groups		p-value
		GROUP A	GROUP B	
Illiterate (n=70)	Yes(n=52)	33	19	0.005
	NO(n=18)	04	14	
Literate (n=50)	Yes(n=45)	23	22	0.054
	No(n=05)	00	05	

DISCUSSION

Prolonged seizures or recurring seizure without gain of consciousness is termed as status epilepticus. It is the

most frequent neurological emergency with approximately 18-23 cases per 1 lac children in a year with 2-7% mortality rate. The management of status epilepticus involves promptly administering appropriate anticonvulsants, identifying and addressing any triggers for the seizures, and managing complications associated with seizure activity. Status epilepticus poses children at greater risk of long-term complications such damage to the neurons, synapses network. These complications mainly depend on the duration and the type of seizure activity. A total of 120 patients were enrolled for the study following strict inclusion criteria. Out of 120 cases male patients comprises 72(60%) whereas 48(40%) were females. Ibrahim *et al.*, in his study reported male predominance with 66.7%, which is consistent with our findings [17]. Ahmed *et al.*, in study conducted in Karachi have reported predominance of male gender at 58%, which is similar to our findings [18]. Saeed *et al.*, conducted a study in Rawalpindi also reported a predominance of male gender at 52%, consistent with our study findings [19]. A study conducted by Burman *et al.*, in South Africa reported, that 52% of the study participants comprises of male gender which is consistent with our findings [20]. The mean age of the study participants was 3.67 ± 1.81 years, the minimum age was 01 year whereas the maximum age was noted to be 8 years. The mean age of male participants was 3.58 ± 1.65 years whereas for female participants it was noted to be 3.79 ± 2.03 years. The major junk of patients i.e., 109(90.8%) were aged up to 6 years. Ibrahim *et al.*, in his study reported that 58 months as the mean age of the participants which is consistent with our findings [17]. Ahmed *et al.*, conducted a study in Karachi also reported 51 ± 41 months as the mean age which in similar to our study findings [18]. Saeed *et al.*, conducted a study in Rawalpindi reported 4.66 ± 2.95 years as the mean age of study participants which is consistent with our study. A study conducted by Burman *et al.*, also concluded the similar range for mean age of the participants. Burman *et al.*, from South Africa has also reported similar range for age in children presenting with status epilepticus [20]. Out of the total 120 cases, 77(64.2%) were resident of rural areas whereas 43(35.8%) belongs to urban population. 79(65.8%) of the study participants belong to a poor socioeconomic class whereas 41(34.2%) belongs to middle income class, ninety-eight (81.7%) were employed. 58(48.3%) of parents had cousin marriages and 70 (58.3%) were illiterate. Ibrahim *et al.*, in his study also concluded the same findings. Out of the total study cases efficacy was noted in 97(80.8%) of cases, in group A it was 56(93.3%) whereas in group B the efficacy was noted in 41 (68.3%) ($p = 0.001$) [17]. Saeed *et al.*, in his study also concluded an efficacy in 92% in the Midazolam group versus 77% ($p=0.005$) in the Diazepam group [19].

These findings are consistent with our study results. In another study, Koul *et al.*, concluded that 95% of children on continuous infusion of midazolam recovered from status epilepticus which is similar to that of our study results [14]. In another study, Chamberlain *et al.*, concluded that 92.3% of children subjected to midazolam recovered from status epilepticus compared to 90.1% patients in the diazepam group which is comparable to our findings [15]. A study by Portela *et al.*, concluded that the mean time between active treatment start and cessation of seizures was 4.4 ± 0.5 mins in midazolam group compared to 3.3 ± 0.8 mins in diazepam group, these findings are consistent with our study results [16].

CONCLUSIONS

Our study results support the use of Midazolam as it was found to be safe, effective and reliable as compared with Diazepam, as efficacy was significantly more common in Midazolam group. The overall efficacy among the total cases was noted in 97(80.8%), in Group A (received Midazolam) the efficacy was noted in 56 (93.3%) whereas the efficacy in Group B (received Diazepam) was 41 (68.3%) ($p=0.001$).

Authors Contribution

Conceptualization: AK

Methodology: SA, MQK

Formal analysis: KA, TJ, MS

Writing-review and editing: AK, TJ, MS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

REFERENCE

- [1] Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, *et al.* A definition and classification of status epilepticus—Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*. 2015 Oct; 56(10): 1515-23. doi: 10.1111/epi.13121.
- [2] Neligan A and Walker MC. Letter Re" Status epilepticus-related etiology, incidence and mortality: A meta-analysis" by Lv RJ *et al.*, 2017. *Epilepsy Research*. 2017 Nov; 137: 121-2. doi: 10.1016/j.eplepsyres.2017.08.015.
- [3] Betjemann JP, Josephson SA, Lowenstein DH, Burke JF. Trends in status epilepticus—related hospitalizations and mortality: redefined in US

- practice over time. *JAMA Neurology*. 2015 Jun; 72(6): 650-5. doi: 10.1001/jamaneurol.2015.0188.
- [4] Dham BS, Hunter K, Rincon F. The epidemiology of status epilepticus in the United States. *Neurocritical Care*. 2014 June; 20(3):476-83. doi: 10.1007/s12028-013-9935-x.
- [5] Sutter R, Dittrich T, Semmlack S, Rüegg S, Marsch S, Kaplan PW. Acute systemic complications of convulsive status epilepticus—a systematic review. *Critical Care Medicine* 2018 Jan; 46(1): 138-45. doi: 10.1097/CCM.0000000000002843.
- [6] Lai A, Outin HD, Jabot J, Mégarbane B, Gaudry S, Coudroy R, et al. Functional outcome of prolonged refractory status epilepticus. *Critical Care*. 2015 April; 19(1): 199. doi: 10.1186/s13054-015-0914-9.
- [7] Yasiry Z and Shorvon SD. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: a meta-analysis of published studies. *Seizure*. 2014 Mar; 23(3): 167-74. doi: 10.1016/j.seizure.2013.12.007.
- [8] Rogalski R and Rogalski A. Benzodiazepine selection in the management of status epilepticus: a review. *Advanced Emergency Nursing Journal*. 2015 April; 37(2): 83-94. doi: 10.1097/TME.000000000000064
- [9] Lawton B, Davis T, Goldstein H, Tagg A. An update in the initial management of paediatric status epilepticus. *Current Opinion Pediatric*. 2018 Jun; 30(3): 359-63. doi: 10.1097/MOP.0000000000000616.
- [10] Chamberlain JM, Okada P, Holsti M, Mahajan P, Brown KM, Vance C, et al. Lorazepam vs diazepam for pediatric status epilepticus: a randomized clinical trial. *JAMA* 2014 April; 311(16): 1652-60. doi: 10.1001/jama.2014.2625.
- [11] Brigo F, Bragazzi NL, Bacigaluppi S, Nardone R, Trinka E. Is intravenous lorazepam really more effective and safe than intravenous diazepam as first-line treatment for convulsive status epilepticus? a systematic review with meta-analysis of randomized controlled trials. *Epilepsy and Behavior*. 2016 Nov; 64: 29-36. doi: 10.1016/j.yebeh.2016.09.020.
- [12] Fernandez A, Lantigua H, Lesch C, Shao B, Foreman B, Schmidt JM, et al. High-dose midazolam infusion for refractory status epilepticus. *Neurology*. 2014 Jan; 82(4): 359-65. doi: 10.1212/WNL.000000000000054.
- [13] Welch RD, Nicholas K, Durkalski-Mauldin VL, Lowenstein DH, Conwit R, Mahajan PV, et al. Neurological Emergencies Treatment Trials (NETT) Network Investigators. Intramuscular midazolam versus intravenous lorazepam for the prehospital treatment of status epilepticus in the pediatric population. *Epilepsia*. 2015 Feb; 56(2): 254-62. doi: 10.1111/epi.12905.
- [14] Koul RL, Aithala GR, Chacko A, Joshi R, Elbualy MS. Continuous midazolam infusion as treatment of status epilepticus. *Archives of Disease in Childhood*. 1997 May; 76(5): 445-8. doi: 10.1136/adc.76.5.445.
- [15] Chamberlain JM, Altieri MA, Futterman C, Young GM, Ochsenchlager DW, Waisman Y. A prospective, randomized study comparing intramuscular midazolam with intravenous diazepam for the treatment of seizures in children. *Pediatric Emergency Care*. 1997 April; 13(2): 92-4. doi: 10.1097/00006565-199704000-00002.
- [16] Portela JL, Garcia PC, Piva JP, Barcelos A, Bruno F, Branco R. Intramuscular midazolam versus intravenous diazepam for treatment of seizures in the pediatric emergency department: a randomized clinical trial. *Medicina Intensiva*. 2015 April; 39(3): 160-6. doi: 10.1016/j.medin.2014.04.003.
- [17] Ibrahim SH, Yezdan MA, Nizami SQ. Status Epilepticus in Children: a five-year Experience at Aga Khan University Hospital. *Journal of Pakistan Medical Association*. 2003 Dec; 53(12): 597-9.
- [18] Ahmed K, Jafr SK, Bhatti F, Rafique A, Haque A. Clinical profile and outcome of children admitted with status epileptics in PICU of a developing country. *Pakistan Journal of Neurological Sciences*. 2013; 8(2): 1-6.
- [19] Saeed T, Haq MZ, Kiani NM. Comparison of Buccal Midazolam with Rectal diazepam in Status Epilepticus in Terms of Recurrence of Seizures and Risk for Treatment Failure. *Journal of Rawalpindi Medical College*. 2015 Dec; 19(3): 197-9.
- [20] Burman RJ, Ackermann S, Shapson-Coe A, Ndong A, Buys H, Wilmshurst JM. A Comparison of Parenteral Phenobarbital vs. Parenteral Phenytoin as Second-Line Management for Pediatric Convulsive Status Epilepticus in a Resource-Limited Setting. *Frontier in Neurology*. 2019 May; 10: 506. doi: 10.3389/fneur.2019.00506.