ECRONICON OPEN ACCESS

EC PAEDIATRICS
Research Article

Frequency of Successful Outcome of Intramuscular Midazolam for the Treatment of Status Epilepticus in Children

Aiman Islam[1], Afsheen Batool Raza[2]*, Muhammad Khalid Masood[3] and Nadia Nawaz[4]

[1]*The Children's Hospital and University of Child Health Sciences, Lahore, Pakistan*

[2]*Associate Professor of Pediatrics, The Children's Hospital and University of Child Health Sciences, Lahore, Pakistan*

[3]*Professor of Paediatrics, University of Child Health Sciences, Lahore, Pakistan*

[4]*Senior Registrar, Children's Hospital, Lahore, Pakistan*

***Corresponding Author:** Afsheen Batool Raza, Associate Professor of Pediatrics, The Children's Hospital and University of Child Health Sciences, Lahore, Pakistan.

Received: May 06, 2024; **Published:** May 27, 2024

Abstract

Aims and Objectives:

1. To find out the frequency of successful outcome of intramuscular midazolam for the treatment of status epilepticus in children.
2. To compare successful outcome with respect to previous history of convulsions.

Patients and Methods: This cross sectional study was conducted in department of Paediatrics Children's Hospital Lahore. Non-probability consecutive sampling technique was used and a total of 370 patients meeting inclusion criteria were included in this study. After taking an informed consent, patient's contact information and demographic data was obtained. IM midazolam was used with a dose of 0.3 mg/kg and was injected into the left quadriceps muscle and final outcome was noted.

Results: The mean age of cases was 7.68 ± 4.10 years with minimum age as 4 months and maximum 14 years. One hundred (27%) cases had past history of seizures. A total of 350 (94.6%) cases had successful outcome while in 20 (5.4%) of the cases the outcome was not successful.

Conclusion: In this study, IM midazolam is found successful for the treatment of status epilepticus in children. Thus, this mode of treatment can be utilized in treating such cases to gain maximum therapeutic effectiveness.

Keywords: *Status Epilepticus; Seizures; Benzodiazepines; Midazolam; Diazepam*

Introduction

Status epilepticus (SE) is a serious neurological problem in children [1]. Seizures are a common medical emergency, accounting for 1 - 2% of all emergency department (ED) visits, and among these 6% presents as status epilepticus (SE) [2]. SE affects people of all ages, though it is more common and causes greater morbidity and mortality in infants. Age of presentation, etiology, and the duration of seizure activity correlate with mortality [1]. Acute convulsions in children are a common emergency and benzodiazepines are the recommended first line treatment in most settings [3].

The goal of treatment is the rapid termination of the seizure, to minimize the acute and chronic effects of seizures and to allow for the prompt assessment and management of the underlying precipitant [4]. Therapeutic options include diazepam, lorazepam or midazolam, which have different pharmacokinetic properties [3]. Benzodiazepines (BDZs) that act as allosteric modulators of the GABA receptors, increasing Cl- conductance to enhance the inhibitory component of the synapse and, consequently, stop the seizure. This class of drugs is broadly considered to be safe, effective, and easy to administer [5,6].

Standard protocols recommend IV diazepam and lorazepam as the standard first line treatment for status epilepticus but most of the time in many setting especially where expert Paediatric staff is not available, getting IV access is difficult, so, other routes for drug administration should be considered. Rectal, buccal, and nasal routes are well-studied for drug administration in convulsive status epilepticus. Many studies recommend rectal diazepam for home treatment of seizures and even in hospital settings rectal diazepam can be used as initial treatment of seizures [4,7]. Intravenous route is considered as the first choice in resource-rich settings. Besides biological uniqueness of patients, various pharmacokinetic (PK) and pharmacodynamics (PD) characteristics of different BZDs such as rapidity of action, half-life, bioavailability, efficacy in seizure suppression, and side effects, ease of preparation and administration, etc. are vital attributes for selecting a BZD (with a specific route of administration) over others for a particular patient. Previously two approved therapies were rectal diazepam and buccal midazolam, now followed by two newly available treatment options, diazepam and midazolam given by intramuscular and intranasal routes [8]. Midazolam is rapidly absorbed after intramuscular (IM) injection, does not require refrigeration and is less expensive [3]. MDZ has well-known anticonvulsant properties, which led to its proposal as a treatment for SE, especially in the pediatric population [9,10]. As MDZ is water soluble and 3 - 4 times more potent than other BDZs so it can be considered as a good choice in resource constrain settings especially when expert staff for passing IV line is not available and a mean IM dose of 0.1 to 0.3 mg/Kg is considered effective [11]. In one study, the dosage of intramuscular MDZ was set at 0.25 mg/Kg, whilst buccal MDZ was set at a slightly higher dosage, 0.3 mg/Kg [12]. This difference is mainly due to the higher bioavailability of intramuscular MDZ, which is close to 90% vs 75% for the buccal route. Having access to rescue medicines, patients and caregivers may experience an increased sense of control, security, and confidence in managing seizures at home. They may travel with less worry and have enhanced freedom to make long-range plans [13]. A recent study reported that with the use of intramuscular midazolam, the success of treatment was 96% (48/50 of cases) [7].

Not much local data is available on efficacy of IM Midazolam in status epilepticus so this study is done to see outcome of intramuscular Midazolam for the treatment of status epilepticus in children in local setting based on which we can give recommendation that whether this medicine is useful or not in controlling seizures in status epileptics in children.

Patients and Methods

Children of either gender, aged one month to 14 years who presented with status epilepticus were enrolled from Pediatric emergency and Pediatric medicine department of The Children's Hospital and Institute of Child Health, Lahore. Children previously administered through any route of benzodiazepines by parents or paramedics and children who had a history of serious adverse reactions to intramuscular midazolam were excluded from the study. After getting approval from hospital ethical committee a total of 370 patients meeting inclusion criteria were included in this study. Informed consent was taken from all parents. Patient's contact information, demographic data was obtained and documented. IM midazolam was used with a dose of 0.3 mg/kg and was injected into the left quadriceps muscle if the child is younger than two and if the child is older than two the left deltoid muscle was considered for injection. Final outcome was noted as cessation of seizures within 10 minutes after injection. All data was kept by researcher herself on attached proforma. The data was analyzed through SPSS version 20. Quantitative data like age was presented in form of mean ± S.D. Qualitative data like gender history of previous episode, and success of intramuscular midazolam was presented as frequency (%). Data was stratified for age, gender and history of previous episode to address effect modifiers. Post stratified Chi-square test was used considering p-value ≤ 0.05 as significant.

Results

The mean age of cases was 7.68 ± 4.10 years with minimum age as 4 months and maximum 14 years. There were 210 (56.8%) male and 160 (43.2%) female cases. According to previous history, 100 (27) cases had past history of seizures and 270 (73%) cases had no previous history of fits (Figure 1).

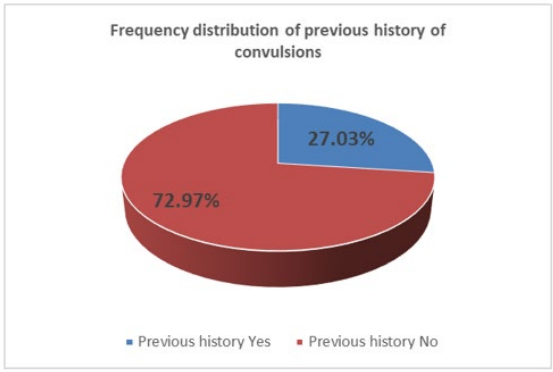

Figure 1: *Frequency distribution of previous history of convulsions.*

A total of 350 (94.6%) cases had successful outcome while in 20 (5.4%) of the cases the outcome was not successful (Figure 2). Among cases who had successful outcome, 137 (39.8%) cases were < 7 years old and 207 (60.2%) cases were 7 - 14 years old while among cases who do not had successful outcome, 12 (46.2%) cases were < 7 years old and 14 (53.8%) cases were 7 - 14 years old, the frequency of successful outcome was statistically same in both age groups, p-value > 0.05 (Table 1). There were 194 (56.4%) male and 150 (43.6%) female cases who had successful outcome and there were 16 (61.5%) male and 10 (38.5%) female cases who do not had successful outcome, the frequency of successful outcome was statistically same in both gender, p-value > 0.05.

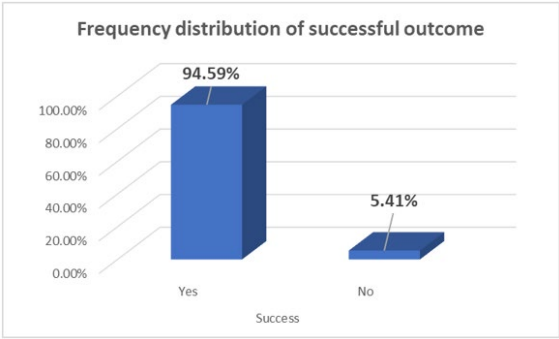

Figure 2: *Frequency distribution of successful outcome.*

There were 96 (27.9%) cases who had previous history of episode and 248 (72.1%) cases did not had previous history of episode among those who had successful outcome and there were 4 (15.4%) cases who had history and 22 (84.6%) cases who do not had previous

history among those who did not had successful outcome, the frequency of successful outcome was statistically same in both groups of previous history, p-value > 0.05.

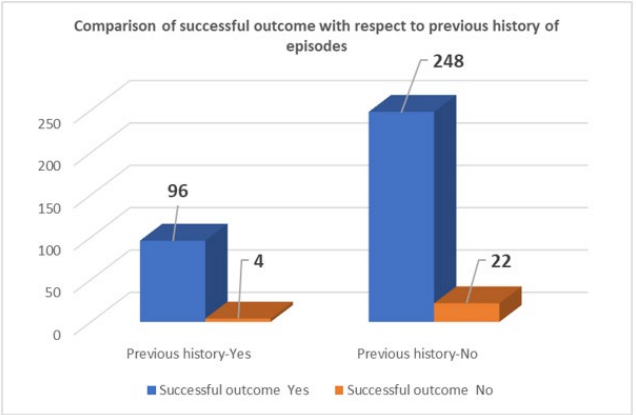

Figure 3: *Comparison of successful outcome with respect to previous history of episodes. Chi-square = 1.92, p-value = 0.166.*

Discussion

Status epilepticus is one of the most common neurological emergencies that occur in children. Such seizures usually are associated with high morbidity and mortality, therefore urgent treatment is warranted. Based on the etiology, co-morbidities, and duration of seizures, long term outcomes would be different and all the previous studies claimed that early treatment by an effective agent usually leads to better outcome. To cease seizures rapidly, the medication should reach the brain quickly while having minimum serious adverse effects. For this purpose, IV administration of anticonvulsants could be the best route but in a child with active convulsions IV access may be very difficult, therefore, other routes for drug administration should be considered [14]. Standard protocols recommend IV diazepam and lorazepam as the standard acute treatment for status epilepticus but as previously mentioned when getting IV access is difficult, other routes for drug administration should be considered. Rectal, buccal, and nasal routes are well-studied for drug administration in convulsive status epilepticus. Alldredge., *et al*. conducted a randomized double blind study that showed a higher rate of seizure termination and a lower risk of complications in patients treated with lorazepam (LZP) and diazepam (DZP) before accessing a hospital as compared to placebo [15]. As because of risk of respiratory depression and apnea BDZs are usually under dosed in SE treatment [16,17], there may be an impact on their efficacy. So, whenever the first-line therapy fails, a switch to second-line treatments such as levetiracetam, fosphenytoin, and valproate [18-20] must be considered [21]. Many studies recommend rectal diazepam for home treatment of status epilepticus and in many emergency departments the rectal diazepam is the main initial treatment for this [22]. A number of studies demonstrated that buccal and nasal midazolam could be an effective and safe choice for controlling seizures but these routes could be unreliable in a number of patients because it may be very difficult to open the mouth of the patient during the seizure when the jaw is locked and nasal congestion and copious discharges during active seizures could lead to insufficient absorption of drug via nasal mucosa [23]. IM drug administration during active seizures could be very easy and safe and a number of studies demonstrated that IM midazolam could be an initial agent for controlling seizures in home, office, and pre-hospital settings. Previous studies indicated that anticonvulsant activity of IM midazolam is equal to or better than diazepam, moreover, after IM administration, midazolam is completely absorbed and reaches brain rapidly [24]. A recent study reported that using intramuscular midazolam, the success of treatment was achieved in 96% (48/50) of cases [7]. These findings support our study. Recently a multicenter clinical trial was done to examine the effectiveness of intramuscular (IM) midazolam

versus intravenous (IV) lorazepam for the treatment of pediatric patients with status epilepticus (SE) in the pre hospital care setting. The primary outcome was met in 41 (68.3%) and 43 (71.7%) of subjects in the IM and IV groups, respectively (risk difference [RD] -3.3%, 99% CI -24.9% to 18.2%) [25]. Time from initiating the treatment protocol was shorter for children who received IM midazolam, mainly due to the shorter time to administer the active treatment. Safety profiles were similar. Hence, it can be concluded that IM midazolam can be rapidly administered and appears to be safe and effective for the management of children with SE treated in the pre hospital setting. In 2005, another study was conducted to determine effectiveness of intramuscular midazolam to control acute seizures in children as compared to intravenous diazepam. The children in the age group of 1 month to 12 years who presented with acute convulsions were enrolled in the study. Effectiveness of IM midazolam in controlling seizures with IM midazolam was 97.22 seconds whereas in diazepam group without prior IV access it was 250.35 seconds and in diazepam group with prior IV access it was 119.4 seconds. IM midazolam acted faster in all age groups and in patients with febrile convulsions, which was statistically significant [26]. 10.8% were having thrombophlebitis associated with IV diazepam whereas none of the patients in the midazolam group had any side effects, which was statistically significant [27]. So, to quickly stop seizures in SE and avoid subsequent invasive management, IM Midazolam is a very good choice especially in situation where patient is away from healthcare facility or expert care is not available and even in hospital setting it's easy to administer during seizure activity.

Conclusion

Through the findings of this study it is concluded that intramuscular midazolam is successful in controlling seizures in status epilepticus in children. It seems suitable to be used in the pre-hospital and hospital settings when IV access is not readily available, with clear efficacy in the management of acute seizures and convulsive status epilepticus. Thus, this mode of treatment can be utilized in treating such cases to gain maximum therapeutic effectiveness.

Bibliography

1. Saz EU., *et al*. "Convulsive status epilepticus in children: etiology, treatment protocol and outcome". *Seizure* 20.2 (2011): 115-118.
2. Brophy GM., *et al*. "Guidelines for the evaluation and management of status epilepticus". *Neurocritical Care* 17.1 (2012): 3-23.
3. Lissauer S., *et al*. "Buccal, intranasal or intravenous lorazepam for the treatment of acute convulsions in children in Malawi: An open randomized trial: Le lorazépam par voieorale, intranasaleouintraveineuse pour le traitement des convulsions aiguës chez l'enfant au Malawi: étudeouverterandomisée". *African Journal of Emergency Medicine* 13.3 (2015): 120-126.
4. Loddenkemper T and Goodkin HP. "Treatment of pediatric status epilepticus". *Current Treatment Options in Neurology* 13.6 (2011): 560-573.
5. Glauser T., *et al*. "Evidence-based guideline: treatment of convulsive Status Epilepticus in Children and Adults: report of the guideline committee of the American Epilepsy society". *Epilepsy Currents* 16.1 (2016): 48-61.
6. Sánchez Fernández I., *et al*. "Pathophysiology of convulsive status epilepticus". *Seizure* 68 (2019): 16-21.
7. Momen AA., *et al*. "Efficacy and safety of intramuscular midazolam versus rectal diazepam in controlling status epilepticus in children". *European Journal of Paediatric Neurology* 19.2 (2015): 149-154.
8. Diastat C-IV diastatAcuDial™ C-IV (diazepam rectal gel) (2021).
9. Verrotti A., *et al*. "Pediatric status epilepticus: improved management with new drug therapies?" *Expert Opinion on Pharmacotherapy* 18.8 (2017): 789-798.

10. Pellock JM. "Use of midazolam for refractory status epilepticus in pediatric patients". *Journal of Child Neurology* 13.12 (1998): 581-587.

11. Samanta D. "Rescue therapies for seizure emergencies: current and future landscape". *Neurological Sciences* 42.10 (2021): 4017-4027.

12. Ahmad S., *et al*. "Efficacy and safety of intranasal lorazepam versus intramuscular paraldehyde for protracted convulsions in children: An open randomised trial". *The Lancet* 367.9522 (2006): 1591-1597.

13. Seizure first aid and safety (2021).

14. Ashrafi MR., *et al*. "Efficacy and usability of buccal midazolam in controlling acute prolonged convulsive seizures in children". *European Journal of Paediatric Neurology* 14.5 (2010): 434-438.

15. Riva A., *et al*. "Intramuscular midazolam for treatment of status epilepticus". *Expert Opinion on Pharmacotherapy* 22.1 (2021): 37-44.

16. Kapur J., *et al*. "Randomized trial of three anticonvulsant medications for status epilepticus". *New England Journal of Medicine* 381.22 (2019): 2103-2113.

17. Kellinghaus C., *et al*. "Factors predicting cessation of status epilepticus in clinical practice: data from a prospective observational registry (SENSE)". *Annals of Neurology* 85.3 (2019): 421-432.

18. Chamberlain JM., *et al*. "Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomized controlled trial". *Lancet* 395.10231 (2020): 1217-1224.

19. Crawshaw AA and Cock HR. "Medical management of status epilepticus: emergency room to intensive care unit". *Seizure* 75 (2020): 145-152.

20. Dalziel SR., *et al*. "Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial". *Lancet* 393.10186 (2019): 2135-2145.

21. Silbergleit R., *et al*. "Intramuscular versus intravenous therapy for prehospital status epilepticus". *New England Journal of Medicine* 366.7 (2012): 591-600.

22. Anderson M. "Buccal midazolam for pediatric convulsive seizures: efficacy, safety, and patient acceptability". *Patient Preference and Adherence* 7 (2013): 27-34.

23. McMullan J., *et al*. "Midazolam versus diazepam for the treatment of status epilepticus in children and young adults: a meta-analysis". *Academic Emergency Medicine* 17.6 (2010): 575-582.

24. Welch RD., *et al*. "Intramuscular midazolam versus intravenous lorazepam for the prehospital treatment of status epilepticus in the pediatric population". *Epilepsia* 56.2 (2015): 254-262.

25. Roger J. "Status epilepticus". *Handbook of Clinical Neurology* 15 (1974): 145-188.

26. Shah I and Deshmukh C. "Intramuscular midazolam vs intravenous diazepam for acute seizures". *Indian Journal of Pediatrics* 72.8 (2005): 667-670.

Volume 13 Issue 6 June 2024