

OUTCOME OF INTRAMUSCULAR MIDAZOLAM VERSUS INTRAVENOUS DIAZEPAM FOR CONTROL OF ACUTE SEIZURES

NAEEMA KHAWAJ¹, SADAF LIAQAT², SAJID HUSSAIN SHERAZI³

¹Lahore Medical & Dental College, Lahore ^{2,3}Assistant Professors of Paediatrics, Rai Medical College, Sargodha Correspondence: Dr. Sadaf Liaqat e-mail: sadafliaqat09@gmail.com

ABSTRACT

Objective: To compare midazolam and diazepam given via intramuscular and intravenous route respectively for management of fits in children presenting in emergency.

Study Design: Randomized controlled study

Place and Duration: This study was conducted in Paediatrics Emergency, Ittefaq Trust Hospital, Lahore from 24th June 2013 to 23rd December 2013.

Materials and Methods: In this study we took 60 cases and assigned them group A and B (30 cases in each group). Group A was given 0.2mg/kg/dose midazolam via intramuscular route and group B was given intravenous diazepam (0.2mg/kg/dose) for management of fits.

Results: Mean age was 2.59 ± 2.88 and 3.55 ± 3.09 years in group A and B respectively. Group A and B included 17 (56.7%) & 18 (60%) males respectively while there were 13 (43.3%) and 12 (40%) females in group-A and B respectively. It was observed that in Group A (I/M midazolam) time interval was significantly less as compared to Group-B (I/v diazepam) (5.89 ± 2.63 vs 8.35 ± 2.88 minute) $p < 0.001$ for control of seizure (minutes).

Conclusion: Intramuscular midazolam is effective in controlling acute seizures significantly as compared to intravenous diazepam.

Key words: Acute seizures, Midazolam, Diazepam

INTRODUCTION

Seizures are the most common presentation of central nervous system disorders in pediatrics age group having incidence of 60 per 1000.¹ Short duration seizures may have good prognosis but long duration fits usually have poor prognosis and also increase morbidity and mortality. Prolonged seizures may lead to cardiac rhythm disturbances, aspiration pneumonia, metabolic derangements, autonomic dysfunction and various sequelae of nervous system dysfunction.²

Duration of seizures has great importance as it is directly related to increase mortality and morbidity. A delay in providing effective and rapid management for control of seizures is associated with increased incidence of status epilepticus³, subsequent development of epilepsy and neuro-developmental disorders in children. Therefore timely management of seizures to prevent morbidity and mortality has great importance. There is no specific seizures duration that is predictable for morbidity, therefore our management focus on control of fits as soon as possible.⁴

According to currently practical protocols, first line treatment for control of acute seizures is

benzodiazepines. Various medicines as lorazepam (0.5 to 0.1mg/kg IV), diazepam (0.1-0.3mg/kg IV, 0.5mg/kg PR) and midazolam (buccal, intranasal, intramuscular) are used effectively as first line agents.⁵⁻⁸ In all above, commonly used benzodiazepines diazepam and it can be administered intravenously as well as per rectal, but for administration of diazepam for control of acute seizures in emergency, intravenous cannulation has to be done and it is a major barrier for rapid and effective management.⁹

In a study Shresti presented that mean time taken for administration of drug was much less in intramuscular midazolam group (0.17 ± 0.046 minutes) as compared intravenous diazepam (4.19 ± 1.15) ($p < 0.001$). There was significant difference in time from presentation in fits state in emergency to control of seizures in group midazolam group was (5.26 ± 2.74) and diazepam group was 7.52 ± 2.57 ($p < 0.001$).¹⁰

The rationale of conducting the study is to emphasize the importance of intramuscular midazolam as an effective first line agent for control of acute seizures. This can be helpful to the patients in pre-hospital setting where patients with epilepsy and other

seizure disorders can be managed with the help of auto injectors thus decrease the morbidity and mortality associated with prolonged and recurrent seizures by timely control of seizures prior to arrival to hospital.¹¹

The study will help to generate local data for the awareness of physicians in Pakistan as there is no previous study being done on this topic before, to best of my knowledge.

MATERIALS AND METHODS

This randomized controlled study was carried out at Paediatrics Emergency, Ittefaq Trust Hospital, Lahore from 24th June 2013 to 23rd December 2013. There were 60 cases (30 cases in each group) in this study. Group A was assigned as midazolam and group B as diazepam group. 0.2mg/kg/dose intramuscular midazolam was given to group A and in group-B, 0.2 mg/kg/dose I/V diazepam was administered. Patients in ranges of 2 month and 12 years with acute seizures longer than 5 minutes or continuous seizures without regain of consciousness were included. Exclusion criteria were: Children having head injury or a major trauma as precipitant of seizure, low glucose level (glucose <60mg/dl) and administration of anticonvulsant therapy before presentation in emergency department. Midazolam with a dose of 0.2mg/kg/dose via intramuscular route was given to group A for control of acute fits and duration was noted from the start of treatment, to complete control of fits. While 0.2 mg/kg/dose I/V diazepam was given to group B children and time duration was noted from maintaining an intravenous line and administration of diazepam via this route to complete control of seizures. Both diazepam and midazolam were taken from emergency tray as both were kept in prepared form in syringes for immediate use. The data was entered and analyzed by SPSS 20. Meantime from the start of treatment to complete control of seizure was compared with groups by using t-test. Significant P value was considered as ≤ 0.05 .

RESULTS

Most common age group in both groups was 1-5 years old with mean age in group A was 2.59 ± 2.88 and mean age in group B was 3.55 ± 3.09 years (Table 1). Regarding gender, group A included 17 males (56.7%) and group B included 18 males (60.0%) whereas there were 13 (43.3%) females in group A and group B had 12 (40.0%) females (Table 2). When both groups were compared with regard to time interval for control of seizure (minute), it was observed that in Group-A (I/m midazolam) time interval was significantly less as compared to Group-B (I/V Diazepam) (5.89 ± 2.63 vs

8.35 ± 2.88 minute) $p < 0.001$ (Table-3).

Table 1: Distribution of cases by age

Age (Year)	I/M midazolam		I/V Diazepam	
	No.	%	No.	%
< 1	12	40.0	04	13.3
1-5	13	43.3	20	66.7
6-11	05	16.7	06	20.0
Mean \pm SD	2.59 ± 2.88		3.55 ± 3.09	

Table 2: Distribution of cases by gender

Gender	I/M midazolam		I/V Diazepam	
	No.	%	No.	%
Male	17	56.7	18	60.0
Female	13	43.3	12	40.0

Table 3: Time interval for control of seizure (minute)

Group	Mean \pm SD	t value/ P value
I/M midazolam	5.89 ± 2.63	3.454/ $p < 0.001$
I/V diazepam	8.35 ± 2.88	

DISCUSSION

Acute seizure puts a great stress over health care personal and also on parents.¹² According to many parents, these episodes are dangerous and most parents consider these attacks as a threat to the lives of their children especially when these seizures appear for the first time.¹³ When seizures become prolonged or recurrent, they impose great morbidity and mortality especially when seizure activity lasts more than 30 minutes.^{14,15} So there should be effective and reliable methods to control seizures completely specifically at home.

An anticonvulsant use in emergency should have certain characteristics such as it should be safe, have rapid onset of action, affordable and should have easy route to administer. Among many anticonvulsants, diazepam has been use in emergency condition for control of seizures in epilepsy and many other convulsive syndromes and nervous system disorders for last four decades and it is effective in 60 to 80 % cases.¹⁶

In present study, midazolam is compared with diazepam for the control of acute seizures in children. It was found in all studies that midazolam effects more rapidly and effectively in controlling seizures as compared to diazepam (5.89 ± 2.63 vs 8.35 ± 2.88 minutes) $p < 0.001$.

Various previous studies show that the time period required for administration of midazolam via intramuscular route is significantly less as compared to

the time required for administration of intravenous diazepam and these results are comparable with results of our study.¹⁷⁻²⁰

In 1997, Chamberlain et al. conducted the randomized comparative study on intramuscular midazolam versus intravenous diazepam in 24 patients of which 22 patients had good effective control of seizures and concluded that intramuscular midazolam has good rapid absorption rate and more rapid cessation of seizures. The administration of drug via intramuscular route was especially effective in pre-hospital settings and for children with difficult intravenous access.²⁰

In 1999, Towne and Delorenzo conducted study on use of intramuscular midazolam for status epilepticus as alternative to diazepam and lorazepam during difficult venous access and showed that pharmacodynamic effect of midazolam was within seconds of administration and seizures arrest within 5-10 min with good local tolerability.²¹

In 2005, Shah and Deshmukh²² conducted prospective trial, 115 children of age group 1 month to 12 years were included in this trial who were given intramuscular midazolam for control of seizures and it was found that midazolam given through intramuscular route is safe and easy to administer for control of acute seizures regardless to type of convulsions and age of the child. So it was suggested that intramuscular midazolam can be used as first line treatment for control of acute seizures where maintenance of intravenous route is difficult.

CONCLUSION

Midazolam given through intramuscular route is safe, easy to administer and highly effective for control of seizures in children. When midazolam was compared with diazepam for control of seizures, it was found that midazolam control seizures more rapidly and effectively. Midazolam given through intramuscular route can be used as a first line therapy for management of seizures especially in emergency situations where establishment of intravenous route is difficult.

REFERENCES

- McDonagh JT. Intramuscular midazolam rapidly terminates seizures in children and adults. *Emerg Med* 2009;4:77-81.
- McDonough JH, Van Shura KE, LaMont JC, McMonagle JD, Shih TM. Comparison of the intramuscular, intranasal or sublingual routes of midazolam administration for the control of soman-induced seizures. *Basic Clin Pharmacol Toxicol* 2009;104:27-34.
- Tang RH, Zhou JB. A control study on the treatment of acute seizures with midazolam and diazepam in children. *Zhongguo Dang Dai Er Ke Za Zhi* 2010;12:530-2.
- 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.
- McGillivray D, Dayan P, Pusic M, Appleton R, MacLeod S, Martland T. Commentary on 'Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children', with a response from the review authors. *A Chochrane Rev J* 2009;4:1810-12.
- Sofou K, Kristjánssdóttir R, Papachatzakis NE, Ahmadzadeh A, Uvebrant P. Management of prolonged seizures and status epilepticus in childhood: a systematic review. *J Child Neurol* 2009;24:918-26.
- Guidelines for prolonged seizures and status epilepticus in infants (age 1 month), children and adolescents. In: Lau E, editor. 2009/10 drug handbook and formulary. Toronto: the hospital for sick children, 2009. P. 322-4.
- Portela JL, Piva J. Midazolam versus diazepam for the treatment of status epilepticus in pediatric emergency. *Scientia Medica* 2011;21:176.
- Xie Y, Morgan R, Schiff L, Hannah D, Wheless J. A computerized standard protocol order entry for pediatric inpatient acute seizure emergencies reduces time to treatment. *J Child Neurol* 2013;6:224-7.
- Shresti SV. Intramuscular midazolam versus intravenous diazepam for control of seizures in children. *Pediatrics* 2010;119:82-96.
- Richard DW, Atkinson AJ, Hong SP, Burbach BL, Corwin MJ, Johnson JD. Human safety and pharmacokinetic study of intramuscular midazolam administered by autoinjector. *J Clin Pharmacol* 2010;50:1128-35.
- Koren G. Intranasal midazolam for febrile seizures. A step forward in treating a common and distressing condition. *BMJ* 2000;321:64-5.
- van Stuijvenberg M, deVos S, Tjiang GC, et al. Parents fear regarding fever and febrile seizures. *Acta Paediatr* 1999;88:618-22.
- Abend NS, Huh JW, Helfaer MA, Dlugos DJ. Anticonvulsant medications in the pediatric emergency room and intensive care unit. *Pediatr Emerg Care* 2008;24:705-21.
- Wermeling DP. Intranasal delivery of antiepileptic medications for treatment of seizures. *Neurotherapeutics* 2009;6:352-8.

16. Walker M. Status epilepticus: an evidence based guide. *BMJ* 2005;331:673-7.
17. Bhattacharyya M, Kalra V, Gulati S. Intranasal midazolam vs rectal diazepam in acute childhood seizures. *Pediatr Neurol* 2006;34:355-9.
18. Lahat E, Goldman M, Barr J, Bistrizer T, Berkovitch M. Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomised study. *BMJ* 2000;321:83-6.
19. Mittal P, Manohar R, Rawat AK. Comparative study of intranasal midazolam and intravenous diazepam sedation for procedures and seizures. *Indian J Pediatr* 2006;73:975-8.
20. Chamberlain JM, Altieri MA, Futterman C, Young GM, Ochsenschlager 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.
21. Towne AR, Delorenzo RJ. Use of intramuscular midazolam for status epilepticus. *J Emerg Med* 1999;17:323-8.
22. Shah I, Deshmukh CT. Intramuscular midazolam vs intravenous diazepam for acute seizures. *Indian J Pediatr* 2005;72:667-70.