Comparison of intranasal midazolam with intravenous diazepam for treatment of acute seizures in children: A randomized controlled trial

Iffat Batool[1], Hasan Mujtaba[2], Farah Gul[3], Saba Savul[4], Huma Salim Khan[5], Uzma Ather[6]

ABSTRACT

Objective: To compare efficacy and safety of intranasal Midazolam with intravenous Diazepam for control of acute seizures in children

Study Design: Randomized Control Trial

Place and Duration: Department of Paediatrics, Fauji Foundation Hospital, Rawalpindi for a duration of 6 months from 2nd July to 31st December 2018

Methodology: Children between the ages of 3 months to 12 years presenting during a seizure episode were randomized into two groups. In Group A, patients were given 0.2mg/kg intranasal Midazolam administrated as drops in both nostrils. In Group B, patients were given 0.3mg/kg Diazepam intravenously. Sedation levels and vital signs were noted before, after 5 minutes and 10 minutes of administration of the two drugs. The time duration from arrival of patient in the hospital to start of treatment, and from commencement of treatment to cessation of seizures was recorded and compared between the two groups.

Results: Results showed that the mean time from arrival at hospital to start of treatment was significantly shorter ($p < 0.05$) in the Midazolam group as compared to the Diazepam group (2.07+0.27 vs. 5.06+0.81 minutes). The mean time to control seizures after arrival in hospital was also significantly shorter (<0.05) in IN Midazolam group in comparison to Diazepam group (5.43+2.82 vs. 7.66+2.39 minutes). No serious adverse side effect was observed in Midazolam group.

Conclusion: Intranasal Midazolam is an effective noninvasive method for control of acute seizures in children.

Keywords: Seizures, Sedation, Midazolam, Intranasal, Intravenous, Diazepam, Children

How to Cite This:

Batool I, Mujtaba H, Gul F, Savul S, Khan HS, Ather U. Comparison of intranasal midazolam with intravenous diazepam for treatment of acute seizures in children: A randomized controlled trial. Isra Med J. 2020; 12(1): 7-11.

1. Senior Child Specialist of Peadiatrics, Fauji Foundation Hospital, Rawalpindi
2. Assistant Professor of Oral Pathology, Shifa College of Dentistry, Shifa Tameer-e-Millat University, Islamabad
3. Assistant Professor of Community and Family Medicine, Shifa College of Medicine, Shifa Tameer-e-Millat University, Islamabad, Pakistan
4. Lecturer of Community and Family Medicine, Shifa College of Medicine, Shifa Tameer-e-Millat University, Islamabad
5. Associate Professor of Peadiatrics, Fauji Foundation Hospital, Rawalpindi
6. Associate Professor of Physiology, Pak Red Crescent Medical College, Lahore

Correspondence:
Iffat Batool
Senior Child Specialist of Peadiatrics,
Fauji Foundation Hospital, Rawalpindi
Email: dr.batool1982@gmail.com

Received for Publication: October 26, 2019
1st Revision of Manuscript: February 03, 2020
2nd Revision of Manuscript: May 24, 2020
3rd Revision of Manuscript: June 09, 2020
4th Revision of Manuscript: June 16, 2020
Accepted for Publication: July 14, 2020

INTRODUCTION

Seizures are common during childhood and around 10 % of children experience at least one seizure. [1] Febrile seizures occur most frequently affecting up to 4% of children and constitute a common paediatric emergency outside the hospital[1]. Important causes of seizures in children include birth trauma, congenital abnormalities and infections such as meningitis[2]. Seizures if not adequately treated can lead to significant brain damage and increased risk of morbidity and mortality[3]. The spectrum of seizure disorders range from single prolonged seizure to acute repetitive or cluster seizures with progression to status epilepticus[4]. Status epilepticus is associated with high mortality rates in children and is classified as a medical emergency necessitating rapid diagnosis and treatment[3]. To prevent the progression of seizures (prolonged and cluster) to status epilepticus timely administration of medication is necessary.

Benzodiazepines are the drug of choice for treatment of seizure emergencies, both in and out of hospital settings[5]. The most commonly used Benzodiazepines in children are Diazepam, Midazolam and Lorazepam[6]. Generally, there is no competitive advantage of one Benzodiazepine over another with regards to pharmacology, but there are important differences in their route of administration, rate of absorption and duration of

action which affects their choice in a particular patient or situation[7].

Intravenous (IV) Diazepam is the most widely used benzodiazepine in hospital settings for control of acute seizures[5]. However, it has a short duration of action and the tendency to accumulate with repeated doses which can cause respiratory depression[8]. It also requires IV access which necessitates clinical expertise and can only be delivered under medical supervision[9]. Midazolam, in contrast, is water soluble and can be administered by oral, intravenous (IV), intramuscular (IM) and intranasal (IN) routes. IN Midazolam has rapid bioavailability and offers the advantages of early and rapid absorption due to rich vascular plexuses of nasopharyngeal mucosa as well as ease of administration. These characteristics make it a convenient drug in outpatient settings and emergency situations where expert medical help is not available[10].

Although there are few studies establishing the efficacy, safety and ease of administration of Midazolam as compared to IV Diazepam, no study has been conducted in Pakistan which has a unique population with distinct genetic, social and financial parameters. Like any other third world country, a large proportion of our population has limited access to hospitals and clinical facilities. Hence, an intervention which is effective, safe and easily administrable to control seizures in children in community settings is highly needed. The objective of our study was to evaluate the safety and efficacy of IN Midazolam in comparison with IV Diazepam for control of acute seizures in children.

METHODOLOGY

A randomized controlled trial (RCT) was conducted at the Department of Paediatrics, Fauji Foundation Hospital (FFH), Rawalpindi, from 2nd July to 31st December 2018 for a total period of 6 months. The FFH is a tertiary care hospital where children presenting with seizures are assessed at a dedicated paediatric emergency section. All children aged 3 months to 12 years presenting during a seizure episode within the study duration were included in the study. Neonates, children with concomitant upper respiratory tract infections, patients admitted in paediatric ward with refractory status epilepticus taking multiple drugs and children presenting during seizure episode with an IV line already in place were excluded from the study.

A sample size of 64 patients was calculated using WHO sample size calculator by considering the following parameters: absolute precision as 0.05, power as 80% and seizure prevalence as 4% in paediatric population.[1] The study was approved by the Research Evaluation Unit of College of Physicians and Surgeons and ethical approval was obtained from Ethical Review Board of Fauji Foundation Hospital. Informed consent was obtained from parents of each participant. The ethical committee of the hospital approved the study on the grounds that there would be no significant delay in treating children randomised to receive IN midazolam as it is taken up rapidly and in case of treatment failure an IV line would immediately established.

Cases were defined as patients having seizure activity for more than 30 seconds. Seizures were defined as paroxysmal involuntary disturbance of brain function manifested as abnormal motor activity (jerky movements of limbs, lip smacking, blinking of eyes or upward-rolling of eye balls, increased tone or neck retraction). Seizure control was considered as cessation of seizures and was further categorized as good, delayed and poor control. Good control was defined as seizure control within 5 minutes, delayed control of seizure was between 5-10 minutes and poor control as no seizures control or sedation in 10 minutes.

Study participants were randomized based on computer generated table of random numbers into two groups. In group A, commercially available intranasal preparation of Midazolam was administered in a dose of 0.2mg/kg as drops in both nostrils by means of 3ml syringe with its needle removed. No difficulty was encountered during administration of IN Midazolam. In group B, IV Diazepam was administered after insertion of an appropriate size cannula in a dose of 0.3mg/kg. Establishing venous access was time consuming requiring multiple attempts in some children. The sedation level was assessed using a 5-point sedation scale [11] (Table-I)

Table-I: Five Point Sedation Scale. Adopted from Wilton et al.[11]

Sedation Score I	**Agitated**	Clinging to parent and/or crying
Sedation Score II	**Alert**	Awake but not clinging to parent and/or crying, may whimper but not cry
Sedation Score III	**Calm**	Sitting or lying comfortably with eyes spontaneously open
Sedation Score IV	**Drowsy**	Sitting or lying comfortably with eyes spontaneously closing but responds to minor stimulation
Sedation Score V	**Asleep**	Eyes closed, rousable but does not respond to minor stimulation

Heart rate, respiratory rate and oxygen saturation (SpO2) were noted before, after 5 minutes and after 10 minutes of administration of a drug. The duration from arrival of patient in the hospital to the start of treatment and cessation of seizures was recorded. All patients were monitored until score I and II of sedation. Difference in mean time interval between patients reporting at the hospital and administration of the two drugs was noted. Difference in mean time interval from administration of drugs and control of seizure was also noted. Frequency of side effects for both drugs was also observed. Patients were followed up for adverse events until hospital discharge.

Data Analysis: Data was analyzed using SPSS version 23. Mean and standard deviation was calculated for quantitative variables. Frequency and percentage was calculated for qualitative data. For comparison of the two groups student's t-test was used. p value equal to or less than 0.05 was considered as statistically significant.

RESULTS

A total of 64 patients were included in the study with 32 patients in each group. Out of the 64 subjects, 43 were male (67%) and 21 were females (33%). Minimum age of patients presenting with seizures was 3 months, whereas maximum age was 11 years. Out of these patients, 3 (4.7%) were less than 1 year, 28 (43.7%) patients were in the age bracket of 1-5 years, 23 (36%) patients were between 5-9 years and 10 (15.6%) patients were in the 9-12 years age group.

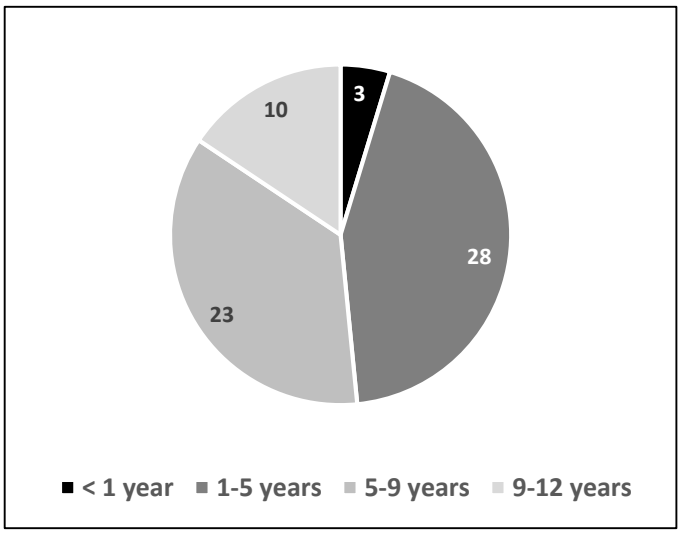

Figure-1: Age distribution of study participants (N=64)

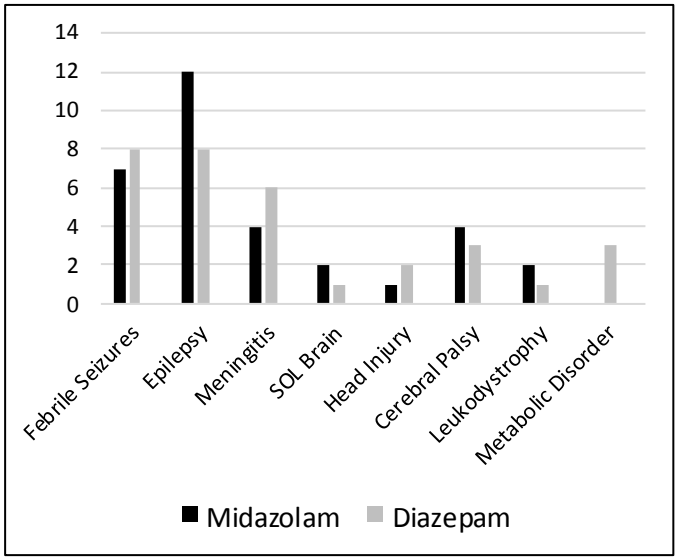

Figure-2: Diagnosis of participants included in the study (N=64)

The heart rate, respiratory rate and oxygen saturation of all patients was recorded before, after 5 minutes and after 10 minutes of drug administration. It was observed that mean heart rate changes were statistically insignificant in both IV Diazepam and IN Midazolam groups (p value 0.39 and 0.67 respectively). Mean respiratory rate decreased at 5 mins (19/min) and 10 mins (19/min) after administration of IV Diazepam from pre-drug mean respiratory rate (22/min). There was an increase in mean respiratory rate at 5 min (23/min) and a slight decrease at 10 minutes (22/min) returning to the original level (19/min) after administration of intranasal Midazolam.

Mean oxygen saturation (99% on air) did not vary significantly after 5 minutes and 10 minutes of drug administration from the pre-drug values in IN Midazolam group. No patient was found to be hypoxic requiring supplemental oxygen. In IV Diazepam group, the mean oxygen saturation decreased at 5 minutes and 10 minutes of drug administration (mean O^2 sat. pre-drug 99% on air 5 minutes 97% and 10 minutes 96% on air). Three patients became severely hypoxic requiring supplemental oxygen through face mask.

Regarding sedation score, in IN Midazolam group 9.4% of the patients were alert (sedation score II), 78.1% patients were calm (sedation score III), whereas 12.5% patients were drowsy (sedation score IV) after 5 mins of drug administration. In IV Diazepam group, 6.3% patients were alert (sedation score II), 15.6% patients were calm (sedation score III), 56.3% patients were drowsy (sedation score IV) while 21.9% patients were asleep (sedation score V).

For all patients, time interval to start of treatment and control of seizures was recorded (Table II). In IN Midazolam group, the mean time interval to start of treatment was 2.07+0.27 minutes (minimum 1.5 minutes, maximum 2.5 minutes) whereas the mean time for cessation of seizures after drug administration was 3.35+2.82 minutes (minimum 1.8 minutes, maximum 12.8 minutes). The total mean time from start of treatment to control of seizures was 5.43+2.82 minutes (minimum 3.5 minutes, maximum 14.7 minutes). In IV Diazepam group, the mean time interval to start treatment was 5.06+0.81 minutes (minimum 3.6 minutes, maximum 6.8 minutes), mean time interval for cessation of seizures after drug administration was 2.60+2.11 minutes (minimum 1.0 minute, maximum 10.6 minutes). The total mean time interval to start of treatment and control of seizures was 7.66+2.39 minutes (minimum 5.2 minutes, maximum 15.8 minutes).

Table-II: Comparison of time interval between IN-Midazolam and IV-Diazepam (N=64)

Time interval (minutes)	IN-Midazolam (n=32)	IV-Diazepam (n=32)	p-Value
Time to administration of drug after arrival in hospital	2.07+0.27	5.06+0.81	0.001 (<0.05)
Time to cessation of seizures after giving drug	3.35+2.82	2.60+2.11	0.43 (>0.05)
Time to cessation of seizures after arrival in hospital	5.43+2.82	7.66+2.39	0.013 (<0.05)

Student's t test was applied on the difference of time intervals in both groups. The mean time interval to the start of treatment revealed a p value of <0.001, indicating that treatment with IN Midazolam was started much earlier than IV Diazepam. Mean

time interval for cessation of seizures after drug administration demonstrated a p value of 0.43 which was insignificant highlighting that IN Midazolam was equally effective as IV diazepam for controlling seizures in terms of time taken for delivering effective sedation. For mean time interval to start of treatment and control of seizures, a p value of 0.013 (statistically significant) was obtained underscoring that IN Midazolam was more effective than IV Diazepam in control of seizures.

At 10 minutes in IN Midazolam, 87.5% patients showed good response, 3.1% exhibited a delayed response while 9.4% patients had poor response. In IV Diazepam group, 87.5% patients showed good response, 6.3% of the patients showed delayed and 7.2% poor response. (P value= 1 (>0.05) which is statistically insignificant indicating that IN Midazolam is equally effective as IV Diazepam in terms of response produced.

No serious adverse side effect was observed in any patient receiving IN Midazolam in our study. Five patients (7.8%) experienced minor side effects including nasal irritation, tearing and sore throat.

DISCUSSION

Our study results revealed that though the efficacy of control of seizures of IN Midazolam and IV Diazepam was the same (87.5% for both drugs within 10 minutes of administration), the time from arrival to start of treatment was significantly shorter in IN Midazolam group (2.07±0.27 minutes vs. 5.06± 0.81 minutes) which resulted in earlier control of seizures (5.43 ± 2.82 minutes vs. 7.66 ± 2.39 minutes) as compared to IV Diazepam group.

Intranasal Midazolam (0.2 mg/Kg) vs. intravenous Diazepam (0.3 mg/kg) have been compared by other studies across the globe. Results of a randomized controlled trial for the control of febrile seizure showed greater efficacy of intravenous Diazepam over IN Midazolam, but the cessation time of seizure was faster in intranasal Midazolam group (6.1 ± 3.6 min vs. 8.0 ± 4.1 min, p<0.01) [12]. A study conducted in Iran reported that the time between initiation of treatment and termination of seizures was more with IN Midazolam as compared to IV Diazepam but Midazolam was quicker to administer[13]. However, in this study the time taken to establish IV line was not taken into account which is an important factor as IV access is more difficult and time consuming especially in young children.

In a randomized control trial of 76 patients conducted in India, the mean time for the control of seizures for Midazolam was (5.25 ± 0.86 min) while that for Diazepam was (6.51 ± 1.06 min, P<0.001) [14]. In a another trial in India, 50 patients aged 1 month to 12 years presenting with acute seizures were administered either intranasal Midazolam (0.2 mg/kg) or intravenous Diazepam (0.3 mg/kg). The mean time for seizure cessation was shorter significantly in Midazolam group (6.67 ± 3.12 minutes) as compared to the Diazepam group (17.18 ±5.09 minutes) without any side effects[15].

In the RCT involving 76 paediatric patients in India, 77% children became drowsy after giving Midazolam which might be considered an undesirable effect. [14] In our study, 78% patients became calm (sedation score III) within 5 minutes of starting treatment, while 12.5% patients became drowsy (sedation score IV). Similar to our results, majority of patients became calm rather than drowsy after starting treatment with IN Midazolam in another study[11].

Analogous to the findings of another study, we found that the postictal phase after the administration of IN Midazolam was significantly shorter as compared to IV Diazepam because of shorter half-life of Midazolam[16]. This factor is quite reassuring for parents as their child regains full consciousness earlier after administration of IN Midazolam.

In our study, the mean heart rate at 5 minutes and 10 minutes did not vary significantly between the two study groups. However, the mean respiratory rate decreased in the Diazepam group, whereas it increased in the Midazolam group from pre-drug values. This indicates that intranasal Midazolam has no significant respiratory depressant effect in children with acute seizures. This finding is in concordance with results of other studies where children became tachypneic after administration of intranasal Midazolam[17,18]. This may be due to nasal mucosal irritation by local application of drug.

In this study, oxygen saturation decreased after IV Diazepam administration and three patients became severely hypoxic requiring supplemental oxygen while there was no significant change in oxygen saturation after giving IN Midazolam to patients. Similar to our results, other studies did reported any significant decrease in oxygen saturation after administration of intranasal Midazolam and no serious side effects[14,19].

Research literature revealed that a time lapse of ten minutes was usually considered before starting treatment to eliminate the possibility of spontaneous cessation of seizures. Considering socio-economic constraints and the time taken to reach hospital in our settings, we included patients who had been having seizures for more than 30 seconds in our study. Another limitation of our study was that neonates were not included in our study. We used a commercially available intravenous preparation of Midazolam which has a strength of 5mg/5ml which is not suitable for neonates because of small nasal mucosal surface area requiring more concentrated solutions. For older children, this preparation of Midazolam results in a larger volume of drug to be administered in a dose of 0.2mg/kg which is difficult to administer and causes local side effects like mucosal irritation[20]. The preparation of more concentrated solution with a water-soluble base for nasal administration can eliminate this problem.

CONCLUSION

Intranasal Midazolam is an effective noninvasive method for control of acute seizures in children.

AUTHOR'S CONTRIBUTION

Batool I: Conceived idea, Designed research methodology, Data collection, Manuscript writing

Mujtaba H: Data analysis, Manuscript drafting

Gul F: Literature search, Statistical analysis

Savul S: Data interpretation, Manuscript writing
Khan HS: Critical review of Manuscript, Bibliography
Ather U: Data collection, Data interpretation, Manuscript writing

Disclaimer: None.
Conflict of Interest: None.
Source of Funding: None.

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