



## Comparative Efficacy of Intranasal Midazolam with Per Rectal Diazepam to Control Acute Seizure in 6 Months to 12 Years' Children: A Randomized Controlled Trial



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### Abstract

**Background:** Convulsions are the most frequent neurological disorders affecting children. Acute seizure is a medical emergency, requires prompt and urgent control of ongoing seizure activity. Among the procedure to control seizure, treatment options like intranasal midazolam and per rectal diazepam are available for immediate management. **Objective:** The study was done to compare the safety and efficacy of intranasal midazolam and per rectal diazepam to control acute seizure. **Method:** This randomized controlled trial was conducted in paediatric department of Dhaka Medical College Hospital from 1st June 2008 to 15th April 2009. Children aged from 6 months to 12 years who came with acute seizure of any aetiology were included. **Results:** Among 110 patients mean time to control acute seizure in diazepam group was 4.1 minute and in midazolam group it was 3.2 minute and the difference was statistically significant. No significant side effects were noted in either of the group except for a transient fall in oxygen saturation. **Conclusion:** In this study midazolam effectively controlled acute seizure compared to diazepam. Time taken to control seizure was significantly less in midazolam group. No serious complications were noted after administration of drugs. Intranasal midazolam could be a better alternative as it is effective in controlling seizure and has no significant side effects compared to the standard. [Journal of National Institute of Neurosciences Bangladesh, July 2023;9(2):103-107]

**Keywords:** Seizure; midazolam; diazepam; intranasal; convulsion

### Introduction

Convulsions are the most frequent neurological disorders affecting children<sup>1</sup>. Seizure or convulsion is a paroxysmal time limited change in motor activity and behaviour that results from abnormal electrical activities in the brain<sup>2</sup>. Acute seizure is a medical emergency, requires prompt and urgent control of ongoing seizure activity<sup>3</sup>. Traditionally for long time diazepam by intravenous or per rectal route was used to control such acute attacks. Administration of diazepam by IV route needs technical manpower, expertise and the use of butterfly needle, syringe and aseptic precautions which ultimately requires long time<sup>4</sup>. Per rectal diazepam is also effective but is not well accepted by parents or adolescent children. On the other hand, midazolam is a water soluble benzodiazepine derivative used as a pre anaesthetic agent, also a safe and

potent anticonvulsant agent. It has a shorter half-life than diazepam<sup>5</sup>. IV midazolam is equivalent to IV diazepam to control acute seizure but it can also be used in other routes like buccal or intranasal as well. We used injection midazolam via the nasal route as the nasal drop and spray forms are not available in our country and there are some studies in support of this method<sup>5</sup>.

Midazolam when used intranasally as nasal spray or instilled into nostril as drop wise by an applicator drop by drop, is also very simple, safe, effective, less time consuming, needs no technical manpower, socially acceptable and without very much untoward side effects. It also has the advantage of being painless and allowing rapid absorption into systemic circulation bypassing the portal circulation<sup>6</sup>. After nasal use the drug is available in the cerebral cortex in 2 to 5 minute<sup>7-8</sup>. The study was

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done with the objective to compare the effectiveness of intranasal midazolam with per rectal diazepam to control acute seizure.

### Methodology

**Study Settings and Population:** This was a prospective randomised controlled clinical trial done in paediatric department of Dhaka Medical College Hospital from 1<sup>st</sup> June 2008 to 15<sup>th</sup> April 2009. Total 110 children aged from 6 months to 12 years who came with acute seizure of any aetiology were included. Children who received anticonvulsant prior to enrolment were excluded.

**Randomization and Blinding:** Equal numbers of sealed, unmarked, identical envelope containing the name of the drug to be administered were randomised by shuffling. A box containing these envelopes was kept in the paediatric ward.

**Allocation and Intervention:** When a patient was enrolled in the study, randomisation to either group was performed by picking an envelope and the indicated medication was administered. Medication was given irrespective of seizure type and aetiology. Time taken to control seizure in each group was recorded by a stopwatch. Excessive secretions were removed and nasal oxygen given to all patients. Group A received injection diazepam 0.5 mg/kg per rectally and group B received injection midazolam 0.2 mg/kg via nasal route instilled by a dropper, as the nasal formulation and spray forms are not available in our country.

**Follow Up and Outcome Measures:** After 5, 10, 30 and 60 minutes' heart rate, respiratory rate, blood pressure, GCS scoring were monitored. Oxygen saturation was monitored after 5 and 30 minutes. If seizure failed to stop in 10 minutes after the first drug it was considered as treatment failure and was excluded. These treatment failure patients were given Injection phenobarbitone. Treatment was considered as successful if seizure stopped within 10 minutes.

**Statistical Analysis:** Statistical analysis was performed by Windows based software named as Statistical Package for Social Science (SPSS), versions 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Continuous data were expressed as mean, standard deviation, minimum and maximum. Categorical data were summarized in terms of frequency counts and percentages. Chi-square test was used for comparison of categorical variables and Student t test was applied for continuous variables. Every efforts were made to obtain missing data. A two-sided P value of less than 0.05 was considered to

indicate statistical significance. Differences between case and control were tested.

**Ethical Clearance:** All procedures of the present study were carried out in accordance with the principles for human investigations (i.e., Helsinki Declaration) and also with the ethical guidelines of the Institutional research ethics. Formal ethics approval was granted by the Ethics Review Committee of Local Institute. Participants in the study were informed about the procedure and purpose of the study and confidentiality of information provided. All participants consented willingly to be a part of the study during the data collection periods. All data were collected anonymously and analysed using the coding system.

### Results

A total number of 110 patients were studied who had acute seizure. Group A which received per rectal diazepam had 55 children and group B which received intranasal midazolam had 55 children. The age range varied from 6 months to 12 years. The mean age was 48.4 month in group A and 44.8 month in group B. Other baseline characteristics like sex, association of fever, history previous seizure and intake of regular anticonvulsant drug were analysed (Table 1).

Table 1: Comparative Baseline Characteristics of the Two Groups of Children

Baseline Characteristics	Group A (n= 55)	Group B (n= 55)	P value
Gender			
• Male	49.0%	53.0%	0.703
• Female	51.0%	47.0%	0.619
Fever with seizure	62.0%	55.0%	0.171
H/O previous seizure	35.0%	38.0%	0.692
H/O Regular Intake of anticonvulsants	16.0%	11.0%	0.405

After comparing the baseline characteristics between the two groups, which did not vary significantly an analysis of the type of seizure was undertaken (Table 2).

Table 2: Type of Seizure at Presentation in both Groups

Type of Seizure	Group A (n=55)	Group B (n=55)	P value
GTCS	87.0%	89.0%	0.412
Tonic	9.0%	8.0%	0.213
Partial	4.0%	3.0%	0.448
<b>Total</b>	<b>100.0%</b>	<b>100.0%</b>	

The most common type of convulsive episode in both of the group was generalized tonic-clonic seizure. In group A 87% children had generalized tonic-clonic seizure and in group B it was 89%. The mean time to control seizure was 4.1 minutes in group A which received rectal diazepam and in group B which received intranasal midazolam it was 3.2 minutes and the p value (0.012) was highly significant (Table 3).

Table 3: Time to control seizure in minute

Group	Mean±SD	P value
Group A	4.1±1.9	0.012
Group B	3.2±2.0	

Changes in heart rate, respiratory rate, blood pressure and GCS score were monitored at 5, 10, 30 and 60 minute after administration of drug in both groups. No statistically significant changes were observed in any of the parameters (Table 4).

Table 4: Outcome of Different Variables among the Study Population

Variables	Group A (n= 55)	Group B (n= 55)	P value
<b>GCS score</b>			
10 minute	5.3±3.8	5.9±4.5	0.468
30 minute	7.2±5.4	8.0±5.4	0.442
60 minute	7.9±5.5	8.4±5.5	0.614
<b>Tachypnea</b>			
10 minute	3 (5%)	6 (11%)	0.297
30 minute	2(4%)	2(4%)	0.100
<b>Bradycardia</b>			
10 minute	2 (4%)	3(5%)	0.251
60 minute	5(9%)	3(5%)	0.085
<b>Hypotension</b>			
10 minute	2(4%)	1(3%)	0.468
60 minute	4(5%)	2(4%)	0.442

Mean SpO<sub>2</sub> after 5 minutes and after 30 minutes in both the groups were equally reduced (p value <0.001) (Table 5).

Table 5: Outcome measures – Oxygen saturation (SpO<sub>2</sub>)

SpO <sub>2</sub>	Group A (n=55)	Group B (n=55)	P value
5 minute	94.1%	90.1%	<0.001
30 minute	95.0%	91.7%	<0.001

## Discussion

Convulsions are the most frequent neurological disorder affecting children. Acute seizure is a medical

emergency. Urgent treatment is required to control seizure as neurologic complications are directly related to the duration of seizure. Traditionally per rectal diazepam been used for the treatment of acute seizure for over 20 years<sup>9</sup>. It is effective but concerns have been raised about the acceptance by parents and adolescent children and physical difficulty to administer rectal medication to a convulsing patient<sup>10</sup>. Interest has recently been raised in using intranasal midazolam, which is also equally effective and has rapid onset of action like that of rectal diazepam but is easy to administer and more socially acceptable<sup>10</sup>. Application of drugs to nasal mucosa allows rapid absorption of drug into systemic circulation. Midazolam, a water soluble benzodiazepine, was found to end seizures within 1 to 2 minutes of intranasal administration<sup>11</sup>.

In this study, the efficacy and side effects of rectal diazepam with intranasal midazolam were compared in the treatment of acute seizure in children to develop a practical and safe treatment protocol. The outcome measures were time to control acute seizure and side effects or associated changes in baseline characteristics. The baseline characteristics of patients like age, sex, association of fever with seizure, history of previous seizure and anticonvulsant drug were compared in both the study group.

The mean age of children in group A and group B was 44.8 months and 48.7 months respectively. In a similar study, Bhattacharyya M showed mean age in diazepam group was 74.5 months and midazolam group it was 60.4 months<sup>12</sup>. The difference in age of presentation was due to the different hospital setup. In the present study 51% were girls and 49% were boys. Similar sex distribution was also noted by Bhattacharyya M<sup>12</sup>.

A temperature of 100.4°F was described as fever<sup>2</sup>. In group A 37 children had seizure which was associated with fever which included mainly febrile seizure and CNS infection and in group B the number was 30. Between the two groups the percentage of febrile seizure was 31% in group A and 29% in group B. In a study Mahmoudian reported febrile seizure as the most common cause of acute seizure which was 22.7% in diazepam group and 21.7% in midazolam group<sup>4</sup>. In the present study 19 patients (35%) in group A and 21 patients (38%) in group B had history of previous seizure and most of them were suffering from epilepsy. The most common type of convulsive episode in both of the group was generalized tonic-clonic seizure. In group A 87% children had generalized tonic-clonic seizure and in group B it was 89%. In a similar study

Fisgin T found generalized tonic-clonic seizure as the most common type of acute seizure<sup>5</sup>.

In group A which received rectal diazepam the mean time to control seizure was 4.1 minutes and in group B which received intranasal midazolam the mean time to control seizure was 3.2 minutes ( $p=0.012$ ) explaining earlier control in intranasal midazolam compared to rectal diazepam. Kutlu and Fisgin found that intranasal midazolam at a dose of 0.2- 0.3 mg/kg effectively stopped seizures in over 80% children within 5-8 minutes<sup>13,14</sup>. In a later study Fisgin reported that the response rate to intranasal midazolam for seizures lasting more than 5 minutes was 87% compared with 60% for rectal diazepam<sup>5</sup>. Bhattacharyya M in a study showed that the mean time of seizure was significantly less in the midazolam group than the diazepam group<sup>12</sup>. Lahat et al compared the safety and efficacy of intranasal midazolam with intravenous diazepam in children presenting with prolonged febrile seizure. Both the drugs were equally effective but the authors noted that the mean time to control seizure was shorter in the midazolam group<sup>15</sup>.

In the present study mean GCS score after 10 minutes of administration of drug was 5.3 and 5.9 in group A and group B respectively and after 30 minutes it was 7.2 in group A and 8 in group B. There were no significant differences in level of consciousness among this two groups. Bhattacharyya M in a similar study found excessive drowsiness in 10% children in diazepam group but no such side effect in the midazolam group<sup>12</sup>. Tachypnea as defined by WHO guideline in different age groups was found in 5.0% and 4% children in group A after 10 and 60 minutes respectively. In group B after 10 minutes it was 11% and after 60 minutes it was 4% which was not significant. The age of the patients in group A was 13 to 18 months and in group B age varies between 12-25 months. Fisgin et al<sup>14</sup> also detected tachypnea in their study but it was not statistically significant.

Blood pressure values less than the 3<sup>rd</sup> percentile was defined as hypotension<sup>2</sup>. Hypotension was noted in some children but statistically it was not significant. Pulse rate in different age groups were regarded as tachycardia if it was more than 95<sup>th</sup> percentile and bradycardia if below 3<sup>rd</sup> percentile<sup>2</sup>. There was no evidence of tachycardia, significant bradycardia or apnea in any of the groups. Bhattacharyya studied 46 children who received treatment with rectal diazepam and intranasal midazolam, they showed the mean heart rate and blood pressure did not vary significantly

between the two groups<sup>12</sup>. Jeannet et al<sup>16</sup> reported the use of intranasal midazolam in 26 children who had acute seizures either in hospital or at home. All the seizures treated at home responded within 10 minute and no serious adverse side-effects occurred.

Normal oxygen saturation at sea level in a child is 95% - 100%<sup>17</sup>. In this study mean SpO<sub>2</sub> after 5 minutes was 94.1% and after 30 minutes 95% in group A but in group B the mean SpO<sub>2</sub> after 5 minutes was 90.1% and after 30 minutes it was 91.7%. In both groups the values were below the normal level and p value was significant. But subsequently on follow up the SpO<sub>2</sub> was returned to the baseline level. Bhattacharyya reported mean respiratory rate and oxygen saturation differed significantly between the two drug groups at 5, 10 and 30 minutes after administration of medication<sup>12</sup>. In a similar study Regan found a severe decrease in oxygen saturation that was corrected spontaneously in children who received intranasal midazolam<sup>6</sup>. A comparative study of IV or IM midazolam with IV or rectal diazepam found that the respiratory depression was significantly less frequent with midazolam<sup>12</sup>. There was no evidence of pain and irritation after administration of intranasal midazolam in this study.

### Conclusion:

Convulsion can cause permanent brain damage, so they must be controlled as soon as possible. In this study midazolam effectively controlled acute seizure compared to diazepam. Time taken to control seizure was significantly less in midazolam group. No serious complications were noted after administration of drugs only the transient fall in oxygen saturation was observed. Intranasal midazolam could be a better alternative as it is effective in controlling seizure and has no significant side effects.

### Abbreviations:

SpO<sub>2</sub>: peripheral oxygen saturation

IV: intravenous

GCS: Glasgow Coma Scale

WHO: World Health Organization

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### Conflict of interest

Other than technical and logistic support from the scientific partner the investigators did not have any conflict of interest in any means.

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**Contribution to authors**

Ashraf S, Saha NC conceived and designed the study, analyzed the data, interpreted the results, and wrote up the draft manuscript. Taher T, Haque N, Haroon K involved in the manuscript review and editing. All authors read and approved the final manuscript.

**Data Availability**

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

**Ethics Approval and Consent to Participate**

Ethical approval for the study was obtained from the Institutional Review Board. As this was a prospective study the written informed consent was obtained from all study participants. All methods were performed in accordance with the relevant guidelines and regulations.

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