**Original Article**

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# Comparison of Efficacy of Intranasal Midazolam and Conventional Treatment with Intravenous Diazepam for Control of Seizures in Children; A Randomized Controlled Trial

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*[1,4]Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, manuscript writing.*
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**ABSTRACT**

**Objective:** To compare the efficacy of intranasal midazolam and conventional treatment with intravenous diazepam for the control of seizures in children.

**Methodology:** It was a randomized controlled trial registration no NCT04885075 conducted in the Children Hospital, PIMS, Islamabad from January 2022 to June 2022 presenting to the ER department with seizures. The patients were randomly divided into two groups. Group A patients were given a single dose of intranasal midazolam (0.2 mg/kg). Group B patients were treated with a single dose of intravenous Diazepam (0.2mg/kg). We recorded the following parameters: 1) the period elapsed between arrival at emergency and drug administration. 2) The time interval between drug administration and cessation of seizures. 3) The period between admission to the hospital and the end of seizures.

**Results:** Among 60 enrolled patients, there were thirty-one males and twenty-nine females. The mean age of the patient was 5.27 ± 3.31 years. The mean intervals between arrival at the hospital and treatment given were 3.00±0.91 and 7.03±2.91 mins (p-value 0.000) in groups A and B, respectively. The mean intervals between the treatment given and cessation of seizure were 2.70 ± 1.05 and 2.60 ± 1.13 mins (p-value 0.725) in groups A and B, respectively. The mean intervals between arrival at the hospital and the cessation of seizure were 5.70 ± 1.3 and 9.63 ± 2.58 mins (p-value 0.000) in groups A and B, respectively.

**Conclusion:** The intranasal Midazolam was shown to be as effective in suppressing seizure as the intravenous Diazepam. This is the best option if you don't have access to an intravenous line.

**Keywords:** Acute Seizures, Diazepam, Intranasal, Intravenous, Midazolam, Status epilepticus.

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## Introduction

Seizures are prevalent in children, affecting about 10% of children. If seizures are not treated promptly, they can lead to permanent neuronal injury and an increased risk of morbidity and mortality.[1] Seizures cause mental and emotional stress for parents and healthcare professionals. [2] Although most epileptic seizures are self-limiting and last for a few seconds, and less than 2–3 mins. Seizures can range from a single episode to acute recurrent or cluster seizures that develop to status epilepticus. SE is a typical neurological emergency described as seizures lasting more than 5 minutes or several seizures with insufficient inter-seizure recovery.[3] Therefore, reliable prehospital methods to control seizures should be developed to attain rapid seizure termination, reducing associated adverse outcomes. [4]

Acute seizures are most commonly treated with benzodiazepines, both in and out of the hospital. Benzodiazepines such as Diazepam, Midazolam, and Lorazepam are frequently prescribed in acute management.[4] In terms of pharmacology, there is no clear advantage to one benzodiazepine over another. However, significant variances in their delivery routes, absorption rates, and duration of action determine their suitability for a given patient or situation. [5]

Although the intravenous (IV) route is recommended for medicine delivery in patients with an established IV line, this route is not always possible, particularly in an emergency, where an actively convulsing child is to reach the hospital and maintain an intravenous line. Alternative routes of administration must be considered to circumvent this issue. The intramuscular (IM) approach has a slower onset of action and needs advanced training; it is a feasible and effective alternative to the intravenous (IV) route. [6] Rectal (PR) administration of medicines allows direct bloodstream absorption, resulting in quick action without first-pass metabolism. Despite this, rectal administration is often unpleasant for patients, and the time required to position and disrobe the patient may cause the administration to be delayed. [7] The risk of finger biting and aspiration makes the buccal route difficult for patients with convulsive seizures. Given the challenges of these routes, intranasal administration has gained popularity, especially in outpatient settings. [8]

Diazepam is unquestionably the most often used benzodiazepine in the acute treatment of seizures. However, its duration of action is brief. It is often administered intravenously and tends to accumulate with repeated dosages, with the possibility of a rare consequence of brain stem depression resulting in bradypnea or even respiratory arrest.[9] By contrast, Midazolam is a water-soluble, safe, and effective option that can be taken through oral, intravenous, intramuscular, and intranasal routes. Its intranasal formulation may be administered outside hospitals if parents and caregivers are appropriately taught about its administration. [2, 10] Its absorption through the cribriform plate can rapidly raise medication concentrations in the cerebral spinal fluid (CSF). These properties make it a helpful medication in outpatient settings and when specialist medical assistance is unavailable, and patients are cognitively impaired during medical emergencies. [11, 12] It is given in a dose of 0.2mg\kg, and within a few minutes, its level in serum is comparable to the injectables levels.[9]

Despite its numerous benefits and favorable safety profile, intranasal midazolam is not widely used in our setting. Because we are a third-world country, many of our citizens have restricted access to health care services. Consequently, there is a need for a safe, effective, and easy-to-use treatment for children with seizures. This study aimed to demonstrate that intranasal Midazolam is equally effective as intravenous diazepam and is better in many ways. We can recommend it as a first-line agent because it will benefit health care professionals and society.

# Methodology

It is a randomized controlled trial study conducted in the children Hospital PIMS from January 2022 to June 2022 after taking ethical approval from the institutional review board. Sample size has been calculated using WHO calculator and using confidence level of 95%, alpha error of 5%, and study power of 80%. The anticipated mean seizure cessation time was 5.43 minutes in midazolam group while the anticipated mean seizure cessation time was 7.66 minutes in diazepam group, along with assumed standard deviation of 3.0 minutes. The sample size came out 29 cases in each group which was rounded off to 30 cases in each. We enrolled a total of 60 cases in both study groups.[11] We enrolled 60 children of either gender through non-probability sampling technique, presented to the emergency department with acute seizures. We excluded patients with refractory or uncontrolled epilepsy, who needed respiratory support, already had intravenous access, and had any signs and symptoms of upper respiratory infection or concurrent illnesses such as heart, kidney, or liver failure. . Written consent was obtained from parents before enrollment.

Demographic details (name, age, gender) were noted. Then patients were randomly divided into two groups by using the lottery method. Group A patients were given a single dose of intranasal Midazolam (0.2 mg/kg) with a syringe. After maintaining intravenous access, Group B patients were treated with a single dose of intravenous Diazepam (0.2mg/kg). Seizures were defined as an unintentional disruption of brain function that manifests as generalized or local abnormal motor activity lasting more than 30 seconds. All the necessary routine care was provided according to hospital protocol. In situations of failure, if the initial drug was intranasal midazolam, intravenous diazepam was added, and phenobarbital was delivered if the initial medication was intravenous Diazepam. The treatment was labelled as successful if

seizures didn't reoccur within 20 minutes of drug administration. If the seizures did occur within 20 minutes, it was labeled as treatment failure.

We noted the following parameters: The period elapsed between admission to the hospital and drug administration. The time interval between drug administration and cessation of seizures. The period between admission to the hospital and the end of seizures. Data was collected through a structured proforma. Data were analyzed using SPSS version 20.0. Quantitative variables such as age and time were presented as means and standard deviations. Qualitative variables such as age groups and sex were measured as frequencies. The independent-sample t-test compared the outcomes of two groups. A p-value ≤0.05 was considered statistically significant.

# Results

Among 60 enrolled patients, thirty-one males and twenty-nine females with a 1:1 ratio. The mean age of the patient was 5.27 ± 3.31 years. Among the participant in group A, the mean age was 4.77 ± 3.05 years, and in group B 5.77 ± 3.54 years. There were 28 children in age groups 1-4 years, 23 in 5-9 years, and 9 in 10-12 years. Twenty-four children had generalized tonic-clonic fits, 19 had simple partial seizures, and 17 had complicated partial seizures. (Table II)

Table III shows the treatment response in both groups. Twenty-six patients in the midazolam group were successfully treated, and twenty-seven in the diazepam group. However, this difference was statistically not significant (p-value 0.688).

The mean intervals between arrival at the hospital and treatment given were 3.00±0.91 and 7.03±2.91 mins (p-value 0.000) in groups A and B, respectively. The mean intervals between the treatment given and cessation of seizure were 2.70 ± 1.05 and 2.60 ± 1.13 mins (p-value 0.725) in groups A and B, respectively. The mean intervals between arrival at the hospital and the cessation of seizure were 5.70 ± 1.3 and 9.63 ± 2.58 mins (p-value 0.000) in groups A and B, respectively. No severe side effects were observed in both groups. (Table III)

**Table I: Gender distribution among two study groups (n=60)**

| Gender | In Midazolam n (%) | IV Diazepam n (%) | Total n (%) |
|---|---|---|---|
| Male | 16(27) | 15(25) | 31(52) |
| Female | 14(23) | 15(25) | 29(48) |

**Table II: Age groups distribution among study groups (n=60)**

| Age group (years) | IN Midazolam n(%) | IV Diazepam n (%) | Total n (%) |
|---|---|---|---|
| 1-4 years | 16(27) | 12(20) | 28(47) |
| 5-9 years | 11(18) | 12(20) | 23(38) |
| 10-12 years | 3(5) | 6(10) | 9(15) |

**Table III: Outcome time intervals among study groups (n=60)**

| Time intervals | IN Midazolam Mean ± SD (min) | IV Diazepam Mean ± SD (min) | p-value |
|---|---|---|---|
| Arrival at hospital to drug administration | 3.00 ± 0.91 | 7.03 ± 2.51 | 0.000 |
| Drug administration to cessation of seizure | 2.70 ± 1.05 | 2.60 ± 1.13 | 0.725 |
| Arrival at the hospital to the cessation of seizure | 5.70 ± 1.3 | 9.63 ±2.58 | 0.000 |

# Discussion

Both parents and caregivers are terrified when their child has a seizure since it poses a serious threat to their child's life, especially if it's the first occurrence. The longer a seizure lasts, the greater the risk of death and injury. Thus, the immediate need of a convulsing child is to abort an acute attack. Intravenous and intramuscular modes of delivery necessitate a hospital setting and specialized training. So, there has been a lot of interest in intranasal drug administration in the last several years.[12,13] It is safe and effective in children, and it can be used to control epileptic activity with the intranasal administration of Midazolam.[6]

To the best of our knowledge, only one randomized controlled trial in Pakistan compared the efficacy of intranasal Midazolam and intravenous Diazepam in control of seizures. This study reported that the treatment was successful in 87.5% of patients with both drugs, the time interval between arrival at the hospital and administration of the drug was shorter with Midazolam (2.07±0.27 vs 5.06± 0.81 mins) which resulted in earlier cessation of fits (5.43 ± 2.82 vs 7.66 ± 2.39 mins) as compared to Diazepam. [(11)] In our study, the mean interval between arrival at the hospital and treatment given was less in IN midazolam group compared to IV diazepam (3.00±0.91 and 7.03±2.91 mins) (p-value 0.000). The mean intervals between the treatment given and cessation of seizure were almost the same between both groups (2.70 ± 1.05 and 2.60 ± 1.13 mins) (p-value

0.725). The difference in results may be due to patients' selection criteria, dosage of drug and outcome parameter definition as Batool et al.[11] also included neonates, they administered 0.3 mg/kg dose of Diazepam.

Similarly, Lahat et al. reported that 23 of 26 patients with febrile fits responded to IN Midazolam, and 24 of 26 patients responded to IV diazepam in the study. They determined that both medications were similarly effective. Still, the midazolam group's mean time to control seizures was much shorter (6.1±3.6 min vs 8.0 ± 4.1 min, p 0.01), owing to the absence of time required to establish an IV line before delivery. [14] In another trial in India, 50 patients aged one 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 significantly shorter in the midazolam group (6.67 ± 3.12 minutes) than in the diazepam group (17.18 ±5.09 minutes) without any side effects. There is large difference in total mean time between arrival at hospital and cessation of seizures compared to our study, this is mainly due to the mean time in taken in establishing the intravenous access i.e., 14.13±3.39 mins. Overall, the interval between drug administration and cessation of seizures with intranasal midazolam and intravenous diazepam was similar to our study (3.01 ± 2.79 vs 2.67 ± 2.31 respectively) [9] In contrast, a study conducted in Iran discovered that, while Midazolam was easier to administer, the interval between treatment beginning and seizure cessation was longer with IN Midazolam than with IV Diazepam. [15]

Javadzadeh et al. reported that the time needed to control seizure using intranasal midazolam (3.16±1.24) was statistically shorter than intravenous diazepam (6.42±2.59) if the time needed to establish IV line in patients treated by intravenous diazepam is taken into account (P<0.001).[2] Similarly, another randomized control trial from India found that the time taken for the control of seizures for midazolam was (5.25 ± 0.86 min) whereas that for diazepam was (6.51 ± 1.06 min, P<0.001) conversely, in our study, this difference was statistically not significant.[16] Similarly to our investigation, another study found no significant difference in the mean time from drug administration to seizure cessation in both groups, 1.0 ± 0.31 min and 1.0 ± 0.32 min (p> 0.05). There was no statistically significant difference in oxygen saturation or vital indicators between the groups. Intranasal midazolam provided more rapid seizure control than intravenous Midazolam.[13] Kutlu et al. reported intranasal midazolam to be 100% effective in controlling prolonged seizure attacks in children. Only in one patient from their study there was a need for re-administration of drug to control the seizure episode and they did not find any serious side effects or respiratory depression except for one case, who had seizure secondary to serious CNS infection. [17]

Many studies reported that both approaches are safe and effective for status epilepticus management. However, the intranasal route exhibited superiority when the time required to insert an intravenous catheter was included.[18,19] The study has some shortcomings: the absence of neonates, the lack of blinding between study groups, and we did not examine seizure control by EEG. Additionally, the causes of seizure were not taken into an account. More research is needed to see if intranasal Midazolam may be utilized in medical centers and at home after parents of children with acute seizures receive proper guidelines.

# Conclusion

Compared to intravenous Diazepam, we found that intranasal Midazolam was just as effective at reducing acute seizure activity. When intravenous access is unavailable, this method of delivery is ideal.

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