# Intranasal Midazolam versus Intravenous Lorazepam in the Control of Acute Seizures in Children Aged 6 Months to 15 Years - An Open Label, Randomized Trial

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**ABSTRACT**

**BACKGROUND**
The rapidity with which a medication can be delivered to the systemic circulation and then into the brain always play a significant role in reducing the mortality and morbidity. We wanted to determine and compare the efficacy of intranasal midazolam with that of intravenous lorazepam in the control of acute onset seizures and side effects.

**METHODS**
This is an open labelled randomized control trial conducted in the Emergency Department of KIMS Hospital, which is a multi-specialty tertiary care centre in south Kerala, India, among children with acute seizure between 6 months and 15 years of age. They received intranasal midazolam or intravenous lorazepam.

**RESULTS**
65.2 % (15) of the children in whom intranasal midazolam was given, seizures were controlled within 5 minutes from ER presentation, whereas in lorazepam group, only 34.8 % (8) children ceased to seizure within 5 minutes. P value was 0.039.

**CONCLUSIONS**
The overall time to cessation of seizure after arrival at hospital was faster with intranasal midazolam than intravenous lorazepam. No untoward side effects were noticed.

**KEYWORDS**
Acute Seizure in Children, Intranasal Midazolam, Lorazepam, Randomized Trial

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## BACKGROUND

Prolonged seizure activity in a child is a frightening experience for families as well as care providers, because duration of seizure activity has significant impact on the mortality and morbidity. Effective methods for seizure control should be instituted as soon as possible [1]

Acute isolated prolonged seizures, repetitive or recurrent seizures and status epilepticus are all deemed medical emergencies. Mortality and poor neurological outcome are directly associated with the duration of seizure activity. A number of recent reviews have described consensus statements regarding the pharmacologic treatment protocols for seizures when patients are either in institutional or in home-bound settings. Benzodiazepines such as lorazepam, midazolam, and clonazepam are considered to be medications of choice. The rapidity by which a medication can be delivered to the systemic circulation and then in to the brain always play a significant role in reducing the time needed to stop seizures and thereby reduce opportunity for damage to CNS.[2]

Now there is a better way to treat paediatric seizures in situations where no intravenous access is immediately available. Intranasal midazolam, which delivers antiepileptic medication directly to the blood and cerebrospinal fluid via the nasal mucosa, is safe, inexpensive, easy technique to learn by parents and paramedics and provides better seizure control.[1]

Midazolam, the first water soluble benzodiazepine, is widely accepted as a parenteral anxiolytic and pre-anaesthetic drug. Its safety and efficacy as an anticonvulsant drug, given intramuscularly has been shown in several studies in children and adults.[3]

Midazolam given intranasally, as an anaesthetic agent has been shown to be safe and effective in children undergoing various diagnostic studies and minor procedures.[4] intranasal midazolam also suppresses epileptic activity and improves the background electroencephalogram in children with epilepsy.[5]

A recent study had shown that intranasal midazolam is safe and effective in management of acute seizures in children.[6] Intranasal transmucosal delivery of benzodiazepines is useful in reducing time to complete drug dose administration and to accomplish cessation of seizures in the pre-hospital settings, when a child with active seizures arrives in the emergency room and at home where caregivers treat their dependents.[2]

Seizure is a medical emergency. Early cessation of seizure can reduce the morbidity and mortality.[7] As of now no study is available comparing intranasal midazolam nasal spray versus intravenous lorazepam in control of acute seizures. So we conducted such a study based on the hypothesis that, even though control of seizure in children is faster with intravenous lorazepam than with intranasal midazolam, the time taken for cessation of seizure after arrival of a child at hospital is faster with intranasal midazolam nasal atomiser spray. Our aim is to compare the safety and efficacy of intranasal midazolam with intravenous lorazepam in control of acute seizures in children aged 6 months to 15 years and to study any adverse effects of the drugs used in the study.

## METHODS

This is a prospective randomized open labelled controlled study conducted from May 2010 to April 2012 in the emergency room of KIMS hospital, Kerala.

### Sample Size

We included all children presenting in the emergency room with active seizures in the age group of 6 months to 15 years during a study period of two years. The expected sample size was 50, but we could get only 46. Previous studies like Eli Lahatet al[7], Lahat et al [6], Fisgin et al[8] had sample size similar to our study. Sample size calculation was done as per the below mentioned formula-

$$n = \frac{[\mathrm{Z}\alpha\sqrt{\bar{p}\,\bar{q}} + \mathrm{Z}_{\beta}\sqrt{\mathrm{p1q1} + \mathrm{p0q0}}\,]^2}{(\mathrm{p}_1 - \mathrm{p}_2)^2}$$

### Exclusion Criteria

Children less than 6 months or more than 15 years, children who were on prior antiepileptic drugs, children with established intravenous line, and hypersensitivity to medications.

The study was conducted in the emergency department, all children who fulfilled the inclusion criteria were stratified into two specified age groups. i.e., 6 m to 6 years and 6 years to 15 years. After stratification children were randomized into 2 groups based on computer generated block randomization [5 blocks of 10 patients each]. Group A received intranasal midazolam [0.2 mg / kg] and group B received intravenous lorazepam [0.1 mg / kg.] The maximum dosing will be 10 mg. The dosing guidelines of midazolam nasal spray [Insed atomizer] based on the epilepsy report November 2006[9] was used in our study, which was based on weight and the approximate age ranges these apply to [Table 2 and 3]. This was used because most of the times we will not be able to take the exact weight at admission of a child with active seizures. So we used Broselow tape for assessing approximate weight for calculating lorazepam dose. All children with seizures had received routine life support measures on admission to hospital. Informed consent was taken from the parents.

Midazolam nasal spray [5 mg / ml, 0.5 mg / metered dose] which was an atomiser with trade name 'Insed' provided by Samarth pharma was used for the study. The attending trained ER doctor delivered a dose of 0.2 mg / kg; in equal doses into both nostrils based on the dosing schedule and thereafter an intravenous line was immediately introduced. A trained ER nurse had recorded the following times with a stop clock: time of arrival at hospital,

administration of drug, iv cannulation and time to cessation of seizure. Adverse effects like transient irritation of nasal and pharyngeal mucosa, watering of eyes or nose, any allergic reactions and respiratory depression if any were also noted.

Treatment was considered successful, if the seizure ceased within 5 minutes. Seizure that stopped between 5 and 10 min was defined as successful, but delayed control of seizures, seizure that did not stop within 10 minutes after treatment was defined as treatment failure and intravenous lorazepam [0.1 mg / kg] was given. Seizures that were controlled with midazolam or lorazepam but recurred within 60 minutes were defined as recurrent seizures.

During the seizure activity, and for 60 minutes after control, the child was followed up by continuous cardiorespiratory and pulse-oximetry monitoring. Vital signs like heart rate, respiratory rate, and blood pressure and oxygen saturations were recorded every 30 minutes. During seizure activity, high flow oxygen was provided through mask. All the children were admitted to the PICU (Paediatric Intensive Care Unit) / paediatric ward for observation, after cessation of seizures.

### Outcome Measures

*Primary Outcome*

Time from arrival at hospital to starting treatment and time taken for cessation of seizures.

*Secondary Outcome*

Adverse effects of the drugs.

### Statistical Analysis

Continuous data were summarized by arithmetic means and compared between the two treatment groups using student's t-tests. Categorical data that were summarized as percentages were compared by chi-square tests or Fishers exact tests. Kaplan-Meir survival probabilities were estimated and survival curves were drawn for the waiting time to seizure cessation. P Values of < 0.05 were considered to conclude statistical significance.

### Midazolam Atomiser

Midazolam nasal spray is a metered dose atomizer available for intranasal administration containing 50 metered doses of midazolam. Each metered dose of 1000 mcl of midazolam atomizer delivers 0.5 mg midazolam [0.5 mg / metered dose]. It contains 5 mg of midazolam per ml [5 mg /]

## RESULTS

| | | |
|---|---|---|
| **Total Number of Children Enrolled** | | **46** |
| **Total Number of Children in Stratified Age Groups** | | |
| 6 months – 6 yrs. | I. | 35 (76 %) |
| 6 yrs. – 15 yrs. | II. | 11 (23.91 %) |
| **Total Number of Children** | | |
| Male | | 19 (41.3 %) |
| Female | | 27 (58.7 %) |

***Table 1***

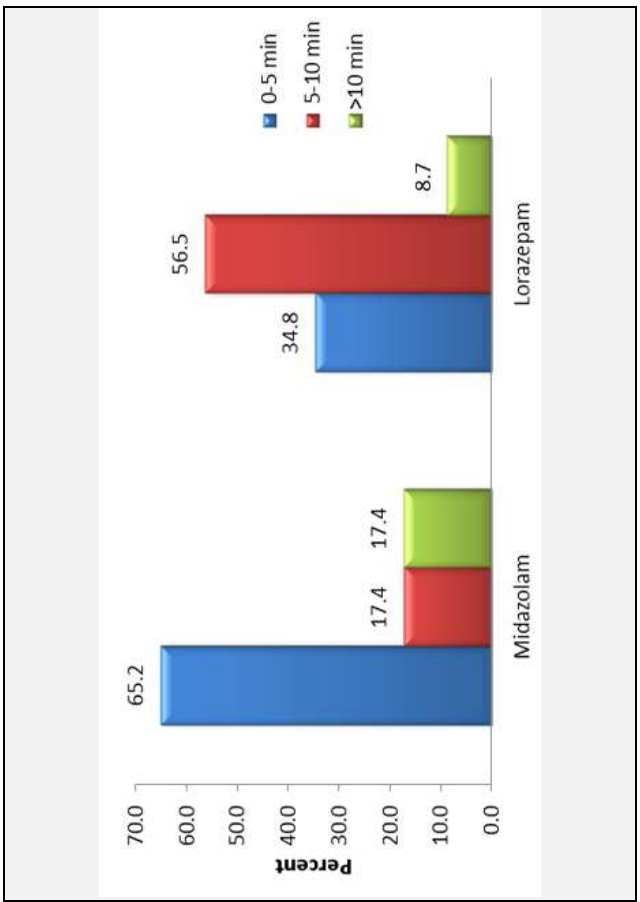


***Figure 1. Comparison of Time to Cessation of Seizures from Presentation at ER***

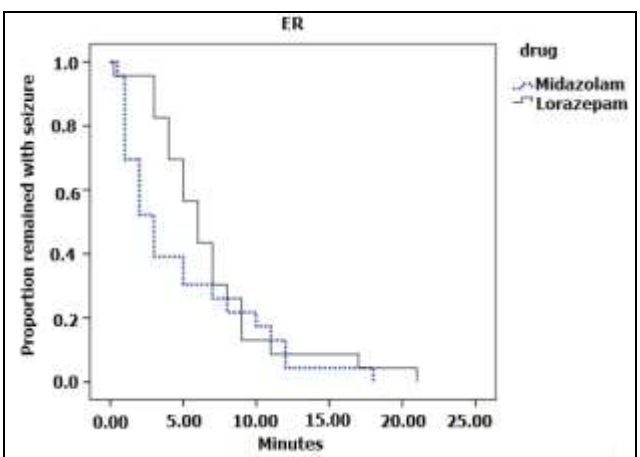


***Figure 2. Time from Arrival at Hospital to Cessation of Seizures in Children Receiving Intranasal Midazolam or Intravenous Lorazepam Presented as Survival Data***

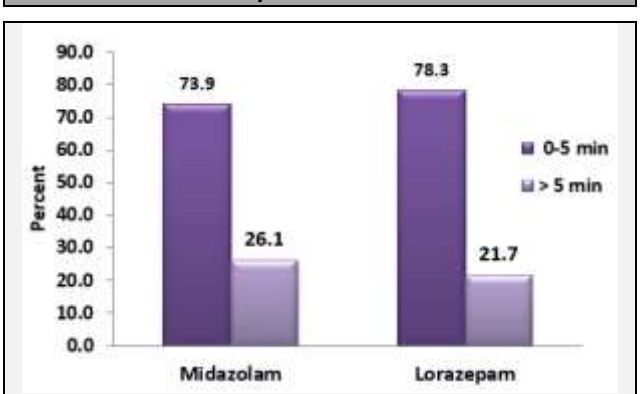


***Figure 3. Time to Cessation of Seizure in Less Than 5 Minutes and More Than 5 Minutes from Administration of Drug***

| Baseline Data | Intranasal Midazolam n = 23 | I.V. Lorazepam n = 23 |
|---|---|---|
| Mean Age, Yr. | 2.63 | 4.93 |
| Male | 10 (43.5 %) | 9 (39.1 %) |
| Female | 13 (56.5 %) | 14 (60.9 %) |
| Presentation | | |
| Status epilepticus | 9 (39.1 %) | 7 (30.4 %) |
| Febrile seizures | 8 (34.8 %) | 6 (26.1 %) |
| Break through seizure | 5 (21.7 %) | 6 (26.1 %) |
| Others | 1 (4.3 %) | 4 (17.4 %) |
| Final Diagnosis : | | |
| Typical febrile seizure | 7 (30.4 %) | 6 (26.1 %) |
| Atypical febrile seizures | 4 (17.4 %) | 2 (8.7 %) |
| Seizure disorder | 8 (34.8 %) | 8 (34.8 %) |
| Meningitis | 0 (0.0 %) | 1 (4.3 %) |
| Encephalitis | 1 (4.3 %) | 2 (8.7 %) |
| Others | 3 (13.0 %) | 4 (17.4 %) |

***Table 2. Baseline Characteristics of Study Subjects***

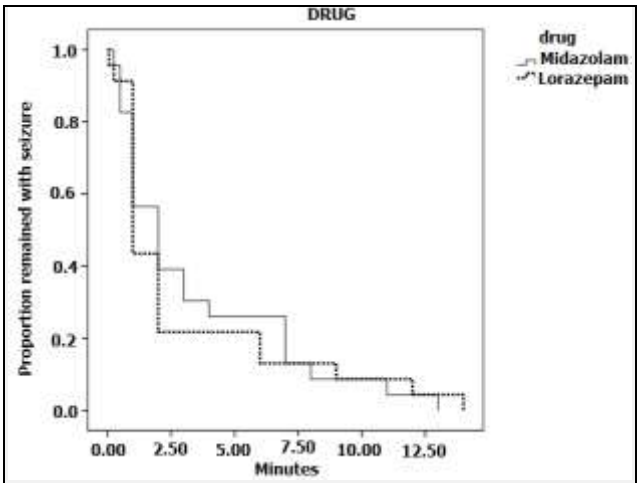


***Figure 4. Time from Administration of Drug to Cessation of Seizures in Children Receiving Intranasal Midazolam or Intravenous Lorazepam Presented as Survival Data***

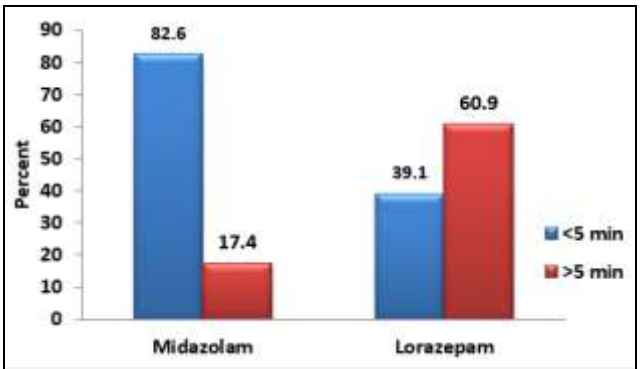


***Figure 5. Time of Administration of Drug from Arrival at ER***

No untoward side effects was noticed in both the drug groups

## DISCUSSION

Midazolam given intranasally is as safe and effective as lorazepam given intravenously in the management of acute seizures in children. The safety and efficacy of midazolam has been shown by several clinical studies in epileptic adults and children. As a result of the popularity of intranasal midazolam as a sedative agent for minor surgical interventions and diagnostic procedures, there is considerable information on its use in young children. Therefore, it seemed pertinent to investigate the use of intranasal midazolam in the management of acute seizures, especially in children, where the introduction of an intravenous line is frequently unsuccessful. To our knowledge, no controlled studies have compared the efficacy of intranasal midazolam with intravenous lorazepam for the management of acute seizures.

In our study, we enrolled 46 children who had come to our emergency room with active seizures within the age group of 6 months to 15 years. We divided them into two stratified age groups assuming that mechanism of response of the body to disease differs with age, and so is the effect of drug.

Out of 46, 35 (76 %) children were in 6 months – 6 years group and 11 (23.9 %) were in > 6 years to 15 years group. Eli Lahatet al[7] in their prospective randomized study included children aged 6 months to 5 years. We had 23 children randomized each into intranasal midazolam and intravenous lorazepam groups. Of these 46 children, 19 (41.3 %) were males and 27 (58.7 %) were females. Mean age in the midazolam group was 2.63 and lorazepam group 4.93. At base line, distribution was almost equal in both the groups. Clinically 16 children presented with status epilepticus, 14 with febrile seizures,[10] with breakthrough seizures and 5 with other causes. All these children were admitted and evaluated and finally diagnosed to have as follows,[11] had typical febrile seizures,[6] had atypical febrile seizures,[12] had seizure disorder,[1] with meningitis,[3] with encephalitis and[7] with miscellaneous diagnosis like hypoglycaemia, intracranial space occupying lesions, lissencephaly, hydrocephalus, etc.

Time to cessation of seizure from presentation at ER (Emergency Room); since, this was the primary objective of our study, a detailed research and critical review of all the possible major studies evaluating the efficacy of intranasal midazolam was analysed. In our study, 65.2 %[13] of the children in whom intranasal midazolam was given, seizures were controlled within 5 Minutes from ER presentation, where as in lorazepam group only 34.8 %[14] children ceased to seizure within 5 minutes. Of that 17.4 %[4] in the midazolam group and 56.5 % [11] in the lorazepam group ceased to seizure in 5 to 10 minutes. More than 10 minutes were required for the control of seizures in 17.4 %[4] of children in the midazolam group as compared to 8.7 %[2] children in the lorazepam group. When we compared the time to cessation of seizures from ER, 65.2 % in the midazolam group stopped the seizures within 5 minutes, whereas majority (65.2 %) of children in the lorazepam group required more than 5 minutes for seizure control. This was statistically significant, hence time to cessation of seizures after arrival at hospital was faster with intranasal midazolam (Figure 8).

Most of the studies viz, Wolf TR et al[1], Wermeling DP et al[2], Lahatet al[6], Fisgin et al,[8] Wilson et al, [15] Mahmoudin T et al[16] documented that intranasal midazolam was faster to control seizures when compared to rectal or intravenous diazepam. Eli Lahatet al [7] who compared the safety and efficacy of midazolam given intranasal with diazepam given intravenously, concluded that, the overall time to cessation of seizures after arrival at hospital was faster with intranasal midazolam than with intravenous diazepam. Maija Holstiet

al[17] compared intranasal midazolam, using a mucosal atomization device, with rectal diazepam for the home treatment of seizures in children with epilepsy, observed that there was no detectable difference in efficacy between IN (Intra-Nasal) midazolam and rectal diazepam as a rescue medication for terminating seizures at home in paediatric patients with epilepsy.

We also compared the results between the two stratified age groups 6 months to 6 years and more than 6 years to 15 years. Time to cessation of seizure from ER in 6 months to 6 years was faster with intranasal midazolam, whereas in more than 6 years it was faster with intravenous lorazepam.

Survival analysis for the time to cessation of seizures after arrival at hospital in the two groups showed better results for intranasal midazolam.

### Time from Drug Administration to Cessation of Seizure

In our study, we observed that 73.9 % [18] children in the intranasal midazolam group and 78.3 %[19] in lorazepam group stopped the seizures within 5 minutes of administration of the respective drugs, whereas 26.1 %[6] in the midazolam group and 21.7 %[5] in the lorazepam group took more than 5 minutes for control of seizures after administration of the drugs, only 8.5 %[2] children in both the groups required more than 10 minutes for seizure control. Though statistically not significant, we observed that time to cessation of seizures after drug administration was almost equal in both the groups.

Mahmoudian T et al,[16] Lahat et al[6] and Eli Lahatet al,[7] in their respective studies observed that time to control seizures after administration of drug was faster for intravenous route.

### Comparison of Means of Time from Drug Administration to Cessation of Seizures in ER

We observed that, the mean time of cessation of seizure after arrival at hospital in midazolam group was 4.84 minutes against 6.9 minutes in the lorazepam group. Hence the mean time to control of seizures was sooner in intranasal midazolam group, but statistically it was not significant. The mean time for cessation of seizure after drug administration in midazolam group was 3.42 minutes and intravenous lorazepam group was 3 minutes, which was almost equal in two groups.

### Time from Arrival at ER to Administration of Drug

We observed that, intranasal midazolam was administered in 82.6 %[20] children in less than 5 minutes, whereas it took more than 5 minutes to administer intravenous lorazepam in 60.9 %[21] children. Intranasal midazolam can be given faster as a means of providing immediate treatment for acute seizures. This may shorten the duration of seizures and simplify the management of these patients in the emergency room. To get an intravenous access in a seizing child is a Herculean task, hence intranasal route is a better option. Our study was at par with Eli Lahat's[7] study, where mean time to administer drug after arrival at hospital was 3.5 minutes in intranasal midazolam group and 5.5 minutes in intravenous diazepam group.

### Tolerability and Adverse Effects

Intranasal midazolam was well tolerated by all children. None of the children in our study in both the stratified age groups had any adverse effects.

### Recurrence of Seizures

We also observed that, in the midazolam group 27.3 %[6] children had recurrence of seizures as compared to 30.4 %[7] children in the lorazepam group. In these children either a second dose, or other higher drugs where required eventually for seizure control.

| Study | Size of Study Group | Intranasal Midazolam | Rectal Diazepam / IV Diazepam / IV Lorazepam |
|---|---|---|---|
| Arif et al | 46 | 65.2 % | 34.8 % (IV Lorazepam) |
| Bhattacharya M et al | 188 | 96.7 % | 88.5 % (Rectal Diazepam) |
| Fisgin T et al | 45 | 87 % | 60 % (Rectal Diazepam) |
| Lahat et al | 52 | 88 % | 92 % (IV Diazepam) |
| Mahumoudin et al | 70 | Equal | Equal (IV Diazepam) |
| Eli Lahat et al | 47 | Equal | Equal (IV Diazepam) |

***Table 3. Comparison of Efficacy of Intranasal Midazolam***

### Strengths of Our Study

- It was a pioneering study in the field of use of intranasal midazolam atomizer in control of acute seizures in children against intravenous lorazepam.
- The stratification and randomization adds strength to our study design.
- We were able to objectively assess the efficacy of intranasal midazolam with precise time to cessation of seizures.

### Limitations

Our study had a few limitations but every effort was made to minimize their effects on the study outcome.

- Although our sample size was large enough to generate a power of 90 %, a larger sample size would have increased the precision of our results.
- We could not 'blind' the intervention due to different routes of drug administration in both the groups.

In retrospect, if we were to perform this study again,

- We would explore impact of intra nasal midazolam in pre-hospital settings.
- We would take into consideration, time to cessation of seizures from the onset of seizures.
- We would evaluate intranasal midazolam's probable economic benefit by conducting a formal cost-effectiveness analysis.

## CONCLUSIONS

### Primary Outcome

The overall time to cessation of seizure after arrival at hospital was faster with intranasal midazolam than intravenous lorazepam. The time to cessation of seizures after drug administration was almost similar in both the groups. The time from arrival at hospital to starting treatment was significantly shorter in the intranasal midazolam group.

### Secondary Outcome

No untoward adverse effects were noted in both the stratified age groups. Hence intranasal midazolam is a safe drug which can possibly be used, not only in medical centre's but also in general practice.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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