

Comparing the effectiveness of intranasal Midazolam and intravenous Lorazepam for the treatment of acute seizures in children

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ABSTRACT

Objective: The objective of this study was to compare the safety and efficacy of intranasal midazolam with intravenous lorazepam in acute seizures in children. **Methods:** Children aged 6 months–12 years with active tonic/clonic/tonic-clonic seizures coming to the pediatric emergency department were enrolled in the study after getting informed consent. Groups were randomly distributed (Group 1: Intranasal midazolam; Group 2: IV lorazepam) and the sample size was 80 (40 in each group). Under clinical and pulse oximetry monitoring, aqueous midazolam 0.2 mg/kg was administered intranasally through automated aqueous intranasal spray (Midacip 0.5mg per puff) in lying down or in 45° propped up position to Group 1, while injectable lorazepam 0.1 mg/kg was administered intravenously slow (to a maximum of 4 mg) to Group 2. **Results:** Both the groups were found to be comparable in baseline characteristics. Mean time to administer the drug after arrival to the doctor in intranasal midazolam and IV lorazepam was 3.65 (standard deviation [SD] 1.167) min and 7.93 (SD 3.23) min, respectively (p=0.0001). Intranasal midazolam group had significant control of seizures in <5 min of arrival (p=0.0006). The control of seizures within 1 min after drug administration was also found to be more effective in midazolam group (p=0.004). No adverse effects or respiratory depression were found in any of the groups. **Conclusion:** The ease to administer, effectiveness, and rapid onset of action of intranasal midazolam without causing any respiratory depression enable it to be considered as a first-line drug for acute seizures in all settings including homes/day-care centers.

Key words: Intranasal, IV - intravenous, Lorazepam, Midazolam, Seizures

Seizures in children are one of the most fearful experiences for parents and caretakers. Epilepsy is defined according to the International League Against Epilepsy as “A disease of the brain defined by any of the following conditions: (a) At least two unprovoked (or reflex) seizures occurring >24 h apart, (b) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years, and (c) diagnosis of an epilepsy syndrome” [1]. The prevalence of pediatric epilepsy in India is 5.35/1000 [2]. In children, less than 5 years, the most common cause of seizure is febrile seizures, of which more than 12% are prolonged lasting more than half an hour [3]. Seizures are one of the most common occurrences in pediatric emergency department.

Intravenous access is not always possible for emergency anticonvulsant treatment for children having a seizure, and an effective and safe alternative which can be useful in all settings including peripheral health centers, homes, and schools is warranted. Conventionally, diazepam is given rectally [4] or parentally, but IV lorazepam is being followed as the first-line drug in most of the centers. For IV administration in a convulsing child, special

arrangement is required along with skilled personals, which is not an easy task in schools, day-care centers and even in some health-care centers. An effective treatment that can be easily administered by a more convenient and socially acceptable route is therefore needed.

More recently, the intranasal [5] or buccal route for midazolam has come up as a safe and effective alternative. Buccal midazolam [6] is effective, but it can be less reliable as it is often practically difficult to insert the liquid between cheek and teeth while the child is actively convulsing and when large doses are needed. Pharmacokinetic data (rapid action and bioavailability) [7] and acceptability to patients indicate that intranasal midazolam is a suitable alternative, and it is easy to administer the drug into the nasal cavity [8].

In this context, the present study was undertaken to compare the efficacy and safety of intranasal midazolam with IV lorazepam (which is the standard treatment) in the treatment of acute and prolonged seizures in children.

MATERIALS AND METHODS

An interventional study was conducted among the children with acute seizures in the pediatric emergency department of a tertiary

hospital in South India. Ethical committee and Institutional scientific committee clearance were obtained before the study. The period of study was 1 year.

Children aged 6 months–12 years with tonic/clonic/tonic-clonic seizures who have not received any medication for the present event from any other hospital/home and whose parents/guardians gave consent to participate were included in the study. Children with absence seizures, atonic seizures, and non-conclusive seizures or patients who had come after receiving any anticonvulsive medication for the present event were excluded.

The sample size was determined to be 80 (40 patients in each group).

$$n = \frac{2 \sigma^2 (Z_{1-\alpha/2} + Z_{1-\beta})^2}{\mu_d^2} = \frac{2 \times 0.42^2 (1.96 + 0.84)^2}{0.3^2} = 31$$

$Z_{1-\alpha/2} = 1.96$ [at 5% α]

$Z_{1-\beta} = 0.84$ [at 20% β]

σ = Pooled SD

μ_d = Clinical significant difference = 0.3

Sample size calculated from the mean time for seizure control by both drugs.

Group 1 patients were administered intranasal midazolam while Group 2 patients were administered IV lorazepam. After emergency management and stabilization of the airway and breathing, aqueous midazolam 0.2 mg/kg was administered intranasally through automated aqueous intranasal spray (Midacip 0.5 mg per puff) in

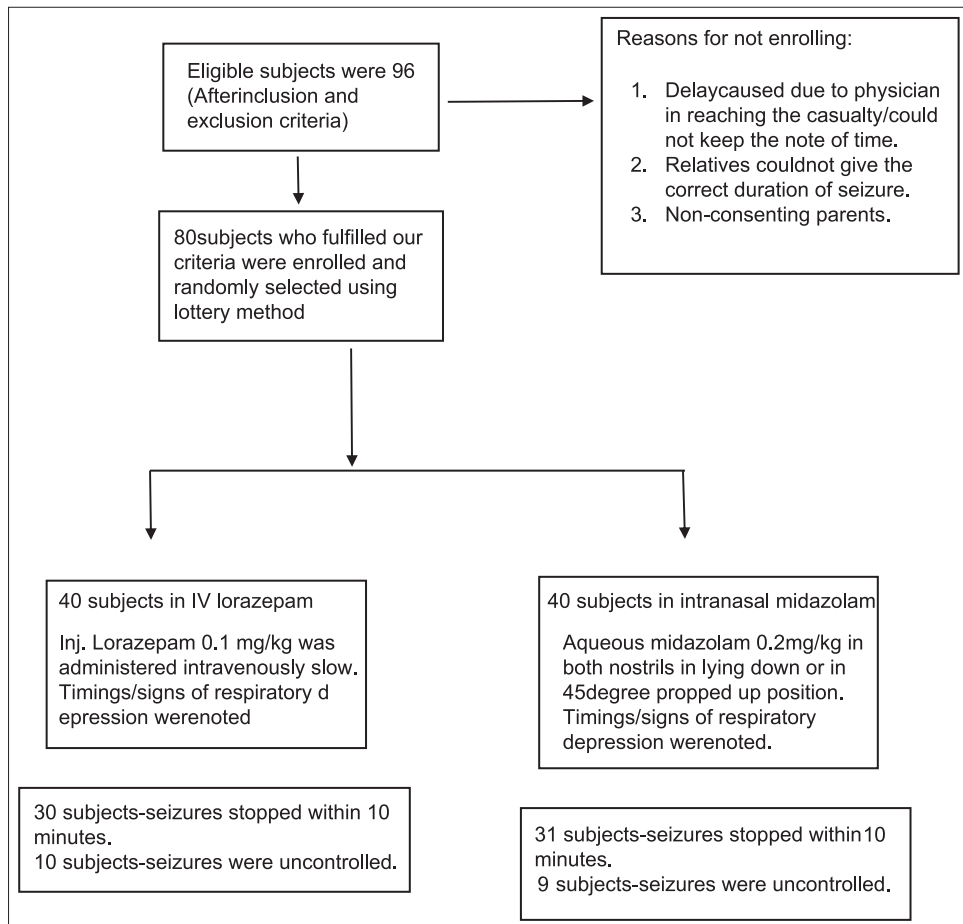
lying down or in 45degree propped up position to Group 1, while injectable lorazepam 0.1 mg/kg was administered intravenously (to a maximum of 4 mg) to Group 2. Continuous monitoring of vitals (heart rate, respiratory rate, and partial pressure of O₂ [SPO₂]) was done until the patient was stabilized and shifted to the ward/intensive care unit (ICU). The duration from the time of arrival of the patient to the control of seizures was noted.

Data collection was done by the patient’s father, mother, or the guardian after stabilization of the patient on a predesigned pro forma. Pre designed pro forma was document with the details collected from the parents or guardian of the patient after they are stabilized. The treatment was considered ‘successful’ if seizures ceased within 5 min; ‘successful but delayed’ if seizures ceased in 5-10min and ‘treatment failure’ if seizures were not controlled within 10 min of drug administration. If not controlled within 10 min, the patient was managed as per hospital protocols.

Qualitative data were analyzed using proportion, and quantitative data with mean and other statistical analysis were used depending on nature of data. Covariates between two groups (midazolam and lorazepam) were compared by Chi-square test, Fisher’s exact test, or Student’s t-test, and $p < 0.05$ was taken as statistically significant.

RESULTS

Total patients in the study were 80 (40 in each group). The analysis of data shows that both the groups were comparable in baseline



characteristics such as age distribution and gender distribution. Some comparisons are charted below (Table 1).

The duration of seizure as on reaching the hospital emergency department was varying, hospital emergency department was varying. So they were categorized as <10min and >15min. There was a statistically significant correlation between IV lorazepam and intranasal midazolam groups in <10 min and >15 min group ($p=0.0123$, 0.0123 , respectively).

The success rate of controlling seizures which lasted for more than 15 min was better with intranasal midazolam compared to IV lorazepam ($p=0.0003$). In case of seizures lasted for more than 30 min, both the drugs were equally effective. Seizure control was not achieved in 10 (25%) subjects of lorazepam group and 9 (22.5%) subjects of midazolam group and their difference was not statistically significant ($p=0.635$).

All the subjects were monitored for respiratory depression signs (respiratory rate, heart rates, and SpO_2) for half an hour, before shifting to the ward/ICU. None of the patients in both the groups had respiratory depression.

Mean time to administer drug after arrival in the intranasal midazolam group (mean 3.65 min standard deviation [SD] 1.167 [0.955–1.498]) when compared to the IV lorazepam group (mean 7.93 min SD 3.23 [2.645–4.147]) was statistically significant

($p=0.0001$). The mean time to control the seizure after arrival of patient in the intranasal midazolam group (mean 12.05 min SD 12.327 [10.091–15.828]) when compared to the IV lorazepam group (mean 15.28 min SD 10.879 [8.911–13.969]), p value - 0.218. The time taken to control the seizures after the drug was administered in the intranasal midazolam group (mean 2.55 min SD 1.915 [1.568–2.458]) when compared to the IV lorazepam group (mean 2.87 min SD 1.915 [1.568–2.458]); p value - 0.481 (Table 2).

DISCUSSION

In the present study, we compared the efficacy, duration, and safety of intranasal midazolam to IV lorazepam (which is considered an effective first-line drug in acute seizure management [9]). Other studies comparing IV lorazepam with intranasal midazolam are not available. In our observation, intranasal midazolam is equally effective as IV lorazepam.

In the present study, seizure control among children with intranasal midazolam was 77.5% which is comparable with other studies and had no incidence of respiratory depression. Harbord *et al.* [5] used intranasal midazolam to treat acute seizures in pediatric community settings and showed good seizure control of 89%, without any safety issues or difficulty in administering

Table 1: Comparison of some of the profile characteristics

Profile characteristics	Lorazepam (n=40)	Midazolam (n=40)	Chi-square	p value
Male/Female	20 (50%)/20 (50%)	21 (52.5%)/19 (47.5%)	0.05	0.823
Afebrile seizures	25 (62.5%)	26 (65%)	0.05	0.81
Previous status epileptics	9 (22.5%)	10 (25%)	0.06	0.792
H/O missed drugs	6 (15%)	2 (5%)	2.2	0.136
Developmental delay	3 (7.5%)	7 (17.5%)	1.8	0.176
Family h/o epilepsy	8 (20%)	3 (7.5%)	2.63	0.104
Hypocalcemia	1 (2.5%)	2 (5%)	0.34	0.554
Seizure type:			3.913	0.047*
Generalized	39 (97.5%)	34 (85%)		
Focal	1 (2.5%)	6 (15%)		

* $p<0.05$; significant

Table 2: Time taken for administration of drug and seizure control

Time taken to administer drug from the time of arrival	<3 mins	<5 mins	<10 mins	<15 mins	
IV lorazepam	1	15	33	40	
Intranasal midazolam	19	40	-	-	
p value	0.0001*	0.0006*	0.159	0.0001*	
Time taken to control seizure from the time of arrival	<3 min	<5 min	<10 min	<15 min	Uncontrolled
IV lorazepam	0	01	23	24 [#]	10
Intranasal midazolam	04	14	29	31	09
p value	0.123	0.0006*	0.241	0.147	0.792
Time to control seizure after drugs administered	<1 min	<5 min	<10 min	<15 min	Uncontrolled
IV lorazepam	0	27	30	10	
Intranasal midazolam	09	28	31	09	
p value	0.004*	0.809	0.798	0.792	

[#]There were 6 cases in which time taken to control seizure from the time of arrival was more than 15 min but was controlled within 10 minutes of drug administration. * $p<0.05$; significant

the drug. Fisgin *et al.* [10], Bhattacharyya *et al.* [11], and Lahat *et al.* [12] compared intranasal midazolam to rectal diazepam in which the midazolam aborted seizures in 87%, 96.7%, and 88%, respectively, and found to be safe. In the present study, IV LORAZEPAM had 75% seizure control, which is comparable with Arya *et al.* [13] study which was found to be 80%.

Some of the added advantages in the usage of intranasal midazolam over IV lorazepam were the shorter duration taken to administer intranasal midazolam and its fast action after administration.

The mean time for administration of the drug from the time of arrival of the patient was significantly less in the intranasal midazolam group when compared with the IV lorazepam group ($p=0.0001$) in the present study. The mean time was 3.65 min (SD 1.167), 95% confidence interval 0.955–1.498 in the intranasal midazolam group, which is comparable with Lahat *et al.* [12] study where the mean time was 3.5 min (SD 1.8), 95% confidence interval 3.3–3.7. In the IV lorazepam group, the mean time of administration of the drug after arrival of the patient was 7.93 min (SD 3.23), 95% confidence interval 2.645–4.147. This was longer than the Arya *et al.* study [13] where this time was 4 min.

We also found that intranasal midazolam group, the drug could be rapidly administered (i.e. 47.5% of patients received the drug within 3 min and the rest 52.5% within 5 min) than IV lorazepam group (where only 37.5% received by 5 min and it took up to 15 min for all the patients to receive the drug) ($p<0.05$).

The mean time for controlling seizure after arrival of the patient in the present study was 12.05 minutes in the intranasal midazolam group, which was less than the IV lorazepam group (15.28 min). The difference is not statistically significant ($p=0.218$). Panchal *et al.* [14] studied the duration of intranasal midazolam is shorter (3.380 min/SD - 1.19). In the present study, on subdividing the time taken in each group, we found that 35% of patients in the intranasal midazolam group had significant control of seizures within <5 min, while only 2.5% of patients could be controlled in the IV lorazepam group, which was statistically significant ($p=0.0006$).

There was no overall significant difference between the two groups in the time taken to control the seizures after the drug was administered. In the present study, the mean time taken was 2.55 min (SD 1.915) 95% confidence interval 1.568–2.458, in the intranasal midazolam group, and it is comparable with Bhattacharyya *et al.* [11] study where the mean time was 1.945–2.115 minutes. In the IV lorazepam group, the mean time to control seizures from drug administration was 2.87 min (SD 1.929) 95% confidence interval 1.580–2.476, which was comparable with Arya *et al.* [13] study where the time taken varied from 1 to 36 min (median 3 min) and also with Lissauer *et al.* study, where seizures stopped within 10 min in 83% of cases [15]. In the present study, we could find statistically significant control of seizures within 1 minute of administration in intranasal midazolam group in 22.5% of patients, while 0% of patients got controlled in the IV lorazepam group ($p=0.004$). This is comparable with the Conroy *et al.* [16] study with intranasal midazolam where 15% responded within 1 min. Hence, intranasal midazolam can be considered to be as effective as IV lorazepam. Simultaneously, EEG recording has not been done to prove the seizure cessation which is a limitation of this study.

CONCLUSION

The efficacy and safety of intranasal midazolam is comparable with that of IV lorazepam in treating in children in the age group 6 months–12 years. The ease to administer, effective and rapid action without any respiratory depression makes intranasal midazolam a promising first-line drug for acute seizures in peripheral settings or at home/day-care centers, and in tertiary centers, patients where IV access are difficult or delayed due to various reasons.

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