Intranasal midazolam for the treatment of seizures in children in rural India

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ABSTRACT

Background: About 5% of healthy children experience at least one convulsive episode in their lifetime with onset during childhood in more than half the cases. The current evidence suggests that prolonged seizures are best stopped with early treatment. **Objective:** The objective of the study was to assess the role of intranasal administration of midazolam for seizure cessation at home by caregiver in semi-urban and rural settings. **Materials and Methods:** A total of 50 children in the age group of 6 months–14 years were included in the study, who previously had a history of convulsions and were on regular follow-up. The study was conducted over a period of 6 months. The parents were instructed to give intranasal midazolam if seizure activity lasted for more than 3 minutes and the need of giving it 2nd time if the seizure was not aborted and to bring the child to nearest pediatrics emergency set up for the further management. **Results:** The subjects were divided into three groups according to age: Group A consisted of children between 6 months and 4 years, Group B of 4 and 9 years, and Group C had 9 and 14 years old children. Average duration of aborting seizures before INM use was 16.22 min and after its use was 4.66 min. Seizures were aborted in 45 children within 10 min. **Conclusion:** INM is safe and efficacious in aborting seizures at home in semi-urban and rural settings.

Key words: *Domiciliary settings, Intranasal midazolam, Rural, Seizures*

Seizure is the most common neurologic medical disorder in the pediatric population. Almost 5% of healthy children experience at least one convulsive episode in their lifetime with onset during childhood in more than half of the cases [1]. The current evidence suggests that prolonged seizures are best stopped with early treatment [2]. Intravenous midazolam and lorazepam are now used as the first line of therapy in many hospital settings, although intravenous access is not available, intramuscular paraldehyde is an alternative in many parts of world [2,3]. Early domiciliary treatment of seizures in the community, school, or home with drugs that can be administered by parents, teachers, or non-medical staff may be beneficial and can decrease morbidity and mortality [2].

Outside the hospital, where intravenous and intramuscular therapy may be difficult or impossible to administer, rectal diazepam is being used as the primary treatment option for breakthrough seizures till now. However, it has a slow onset of action as compared to its intravenous route and is not effective at controlling seizures. Other disadvantages include the lower social acceptability of the rectal route and serious side effects like respiratory depression. The potential alternative method of benzodiazepine delivery is buccal route.

Recent studies have demonstrated INM to be effective in the management of acute childhood seizures [4-8]. However, it has been found that buccal administration and sublingual delivery being practiced in European countries are difficult to use when the teeth are clenched during a tonic-clonic seizure [9]. In the light of the above background, the present study was undertaken to assess the efficacy and side effects of INM in the treatment of acute childhood seizures in semi-urban/rural settings in North India.

MATERIALS AND METHODS

The present cross-sectional study was carried out by the department of pediatrics in a government medical college over a period of 6 months. A written consent was obtained from the parents or guardians of children regarding their willingness to participate in the study. The study was approved by the Institute Ethical Committee.

A total of 50 children in the age group of 6 months–14 years with the previous history of convulsions were included in this study. The children who had upper respiratory tract infection with large amount of mucus secretions or had bleeding from nose were excluded from the study. The children who had metabolic cause of seizure activity or had seizure lasting for <3 min and more than 30 min were also excluded from the study. For abortion of seizures at home, INM was used by the parents in a dose of 0.2 mg/kg (maximum dose: 10 mg) by puff inhalation method. The technique of drug administration was demonstrated to the parents/attendants beforehand in the outpatient department and ward. Further, this technique was cross-checked by demonstration in front of researcher and office independent colleagues (one PG student and one nurse).

The parents or guardians were instructed to place the child in the recovery position during the seizure episode and to wait for 3 min before giving INM at home in both the nostrils. They were instructed to check the expiry of the spray. They were also told about the need of the second spray of INM. The parents were asked to report to the hospital immediately after that. The data were collected and then analyzed for the purpose of the study.

RESULTS

A total of 50 patients were further divided into three groups depending on their age: Group A consisted of 6 months–4 years, Group B consisted of 4–9 years, and Group C comprised 9–14 years. Maximum number of the patients belonged to Group C (38%) followed by in Group B (36%) and Group A (26%). Etiologies of epileptic conditions of the children included in the study have been given in Table 1. The most common seizure type observed was generalized tonic-clonic in all three age groups [Table 2]. Most of the patients had seizures between 10 and 20 min (54%) at home. Group A had the longest seizure duration at presentation and the shortest duration was seen in Group B. The average duration of seizures at presentation was 14.65 min. The average duration of seizures before administration of INM was 16.22 min.

Seizure termination was quickest in Group A (4.46 min) and slowest in Group B (4.97 min). The average time for seizure termination was 4.66 min. Seizures were controlled within 5 min of INM in 37 patients and between 5 and 10 min in 8 patients. Repeat dose of INM was given in 13 patients; out of which, 8 patients responded. Repeat dose was required mostly in Group B and least in Group C. The mean duration after which INM was repeated was 4 min.

Seizures were present 10 min after receiving INM in five patients and they were immediately brought to the emergency at the nearest district hospital and further treatment was carried out. There was minimal or no side effect of INM use. Common difficulties encountered at home during administration of INM were excessive nasal secretions, head movements, and sneezing [Table 3].

DISCUSSION

Seizures in children are the most frequent neurologic disorder affecting children. As prolonged seizure activity impacts morbidity and mortality, effective methods for seizure control should be instituted preferably before arrival at the hospital. Since parenteral methods of drug delivery are not available to caregivers at home, alternatives like midazolam have been tried sublingually (buccal) in European countries and intranasally in rest of the world. Nasal administration has an advantage of rapid absorption into systemic circulation without the disadvantage of passage through the portal circulation.

O'Regan *et al.* were the first in the literature to state the effectiveness of INM in acute epileptic seizures. They determined that 15 out of 19 patients had positive response as

a dramatic improvement in electroencephalogram or cessation of convulsions [10]. In our study, it was observed in 45 out of 50 patients after INM. The most common seizure type was generalized tonic-clonic (46%) followed by complex partial seizures (32%). While in a study done by Kutlu *et al.*, 44% of patients had generalized tonic-clonic, 22% had complex partial, and 22% of patients had secondary generalized partial seizures [11].

The average time of cessation of seizures after therapy was 4.66 min which is in contrast to the study done by Lahat *et al.* where a total mean time to abort seizures was 6.1±3.6 min [6] while Lather *et al.* found the median duration to be 2.5 min [12].

In Fisgin *et al.* study, the response period following INM was 1 min in 22% of patients, 1–2 min in 39% of patients, 2–5 min in 22% of patients, and 5–10 min in 4% of patients. Seizures were present in 13% of patients after 10 min, while in our study, 10% of patients were having convulsions at 10 min after receiving INM. Seizures stopped in 5 min in 74% of patients and in 10 min in 90% of patients. Fisgin *et al.* had a response rate of 87% in 10 min [5], while Harbord and Kyrkou had a response rate of 89% in their study done over 22 patients [13].

In a study done by Lather *et al.*, 72% of patients responded to INM, while 28% of patients did not respond to INM use [12].

Table 1: Etiology of epileptic conditions included in the study

Diagnosis	Number (%)
Epilepsy (Idiopathic)	17 (34)
Inflammatory granuloma (neurocysticercosis)	18 (36)
Febrile seizures	4 (8)
Tuberous sclerosis	4 (8)
West syndrome	7 (14)

Table 2: Seizure classification according to ILAE

Seizure type	Number
Generalized tonic-clonic	23
Right-sided focal seizures with impaired awareness	10
Left-sided focal seizures with impaired awareness	6
Focal seizures with awareness	2
Myoclonic	9

Table 3: Clinical characteristics with drug used

Characteristics	Outcome
Age	6 months–4 years=13 4–9 years=18 9–14 years=19
Gender	M=29, F=21
Average duration of seizure before therapy	17 min
Average time of cessation seizure after therapy	4 min
Common difficulties during administration	Excessive nasal secretion=6 Excess head movement=5
Number of patients requiring repeat doses	11

Wilson *et al.* carried out a telephone survey to evaluate the effectiveness of INM to terminate seizures in the settings outside the hospital. About 83% of families who had used it found it effective and easy to use [14]. Effectiveness and safety of non-rectal and non-IV benzodiazepines were also supported by a study done by Haut *et al.* [15].

Urgent treatment is required for status epilepticus as neurologic complications are related to the duration of seizure. Chin *et al.* concluded that early treatment of status epilepticus decreased the need for intensive care unit admissions [16]. INM is thus an acceptable treatment option as a first aid response for acute seizures. There were few limitations of our studies. The sample size was small and the study was highly dependent on the parent's reporting.

CONCLUSION

It is concluded that INM is safe and efficacious in aborting seizures at home by caregiver in semi-urban and rural settings. Future studies with larger sample size are required to establish the findings.

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