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Brief Communication

# Impact of prescribing intranasal midazolam as rescue medication for domiciliary management of acute seizure among children with epilepsy☆,☆☆,★

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ABSTRACT

Prescription pattern of rescue medication like intranasal midazolam (INM) for domiciliary management of seizure is highly variable. The present cross-sectional study was designed to determine the impact of the use of INM on healthcare utilization by those who used INM when compared with those who are not on any rescue medications in a resource-constraint setting. Children with epilepsy aged 1–14 years who have used INM to abort seizure at home (INM group) were compared with those who have not used INM (control group). The baseline demographic and seizure characteristics including the severity of epilepsy were comparable between the INM group (n = 50) and controls (n = 50). The INM group had significantly better knowledge of the correct method of administration when compared with controls [43 (86%) vs. 17 (34%); $p < 0.01$]. Seizures were aborted in 36 (72%) users in the INM group; of the rest of 14 children, 4 (8%) used it for the second time. The median Interquartile range (IQR) time taken to abort the seizure was 2.5 (1.0, 5.2) min. The need for intensive care admissions was comparable between the INM group and control group, although the number of emergency visits was significantly higher in the former [2.9 vs. 1.4, $p = 0.04$]. Despite comparable severity of epilepsy and better knowledge of its correct use, children who were prescribed INM required more hospital emergency visits. This study with a limited sample size prompts us to introspect the practice of INM for children with epilepsy.



## 1. Introduction

Epilepsy is a neurological condition with recurrent seizures. Parental counseling is essential to allay their fears, adverse reactions, and apprehensions of stigma or social taboo. Parents of children with epilepsy must be well versed in the domiciliary management of seizures. There is an emphasis on maintaining a recovery position during an active seizure. Rescue medications used at home include but not limited to intranasal midazolam (INM), intranasal lorazepam, and rectal diazepam. Among these medications, INM is the most commonly prescribed medication for domiciliary management of seizures [1]. In some healthcare institutes, rectal diazepam is used to abort seizures, but in our setup, INM is preferred over rectal diazepam because of the discomfort and difficulties associated with the use of rectal preparations. Intranasal midazolam is used in doses of 0.2 mg/kg (maximum: 10 mg) among those with prolonged seizure (>3–5 min) [2]. Regular prescription of rescue medication among pediatric neurologist has witnessed a decrease in the burden of hospital emergency visits [3,4].

However, there is a considerable variation in prescription practice in developing countries. Many patients who are attending local physicians in their first visit often are not prescribed any rescue medication. Owing to the high cost of these medications, poor parents are unable to purchase these medications despite being prescribed. Hence, in their first visit to a pediatric neurology referral clinic at a tertiary level, one tends to encounter both groups of children: those with INM and those without INM prescription or usage.

Majority of studies are from developed countries with better infrastructure, better access to emergency services, and medically insured healthcare system [5–7]. Most of the studies have used rectal diazepam or buccal midazolam as their rescue medication in a prehospital setting [8–10]. However, there are no studies on the impact of prescribing INM in a resource-constraint setup especially in the background of variability in the prescription and usage of INM. This study intended to explore the lacunae in the existing literature on the implication of the current

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practice of administration of INM among children with epilepsy. Hence, the present study was designed to determine the impact of the use of INM on healthcare utilization by those who used INM when compared with those who are not on any rescue medications.

## 2. Methods

This comparative cross-sectional study was performed in the Pediatric Neurology services of a tertiary care teaching hospital. Children with epilepsy aged 1 to 14 years at their first visit to the center were screened. Children who have used the midazolam nasal spray at least once were considered as INM group and those who have never used it served as their controls. Children with progressive neurodegenerative disease and those with myoclonic or absence seizures were excluded. An institutional ethical committee clearance was obtained. Written informed consent was obtained from the parents or caregivers.

Eligible participants were enrolled and evaluated for clinical and demographic parameters. The demographic profile of children was recorded regarding age, gender, residence, parental education, parental occupation, and parental income. Clinical characteristics were also recorded regarding the type of seizure, the frequency of seizure, expanded childhood epilepsy severity score [E CHESS score], type and number of antiepileptic drugs prescribed.

Intranasal midazolam usage was considered as correct when parents placed the child with seizure in a recovery position, checked the expiry date of the spray, waited for 3 min before administering the drug, counted the number of sprays prescribed by the physician, and used it either or both the nostrils. Also, time lag to abort the seizure following INM administration after a 3-minute cutoff, storage conditions of INM, and the need for second dose administration were recorded. Any reported adverse event following the use of INM was recorded. Healthcare utilization was registered regarding the number of emergency department visits following a seizure, subsequent need for intensive care admission, and the need for respiratory support in Emergency department (ED).

As a part of our standard practice once the patient is enrolled in the center, verbal as well as written instructions were provided on the correct usage of midazolam nasal spray to children with epilepsy. Emphasis on recovery position was made, and parents were instructed to administer the right dose of INM in both the nostrils if seizures last for more than 3 min.

All data collected were entered in the Microsoft Excel (MS Excel). Data were analyzed using Statistical Package for Social Sciences (SPSS) 15.0 version. All categorical variables were expressed in numbers (percentage), and all continuous variables were expressed as mean standard deviation (SD) or median (IQR). Categorical variables were compared using Chi-Square Test or Fischer Exact test. Continuous variables were compared between the INM group and controls using Student's 't' test or Wilcoxon Rank Sum test. All tests were two-tailed, and $p < 0.05$ was considered to be statistically significant.

## 3. Results

A total of 50 INM users and 50 controls were enrolled over the duration of four months. The baseline demographic like age, gender, and parental education were comparable between the INM group and controls (Table 1). Similarly, the clinical profile including the severity of epilepsy in terms of E CHESS scores and the type of seizure were comparable (Table 1).

The etiology of seizures among INM group and controls was comparable: perinatal insults [9 (18%) vs. 7 (14%)], neurocysticercosis [16 (34%) vs. 14 (28%)], febrile seizures [7 (14%) vs. 7 (14%)], focal structural pathology other than neurocysticercosis [16 (32%) vs. 17 (34%)], and idiopathic [2 (4%) vs. 5 (10%)].

Majority of INM users knew the correct method of administration [43 (86%)]. Majority of INM users purchased it on the day of prescription [46 (92%)]. Median (IQR) number of times parents used INM was 2 (1, 3). A total of 36 (72%) of children achieved a cessation of convulsion. Of the rest, 14 (28%) of INM users did not reach a termination of seizure with the administration of INM; 4 (8%) used it for the second time. Median (IQR) time taken to abort the seizure after administration of INM was 2.5 (1.0, 5.25) min. Intranasal midazolam was administered in both nostrils in 47 (94%) INM users. Five of them showed signs of airway irritation after dose administration. The number of emergency visits was significantly high in the INM group as compared with controls [$p = 0.04$]. However, subsequent inpatient admission and intensive

**Table 1**
Table comparing the demographic and clinical profile of children with epilepsy who have used intranasal midazolam (INM group) and those who have never used intranasal midazolam (controls).

| Parameter | INM group | Controls | p value |
|---|---|---|---|
| Age (in months) [median (IQR)] | 96 (58.5, 132) | 84 (45, 132) | 0.61 |
| Male gender [n(%)] | 32 (64%) | 38 (72%) | 0.43 |
| Mother education | | | |
| Illiterate | 13 (26%) | 5 (10%) | 0.32 |
| School education | 26 (52%) | 29 (58%) | |
| Graduate or postgraduate | 11 (22%) | 16 (32%) | |
| Father education | | | |
| Illiterate | 7 (14%) | 2 (4%) | 0.42 |
| School education | 29 (58%) | 31 (62%) | |
| Graduate or postgraduate | 14 (28%) | 17 (34%) | |
| Type of seizure | | | |
| Generalized tonic | 8 (16%) | 10 (20%) | 0.32 |
| Generalized tonic–clonic | 23 (46%) | 25 (50%) | |
| Focal seizures | 19 (38%) | 15 (30%) | |
| Frequency of seizure | | | |
| Daily | 6 (12%) | 11 (22%) | 0.31 |
| Weekly | 9 (18%) | 4 (8%) | |
| Monthly | 2 (4%) | 16 (32%) | |
| Six monthly | 5 (10%) | 4 (8%) | |
| Yearly | 5 (10%) | 15 (30%) | |
| Age at onset of a seizure in months [median (IQR)] | 33 (12, 72.5) | 36 (12, 67.5) | 0.92 |
| Seizure duration in minutes [median (IQR)] | 5 (3, 15) | 5 (2, 17.5) | 0.82 |
| E CHESS [median (IQR)] | 8.5 (6, 9.2) | 7 (6, 9) | 0.15 |
| Control of epilepsy | | | |
| Well-controlled | 10 (20%) | 17 (34%) | 0.14 |
| Poorly controlled | 32 (64%) | 27 (54%) | |
| Uncontrolled | 08 (16%) | 06 (12%) | |
| Antiepileptic drug | | | |
| Monotherapy | 23 (46%) | 27 (54%) | 0.12 |
| Polytherapy | 27 (54%) | 23 (46%) | |

**Table 2**
Table comparing the healthcare utilization characteristics of children with epilepsy who have used intranasal midazolam (INM group) and those who have never used intranasal midazolam (controls).

| Parameters | INM group | Controls | p value |
|---|---|---|---|
| Number of emergency visits | 2.9 (5.1) | 1.38 (1.51) | 0.04 |
| Repeat seizures within 12 h | 9 (18%) | 6 (12%) | 0.15 |
| Condition of child | | | |
| Normal | 10 (20%) | 13 (26%) | 0.29 |
| Seizing | 18 (36%) | 9 (18%) | |
| Unconscious | 5 (10%) | 1 (2%) | |
| Not known | 5 (10%) | 8 (16%) | |
| Not presented to ED | 12 (24%) | 19 (38%) | |
| Intensive care requirement on admission | | | |
| Yes | 19 (38%) | 11 (22%) | 0.29 |
| No | 18 (36%) | 19 (38%) | |
| Not known | 1 (2%) | 1 (2%) | |
| Inpatient care requirement | | | |
| Yes | 27 (54%) | 18 (36%) | 0.19 |
| No | 10 (20%) | 13 (26%) | |
| Not known | 13 (26%) | 19 (38%) | |

care requirement were comparable between the INM group and controls (Table 2).

## 4. Discussion

The present study revealed that despite a comparable severity of epilepsy, type of seizures, educational background of parents, and knowledge of INM usage, children with epilepsy who had used INM required a significantly higher emergency visit when compared with those who did not use any rescue medication. Moreover, INM was effective only in three-fourths of children with an acute seizure. It was surprising to observe this finding that INM usage did not result in a reduction of healthcare utilization regarding the need for intensive care unit admission and the need for an inpatient hospital stay.

It is rather difficult to attribute the reason behind the significantly higher number of emergency visits among those who used INM. Some of the apparent reasons could have been that children in the INM group had a higher severity of epilepsy, and parents were not well versed with INM usage. However, the two groups in the present study were comparable with regard to these parameters. These findings were in contrast to the results of Chin et al. [11] where authors found that early treatment of status epilepticus at prehospital settings decreases the need for intensive care unit admission [11]. Although the domiciliary use of rescue medication intends to minimize the hospital visit, it probably increases the parental apprehension. Authors presume greater anxiety among the INM users that could have possibly brought them to ED. This reemphasizes the need for parental education and hands-on training for the use of rescue medication [8,9].

The present study found that the median duration of seizure after INM use after a 3-minute cutoff was around 2.5 min. These results are consistent with a study by Lahat et al., where authors had reported that total mean (SD) time to abort seizure was 6.1 (3.6) min. Moreover, only a few developed minor nose irritation following its use. Interestingly, none of them faced any problems in administering the drug in contrast to 13% of patients reporting problems with other abortive medications like rectal diazepam [12]. These findings reemphasize the relative safety and ease of use of INM in aborting a seizure. In a systematic review, it was observed that the majority of nonrectal benzodiazepine preparations provide good efficacy and safety outcomes [13]. However, there is a concern about the efficacy of INM in the present study considering that only three-fourths had control of seizure. However, it is this group of children who required subsequent inpatient admission and intensive care admission. Hence, these observations of higher ED admissions and lower efficacy rates need to be interpreted in the context of study design.

The study findings need to be interpreted in the context of a comparison between those who used INM and those who did not use it. Ideally, the comparison should have been made between children who were prescribed INM and those who were not. This was not feasible as INM was prescribed to all those who presented with seizure in the ED or on their first visit to our center. Owing to variability in the prescription practice and the high cost of INM, at the first encounter in pediatric neurology services, one tends to encounter both groups of children: one who had used INM and second who had not used INM either because they were not prescribed or they could not purchase owing to the cost.

In the United Kingdom and other European Union (EU) countries, the Practices in Emergency and Rescue medication For Epilepsy managed with Community-administered Therapy (PERFECT) initiative was undertaken to improve the out-of-hospital management of seizures [9]. It is difficult to extrapolate these findings directly in the context of a resource-constraint setting, where there are logistics of distant healthcare services, lack of ambulance service for all, and out-of-pocket expenses for travel and other contingencies. Hence, authors perceive an urgent need to develop guidelines for out-of-hospital management of children with prolonged seizures for resource-constrained setup.

This study describes the practice of INM and introspects the practice of prescribing INM in a resource-constraint setting handling children with epilepsy. These preliminary findings need to be interpreted in light of limited sample size and study design. Further studies are required with a larger sample size from other developing countries with a focus on efficacy and safety of INM in aborting the seizure.

## 5. Conclusion

The present study demonstrates that the use of INM as rescue medication for children with prolonged seizure was safe and effective in three-fourths of those who used it. However, it did not result in a decrease in healthcare utilization parameters like the number of emergency visits, and intensive care requirement. The study findings emphasize the need for improved parent education and training for the use of rescue medication for the management of seizure in children with epilepsy.

## Conflicting/competing interests

No financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

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