



# A hospital-based study on caregiver preferences on acute seizure rescue medications in pediatric patients with epilepsy: Intranasal midazolam versus rectal diazepam

Sunjay Nunley<sup>a,\*</sup>, Peter Glynn<sup>b</sup>, Steve Rust<sup>c</sup>, Jorge Vidaurre<sup>b</sup>, Dara V.F. Albert<sup>b</sup>, Anup D. Patel<sup>b</sup>

<sup>a</sup> Pediatric Neurology, Greenville Health System, 200 Patewood Drive, Suite A350, Greenville, SC 29615, United States

<sup>b</sup> Division of Neurology, FB Suite 4B.3, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, United States

<sup>c</sup> Research Information Solutions & Innovation, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, United States

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## ABSTRACT

**Rationale:** About 20 per 100,000 children have convulsive status epilepticus every year, a life-threatening condition. Benzodiazepines are the first-line treatment for prolonged and recurrent seizures. Our study was designed to gain understanding of caregiver perception of acute seizure treatments.

**Methods:** Our project uses a cross-sectional survey study design using the electronic medical record and a survey at a large academic tertiary children's medical center. Subjects were patients with epilepsy prescribed intranasal (IN) midazolam and/or per rectum (PR) diazepam. The survey was administered to caregivers of children with epilepsy regarding information on the comfort, efficacy, ease of use, and time of administration for patients receiving both abortive seizure medications. Exact binomial tests were employed to determine whether or not differences in caregiver preference exist.

**Results:** One hundred and sixty responses were obtained. Incomplete and duplicate surveys were excluded, leaving 153 responses. Of those responses, 59 respondents reported administering both medications. Among parents who expressed a preference for one medication over the other, more parents felt overall greater comfort with IN midazolam compared with rectal diazepam ( $p = 0.0004$  and  $p = 0.001$ ), IN midazolam was perceived as easier to use (68%,  $p = 0.0038$  and 74%,  $p = 0.0004$ ) and more effective (87%,  $p < 0.0001$ ) than rectal diazepam. Intranasal midazolam was found to be superior to rectal diazepam in several other categories as well.

**Conclusions:** These parents of children with epilepsy report increased ease of use, comfort, and efficacy with IN midazolam as compared with rectal diazepam suggesting that a readily available form of IN midazolam would be well received in the pediatric population.

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## 1. Introduction

Convulsive status epilepticus occurs in an estimated 20 per 100,000 children per year and is associated with a high risk of mortality [1]. The International League Against Epilepsy (ILAE) recommends that treatment of continuous convulsive seizures starts at 5 min. Seizures occurring in clusters also require acute treatment, as these repetitive seizures can lead to status epilepticus [2]. Benzodiazepines are the first-line treatment of convulsive status epilepticus, and several formulations of benzodiazepines are available for usage [3]. There is level A evidence for the use of intramuscular (IM) midazolam, intravenous (IV) lorazepam, and IV diazepam for seizures lasting greater than 5 min [4]; however, these routes of administration are not practical for use by

parents and caregivers outside the hospital. Per rectum (PR) diazepam, intranasal (IN) midazolam, and buccal midazolam, on the other hand, have level B evidence to be used in the home and community setting [4]. The US Food and Drug Administration (FDA) approved the usage of PR diazepam (Diasat®) in 1997 for acute repetitive seizures, and it has been widely used since for this indication and also off label for prolonged seizures. More recently, research shows that IN midazolam achieves seizure cessation more quickly, has a better safety profile, and also reduces hospital admissions when compared with PR diazepam [5–7]. A recent retrospective study at our institution also demonstrated that patients prescribed IN midazolam had fewer visits to the emergency department (ED) and urgent care compared with PR diazepam [8].

The aim of our study was to gain further understanding regarding parental and caregiver perception of IN midazolam and PR diazepam at a tertiary level IV epilepsy center and large academic medical institution, Nationwide Children's Hospital. We sought to gather information from caregivers of patients with epilepsy and to gather demographic

\* Corresponding author at: Pediatric Neurology, Greenville Health System, 200 Patewood Drive, Suite A350, Greenville, SC 29615, United States.

E-mail address: [SNunley@ghs.org](mailto:SNunley@ghs.org) (S. Nunley).

data of patients prescribed both medications. We hypothesized that caregivers would find IN midazolam easier to use, have more comfort giving it, and find it more efficacious than PR diazepam.

## 2. Methods

### 2.1. Study design

Our study was a cross-sectional survey study design that was reviewed and approved by the Institutional Review Board (IRB) at Nationwide Children's Hospital. We utilized the electronic medical record. We implemented a survey managed in REDCap™ [9]. Subjects were children with epilepsy prescribed IN midazolam, PR diazepam, or both medications for acute seizure rescue treatment. Patients with epilepsy aged 0–23 years were eligible for inclusion in our study. Patients who met our inclusion criteria were identified and approached for participation in the study. Those who agreed to participate were administered the survey instrument by the study coordinator.

### 2.2. Participant recruitment

Patients with epilepsy aged 0–23 years who had been prescribed either IN midazolam or PR diazepam, had received a refill of either medication at least 12 months prior to study start date, and had at least one outpatient neurology clinic appointments in the preceding 12 months of study start date were eligible for inclusion in our study. Patients who met our inclusion criteria were identified by the study coordinator and approached in outpatient neurology clinic for participation in the study. We did this by querying the electronic health record (EHR) database for all patients prescribed a rescue medication, had refilled that medication within the past 12 months, and had a neurology outpatient clinic appointment in the next 6–12 months. Those who were agreed to participate were consented, and the survey instrument was administered by the study coordinator. Families were offered compensation for their time and effort to help with willingness to take the survey.

### 2.3. Survey instrument

The survey instrument (see Supplementary material) was developed by the study group and utilized 5-point and 3-point Likert scales to ask questions regarding comfort, perceived efficacy, ease of use, and time of administration for patients receiving one or both abortive seizure medications. The survey was piloted by a small group of 10 families of children with epilepsy for feedback and comment on the instrument itself. Amendments were made to the survey as needed based on feedback from the pilot participants. A research coordinator who did not know the patient obtained consent and administered the survey. The IRB did not require a cooling off period between delivery of the study information to potential participants and collection of survey data from those potential participants that were consented. The likely basis for this decision is the fact that neither participation in the study nor a decision not to participate in the study had any effect on the medical care received by the patient. Survey administration occurred while the patient was present in clinic electronically on an iPad, over the phone, or online via an online link provided in clinic. Data were automatically entered into a REDCap™ database [9].

For internal validity, select comparison questions were asked a second time using a 3-point Likert scale to confirm the caregiver's perception regarding the medications.

### 2.4. Analysis

Results for 11 comparison questions (Table 1) were statistically analyzed. The results for comparison questions employing a 5-point Likert scale were converted to a 3-point Likert scale prior to statistical analysis. For each question, the percentage of caregivers expressing a preference

**Table 1**

Questions comparing IN midazolam to PR diazepam posed to respondents that have administered both rescue medications.

Comparison question number	Question	Likert scale points
1	My child's Versed <sup>a</sup> is easier to use than his/her Diastat <sup>a</sup> .	5
2	My child experiences less side effects from his/her Versed compared to his/her Diastat.	5
3	It would be easier for me to explain how to use my child's Versed with my child's other caregivers and school than explaining Diastat.	5
4	I am more comfortable with my child's Versed compared to their Diastat	5
5	Which medication do you think is easier to use?	3
6	Which medicine do you think takes more time to administer?	3
7	Which medication are you more comfortable using?	3
8	Which medication costs you more?	3
9	Which medication do you think is more effective?	3
10	Which medication do you think has fewer side effects?	3
11	Which medication is available for your child's school?	3

<sup>a</sup> Brand names were used on the survey as caregivers were more familiar with these names.

for one medication over the other and the percentage of those respondents that expressed a preference for IN midazolam were calculated. The latter percentages were tested to determine whether or not they are statistically greater than 50% using an exact binomial test conditioned on the number of caregivers expressing a preference. One-sided p-values are reported since our a priori hypothesis was that IN midazolam would be preferred over PR diazepam. A descriptive analysis of the length each medication that had been prescribed was also performed.

## 3. Results

One hundred and sixty responses were obtained. Seven surveys were excluded because of surveys that were not completely finished or duplicate surveys that were completed, leaving 153 for analysis. Of these respondents, 36 (24%) reported their child was prescribed IN midazolam, 19 (12%) were prescribed PR diazepam, and 98 (64%) were prescribed both during the patient's course of epilepsy. For the 98 patients prescribed both medications, patient ages ranged from 3 to 22 years with a mean age of 10.5 years, and there were 46 female (47%) and 52 male patients (53%). Of the patients prescribed both medications, fifty-nine (59) respondents reported administration of both medications, and these respondents are the focus of the analysis in this manuscript. For this smaller group of 59 patients, patient ages ranged from 3 to 22 years with a mean age of 10.6 years, and there were 30 female (51%) and 29 male patients (49%). Based on gender and age, the 59 patients that were administered both medications appear to be a representative sample of the 98 patients that were prescribed both medications.

More caregivers felt that IN midazolam was easier to use (68%,  $p = 0.0038$  and 74%,  $p = 0.0004$ ), was more effective (87%,  $p < 0.0001$ ), and felt more comfortable with IN midazolam (74%,  $p = 0.0004$  and 75%,  $p = 0.001$ ). In addition, caregivers perceived that IN midazolam has less side effects (71%,  $p = 0.0083$  and 68%,  $p = 0.0436$ ), is easier to explain how to use from one caregiver to another (71%,  $p = 0.0019$ ), and is more readily available at school (82%,  $p = 0.0002$ ). Further comparisons are shown in Table 2.

Caregivers have more comfort with IN midazolam despite often being prescribed for a shorter period of time compared with PR diazepam. Of the patients prescribed both medications, 25 out of 53 (data for all 59 were not available, 4 patients had no response for how long they had been prescribed midazolam, and 2 different participants had no response for how long they had been prescribed diazepam) patients

**Table 2**

Results for questions comparing IN midazolam to PR diazepam posed to respondents that have administered both rescue medications.

Comparison question number	Concept	% with a preference	% favoring IN midazolam	p-Value
<b>1</b>	<b>Ease of use</b>	<b>97%</b>	<b>68%</b>	<b>0.0038</b>
<b>2</b>	<b>Fewer side effects</b>	<b>59%</b>	<b>71%</b>	<b>0.0083</b>
<b>3</b>	<b>Easier to explain</b>	<b>83%</b>	<b>71%</b>	<b>0.0019</b>
<b>4</b>	<b>Comfort with medication</b>	<b>90%</b>	<b>74%</b>	<b>0.0004</b>
<b>5</b>	<b>Ease of use</b>	<b>90%</b>	<b>74%</b>	<b>0.0004</b>
6	Less time to administer	76%	62%	0.0676
<b>7</b>	<b>Comfort using medication</b>	<b>73%</b>	<b>75%</b>	<b>0.0010</b>
8	Lower medication cost	34%	55%	0.4119
<b>9</b>	<b>Medication effectiveness</b>	<b>64%</b>	<b>87%</b>	<b>&lt;0.0001</b>
<b>10</b>	<b>Fewer side effects</b>	<b>47%</b>	<b>68%</b>	<b>0.0436</b>
<b>11</b>	<b>Availability at school</b>	<b>56%</b>	<b>82%</b>	<b>0.0002</b>

Items in bold are statistically significant.

had their prescription for PR diazepam longer than IN midazolam versus only 4 patients who had their IN midazolam prescription longer than PR diazepam. It is unclear whether the novelty of IN midazolam contributes to this finding. Table 3 is a cross-tabulation of length prescribed for the two medications for the 53 caregivers providing data for both variables. In Table 3, results for 25 caregivers are below the diagonal (PR diazepam prescription length longer than for IN midazolam) while the results for only four caregivers are above the diagonal.

#### 4. Discussion

This study shows that caregivers are more comfortable giving IN midazolam and find it easier to use compared with PR diazepam. Prior studies have shown that IN midazolam is more efficacious at stopping seizures, has fewer side effects, and is more cost-effective than PR diazepam [5,8,10,11]. Caregivers report better ease of use and more comfort with IN midazolam which may lead to a greater number of seizures stopped in the home and community setting. Our survey findings may provide one explanation for the results of our prior study showing that patients using IN midazolam utilize the emergency and urgent care departments less than patients using PR diazepam [8]. Practitioners might also be more apt to prescribe the relatively novel medication after learning that parents are more comfortable administering this medication outside of the hospital.

We found that these caregivers believe that IN midazolam had fewer side effects than PR diazepam. Since caregivers perceive that IN midazolam is easier to use, they are likely able to give their child the medication more quickly which may lead to less overall side effects from the seizure itself. Caregivers found IN midazolam to be superior in multiple categories despite being prescribed the medication for a shorter period of time. A pharmacist is available in our clinic to provide caregiver education for seizure rescue medications, which can ease a parent's mind regarding administration of seizure rescue medications. Patients also receive a seizure action plan at the end of the clinic visit.

A prior study showed that, depending on delivery of the medication to treat pediatric status epilepticus, delays in administration can be seen in the outpatient setting [12]. Another study found that parents prefer a nonrectal rescue medications [13]. Our study suggests that parents

and caregivers have a greater understanding of IN midazolam as an acceptable form of a seizure rescue medication. Indeed, results of a randomized, controlled trial showed evidence of safety and tolerability of an IN formulation of midazolam and were presented at the American Epilepsy Society annual meeting in 2017 [14]. In addition, they may be more likely to give the medication in the prehospital setting given its perceived increased ease of use over PR diazepam. Once the novelty of IN medications is diminished, time to administration may be decreased. Further analyzing how long caregivers have had IN midazolam and correlating this with their perception could help confirm this hypothesis in a separate study.

##### 4.1. Strengths and limitations

The study utilized a survey administered to caregivers. By administering most surveys in person, we minimized error since the survey was given in a uniform fashion. Other surveys were either performed over the phone or rarely by the caregiver online. However, limitations were present in our study. Although many more patients were identified from the EHR database as eligible, participants were recruited during their appointment, therefore, there may be a selection bias because of convenience sampling in those who were seen in clinic during the study period. Furthermore, offering monetary compensation for participation may have led to some additional responder bias. The survey instrument used a Likert scale for responses. Free text options were available for some questions to provide further explanation, but these were not mandatory. Perhaps, in future studies, obtaining a more qualitative understanding of parental preferences may shed more light on where differences may lie. In addition, recall bias may have been present when parents answered retrospective questions in the survey. The person surveyed was the primary caregiver such as the parent or guardian rather than other family members, teachers, or other caregivers who may have also given the rescue medications to the patient and can also provide valuable information. While we had an overall sample size of 160, only 59 caregivers (37%) reported using both medications allowing for comparison between the two. There was no way of knowing whether or not a caregiver actually ever gave their child a rescue med prior to administering the survey. Further, information was collected from only one site, which may not represent thoughts of caregivers in other regions of the country.

#### 5. Conclusions

This study demonstrates evidence that IN midazolam is superior to PR diazepam for cessation of prolonged seizures and seizure clusters, in the eyes of caregivers. By understanding more about caregiver perception regarding the medications, we are able to better predict whether the medication will be more likely used in the prehospital setting. Our results suggest that IN midazolam should be more widely accepted in the community setting as a safe and effective way to stop

**Table 3**

Length of time prescribed PR diazepam vs. IN midazolam.

		How long prescribed IN midazolam?				Total
		0–5 months	6–12 months	13–24 months	>24 months	
How long prescribed PR diazepam?	0–5 months	0	0	0	2	2
	6–12 months	1	2	0	0	3
	13–24 months	0	2	2	2	6
	>24 months	3	9	10	20	42
Total		4	13	12	24	53

prolonged seizures and seizure clusters based on a greater sense of comfort and better safety profile recognized by caregivers of children with epilepsy. With greater usage of IN midazolam in communities across the country, larger prospective studies can be done to further examine its use. Implementing a clinical pharmacist into epilepsy clinics may help with the education of families and lead to better comfort with rescue medications. Considering this study along with others, IN midazolam usage in children with epilepsy stops seizures sooner [5], reduces healthcare utilization [8], and is associated with greater parental satisfaction and better perception of side effects. Therefore, the information obtained in this study adds to a growing body of evidence of the benefits of using IN midazolam to stop prolonged seizures and seizure clusters in the prehospital setting, which may ultimately save lives as well as healthcare dollars.

### Conflict of interest

A.P. conducts research with Greenwich Biosciences, Pediatric Epilepsy Research Foundation (PERF), and National Institutes of Health (NIH). He also consults for Greenwich Biosciences and LivaNova. No other authors have any conflicts of interest.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.yebeh.2018.12.007>.

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