

# Prehospital Intranasal Midazolam for the Treatment of Pediatric Seizures

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**Background:** The local emergency medical services (EMS) council implemented a new pediatric treatment protocol using a Mucosal Atomization Device (MAD) to deliver intranasal (IN) midazolam for seizure activity.

**Methods:** We sought to compare outcomes in seizing pediatric patients treated with IN midazolam using a MAD (IN-MAD midazolam) to those treated with rectal (PR) diazepam, 18 months before and after the implementation of the protocol.

**Results:** Of 857 seizure patients brought by EMS to our emergency department (ED), 124 patients (14%) had seizure activity in the presence of EMS and were eligible for inclusion in this study. Of the 124 patients eligible for this study, 67 patients (54%) received no medications in the prehospital setting, 39 patients (32%) were treated with IN-MAD midazolam, and 18 patients (15%) were treated with PR diazepam. Median seizure time noted by EMS was 19 minutes longer for PR diazepam (30 minutes) when compared with IN-MAD midazolam (11 minutes,  $P = 0.003$ ). Patients treated with PR diazepam in the prehospital setting were significantly more likely to have a seizure in the ED (odds ratio [OR], 8.4; confidence interval [CI], 1.6–43.7), ED intubation (OR, 12.2; CI, 2.0–75.4), seizure medications in the ED to treat ongoing seizure activity (OR, 12.1; CI, 2.2–67.8), admission to the hospital (OR, 29.3; CI, 3.0–288.6), and admission to the pediatric intensive care unit (OR, 53.5; CI, 2.7–1046.8).

**Conclusions:** The IN-MAD midazolam controlled seizures better than PR diazepam in the prehospital setting and resulted in fewer respiratory complications and fewer admissions.

**Key Words:** seizures, prehospital, emergency medical services (EMS), intranasal

Seizures are the most common medical problem for emergency medical services (EMS) transport in pediatric

patients, accounting for roughly 15% of all pediatric EMS calls in the United States.<sup>1</sup> Prolonged or recurrent seizure activity persisting for 30 minutes or more can cause significant morbidity and mortality that is directly correlated with seizure duration.<sup>1–3</sup> The sooner that a seizure is treated, the more likely the seizure will be controlled.<sup>1</sup> It is recommended that seizures lasting longer than 5 minutes should be treated with an anticonvulsant.<sup>1</sup> The administration of anticonvulsant therapy in the prehospital setting may shorten the duration of a seizure.<sup>4</sup>

Benzodiazepines are currently the first-line therapy for seizures. Diazepam is typically the sole anticonvulsant medication available on most ambulances for the acute management of all types of seizures in the prehospital setting.<sup>1</sup> Diazepam may be administered intravenously (IV), rectally (PR), or through an endotracheal tube; it is ineffective for seizure control when given intramuscularly (IM) and is not suitable for intranasal (IN) administration.<sup>5,6</sup>

Rectal diazepam has been available for seizure control in the prehospital setting for more than 20 years.<sup>7–9</sup> Its popularity is due partly to the potential difficulty of IV placement, especially in a child with seizures. However, disadvantages of PR diazepam include the social awkwardness for patients and providers, potential for rejection, variable and unpredictable drug absorption, hepatic first-pass metabolism, and higher doses may be required for a clinical response.<sup>8,9</sup> Diazepam accumulation can cause respiratory depression, which may require endotracheal intubation, especially if used in conjunction with other anticonvulsants.<sup>10</sup> The cost of PR diazepam (Diastat) is roughly \$100/dose.

In the prehospital setting, midazolam may provide an alternative to PR diazepam.<sup>7,8,10–22</sup> Midazolam can be administered via different routes: IV, IM, endotracheal tube, PR, buccal, and IN.<sup>23</sup> Its cost ranges from \$10 to \$13/dose. Midazolam is water soluble but becomes fat soluble at physiological pH allowing it to cross the nasal mucosa into the cerebral spinal fluid with a rapid onset of action and rapid metabolism.<sup>23</sup> Because IN midazolam is directly absorbed into the cerebral spinal fluid, it is not subject to hepatic first-pass metabolism and less likely to accumulate.<sup>23</sup> Because PR diazepam is absorbed through the gastrointestinal tract, it is subject to “first pass metabolism” and is more likely to accumulate with successive doses than diazepam.<sup>23</sup> In addition to the pharmacological advantages, the convenience of IN administration and the social acceptability may make IN midazolam the preferred treatment of seizures in the prehospital setting.<sup>7</sup>

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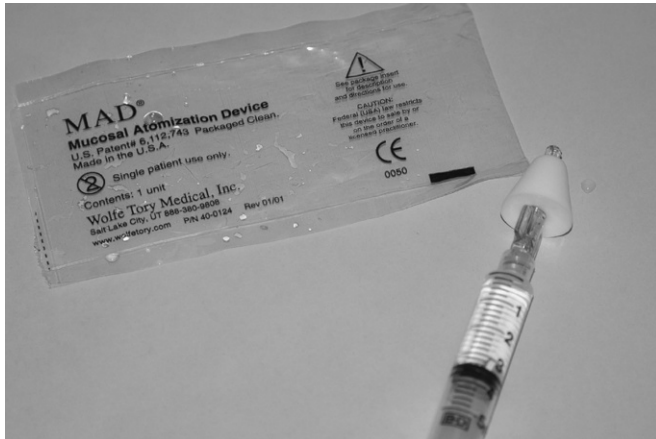


FIGURE 1. Mucosal Atomization Device.

The local EMS council enacted a new protocol using IN midazolam for first-line treatment of seizures, and emergency medical technician (EMT) paramedics received training for the administration of IN midazolam.<sup>24</sup> Adults and children with active seizure activity (of any type) received IN midazolam using a Mucosal Atomization Device (MAD) instead of the traditional treatment with PR diazepam.<sup>24</sup> The MAD is an applicator placed on top of a syringe that distributes midazolam in a 30- $\mu$  particle size, coating the nasal mucosa (Fig. 1), and its cost is \$2.45.<sup>25</sup> Intranasal midazolam administered with the MAD (IN-MAD midazolam) should enhance rapid nasal absorption, achieving effective plasma and cerebral spinal fluid concentrations.<sup>25</sup> This study uniquely uses the MAD for administration of midazolam.

We sought to compare the effectiveness and complications of IN-MAD midazolam with that of PR diazepam for treatment of childhood seizures in the prehospital setting.

## METHODS

The setting for this study was a freestanding children's hospital that serves as an American College of Surgeons level I trauma and referral center for 5 states. The EMS council oversees prehospital care for the most populous region in the state. The EMS council has representatives from roughly 70 organizations, including 13 hospitals, law enforcement, and other nonresponder agencies. The county surrounding this children's hospital has approximately 50 EMS agencies.

The local EMS council's new protocol directed EMT paramedics to treat seizure activity in children and adults using IN-MAD midazolam. Paramedics received training to use IN-MAD midazolam as a first-line therapy for the treatment of seizures lasting longer than 5 minutes. This new protocol replaced diazepam as the first-line treatment of seizure activity; other protocol changes are outlined in Table 1. All patients who received IN-MAD midazolam were transported to an ED by EMT paramedics. The State Department of Health Bureau approved the protocol changes.

Implementation of this new protocol provided the opportunity to compare IN-MAD midazolam with PR diazepam. Patients treated with IN-MAD midazolam for seizures after July 1, 2003, were compared with historical controls treated with PR diazepam. Historical controls were patients younger than 18 years treated with PR diazepam by EMS for seizure activity that came directly to our hospital. Patients were identified using an ED computerized patient tracking system (Logicare, Eau Claire, Wis). All patients who were transported to the ED via ambulance or helicopter from January 1, 2002, to December 31, 2004, with a chief complaint or discharge diagnosis of seizure (of any type) were eligible for inclusion in the study.

Patients were included in the study if they were younger than 18 years, had a seizure in the presence of an EMS provider, received PR diazepam or IN midazolam for their seizure in the prehospital setting, and arrived at the study ED via EMS.

Patients were excluded from the study if they were transferred from another facility, they received a rescue medication at home for seizure activity before EMS arrival, they received more than 1 prehospital medication, or the seizure was not witnessed by EMS providers.

Emergency medical services, ED, and hospital medical records were reviewed. Data collected included demographic information, medications, medical history, seizure activity noted in the ED, respiratory complications, and disposition. Information regarding the prehospital and ED treatment of the seizure and vital signs was recorded. Emergency medical services-witnessed seizure times was defined as prolonged or recurrent seizure activity persisting for 30 minutes or more. Emergency medical services-witnessed seizure time were defined as the time from EMS arrival to time seizure stopped or patient arrival to the hospital. Total seizure time was the estimation of the total length of 1 seizure or the sum time of multiple seizures from parental history, EMS records, and hospital records. When available, EMS-witnessed seizure time, total seizure time, and total hospital charges were calculated.

Our primary outcome measure was the presence of a seizure in the ED. Our secondary outcome measures were total seizure time, EMS seizure duration, respiratory

TABLE 1. Comparison of Midazolam and Diazepam Protocols

Instructions	Midazolam	Diazepam
Preparation	Apply oxygen Suction nose if there are secretions	Apply oxygen
Indication	Seizure >5 min	Seizure >5 min
Dose	0.2 mg/kg	0.3–0.5 mg/kg
Route	Intranasal: divided into each nares using the MAD	Rectal
Maximum dose	10 mg	20 mg
Repeat dose	0.2 mg/kg 5 min after first dose	0.25 mg/kg if seizure persists

**TABLE 2.** Demographic Data and Seizure Time for Patients Treated With IN-MAD Midazolam and PR Diazepam

Characteristics	IN Midazolam	PR Diazepam	P
Demographic data			
No. patients (n = 57)	39	18	—
Median age	4.5 yrs	2.9 yrs	0.27*
Age range	8 mo–16 yrs	1–17 yrs	
Male, n (%)	18 (46)	10 (56)	0.51 <sup>†</sup>
History of seizures, n (%)	32 (82)	12 (67)	0.20 <sup>†</sup>
History of anticonvulsants, n (%)	24 (62)	12 (67)	0.71 <sup>†</sup>
Median dose of medication given (mg/kg)	0.2	0.3	—
Range of dose given (mg/kg)	0.1–0.4	0.1–0.7	—
EMS-witnessed seizure time (min)			
Median (n)	11 (25)	30 (13)	0.003*
Range	1–50	5–80	—
Total seizure time (min)			
Median (n)	25 (36)	45 (17)	<0.001*
Range	4–105	25–480	—
Median total hospital charges (\$)	1459	6980	<0.0001*

\*Mann-Whitney *U* test.<sup>†</sup> $\chi^2$  test.

complications, status epilepticus (defined as seizure greater than 30 minutes), anticonvulsants given in the ED, disposition, and total hospital charges. We distinguished those patients who received any anticonvulsants in the ED from those who received an anticonvulsant for the acute treatment of ongoing seizure activity.

Data distributions for each variable were assessed and the appropriate parametric or nonparametric test was selected. *T* test, Mann-Whitney *U* test,  $\chi^2$  test (Pearson and Fisher exact), and crude odds ratios (ORs) were used for bivariate analyses. Multivariate analyses were conducted by calculating adjusted ORs controlling for age, sex, history of seizures, and history of seizure medications using unconditional logistic regression. Significance was defined as  $\alpha$  less than 0.05. Approval for research of human subjects was obtained from the University of Utah Institutional Review Board, the State Department of Health, and the Bureau of EMS. This research was not sponsored by any companies. This has no relationship between the authors and the development, evaluation, and promotion of the MAD.

## RESULTS

During the study period, we identified 857 patients who were brought into the ED by EMS with the chief complaint or discharge diagnosis of seizure.

Seven hundred thirty-three patients were excluded from the study for the following reasons: 431 patients (59%) had no seizure activity in the presence of EMS, 265 patients (36%) were transferred from an outside facility to our institution, 27 patients (4%) did not have a seizure, 8 patients (1%) were 18 years or older, and 2 patients (<1%) left without being seen.

Of the 124 patients eligible for inclusion in the study with seizure activity witnessed by EMS, 67 patients (54%) received no medications in the prehospital setting, 39 patients (32%) were treated with IN-MAD midazolam, and 18 patients (15%) were treated with PR diazepam. During the course of the study, it is noteworthy that the proportion of patients treated with an anticonvulsant in the prehospital setting did not vary (14/41 or 34% before July 1, 2003, and 41/83 or 49% after July 1, 2003; OR, 1.78; CI, 0.77–4.14). Fifty-seven patients (39 patients treated with IN-MAD and 18 patients treated with PR diazepam) make up the study group.

Table 2 presents the demographic data and seizure time for the 57 study patients. There were no significant differences between the IN-MAD midazolam and PR diazepam groups with regard to age, sex, history of seizures, and history of seizure medications. As noted in Table 1, the medication dose in the protocol is 0.2 mg/kg up to 10 mg for IN-MAD midazolam and 0.3 to 0.5 mg/kg up to 20 mg for PR diazepam. The median dose and range are noted in Table 2. We compared the difference of the protocol median dose of IN-MAD midazolam (0.2 mg/kg) and PR diazepam (0.4 mg/kg) with that of the actual dose that the patient received. There was no difference noted between the 2 groups ( $P = 0.12$ , Mann-Whitney *U* test).

Distribution of the etiology of the seizure was compared between the 2 groups (Table 3). The seizure was categorized in one of the following groups: seizure not otherwise specified, febrile, generalized, absence, complex partial, simple partial, traumatic, metabolic, ingestion, or status epilepticus. There was no statistical difference in

**TABLE 3.** Etiology of Seizure: IN Midazolam Versus PR Diazepam

Type of Seizure	IN Midazolam, n (%)	PR Diazepam, n (%)	P
Seizure not otherwise specified	7 (18)	0 (0)	—
Febrile seizure	4 (10)	1 (6)	—
Generalized seizure	13 (33)	6 (33)	—
Complex partial seizure	4 (10)	2 (11)	—
Metabolic	1 (3)	0 (0)	—
Status epilepticus	10 (25)	9 (50)	—
Total	39	18	—
Distributional differences in type of seizures between the 2 groups	—	—	0.29*

\*Pearson  $\chi^2$  test.

**TABLE 4.** The Outcome Measures of Patients Treated With IN-MAD Midazolam Versus PR Diazepam for Seizure Activity Noted by EMS

Outcome Measures	IN Midazolam, n (%) (n = 39)	PR Diazepam, n (%) (n = 18)	OR	95% CI	Adjusted OR*	95% CI
Oxygen given by EMS	33 (92)	15 (94)	1.36	0.10–76.29	0.95	0.08–11.70
EMS bag-mask ventilation	2 (6)	5 (31)	<b>7.73</b>	<b>1.03–87.70</b>	6.65	0.90–49.29
EMS intubation	1 (6)	1 (3)	2.24	0.03–179.99	2.79	0.12–65.72
Seizure in ED	15 (38)	13 (72)	<b>4.16</b>	<b>1.08–17.64</b>	<b>8.43</b>	<b>1.63–43.71</b>
Oxygen required at ED disposition	9 (23)	14 (78)	<b>11.67</b>	<b>2.64–58.37</b>	<b>26.97</b>	<b>4.47–162.79</b>
ED intubation	2 (5)	7 (39)	<b>11.77</b>	<b>1.79–125.09</b>	<b>12.21</b>	<b>1.98–75.37</b>
Anticonvulsants given in ED	22 (56)	16 (89)	<b>6.18</b>	<b>1.16–61.00</b>	<b>9.23</b>	<b>1.49–57.19</b>
Anticonvulsants given in ED to treat seizure activity	13 (33)	13 (72)	<b>5.2</b>	<b>1.33–22.23</b>	<b>12.14</b>	<b>2.17–67.79</b>
Status epilepticus (>30 min)	10 (26)	9 (50)	2.8	0.74–10.56	<b>4.35</b>	<b>1.04–18.18</b>
Hospital admission	19 (49)	17 (94)	<b>17.89</b>	<b>2.26–784.27</b>	<b>29.32</b>	<b>2.98–288.63</b>
PICU admission	3 (16)	10 (59)	<b>7.62</b>	<b>1.31–53.32</b>	<b>53.54</b>	<b>2.74–1046.84</b>

\*Adjusted for age, sex, history of seizures, and history of seizure medications.  
Data in boldface are statistically significant.

the distribution of seizure etiology between the IN-MAD midazolam and the PR diazepam group ( $P = 0.29$ ).

Emergency medical services–witnessed seizure time data were available for 25 (64%) of the 39 patients who received IN-MAD midazolam and 13 (72%) of the 18 patients who received PR diazepam. There was no statistical difference noted between the proportion of the 2 groups which had data available ( $P = 0.546$ ). For total seizure time, data were available for 36 of the 39 patients who received IN-MAD midazolam and 17 of the 18 patients who received PR diazepam. Median seizure time noted by EMS was 19 minutes longer (30 minutes vs. 11 minutes,  $P = 0.003$ ), and total seizure time was 20 minutes longer (45 minutes vs. 25 minutes,  $P < 0.001$ ) for PR diazepam when compared with IN-MAD midazolam (Table 2). Median total hospital charges were significantly lower (\$1459 vs. \$6980,  $P < 0.0001$ ) for the patients who received IN-MAD midazolam as compared with PR diazepam.

Univariate and logistic regression analyses were performed to compare outcome variables in both treatment groups (Table 4). Patients treated with PR diazepam were significantly more likely to require EMS bag-mask ventilation, have a seizure in the ED, require ED intubation, require oxygen at ED disposition, require anticonvulsants in the ED, require anticonvulsants in the ED to treat seizure activity, need hospital admission, and need pediatric intensive care unit (PICU) admission. There were no differences between the groups for oxygen given by EMS (standard EMS procedure for both seizure protocols), EMS intubation, or status epilepticus.

Logistic regression analysis was then performed to control for potential effect measure modification or confounding by age, sex, history of seizures, and use of seizure medications (Table 4). Adjusted ORs demonstrated that the need for EMS bag-mask ventilation was no longer significantly different between the 2 groups, but status epilepticus was now more likely for the PR diazepam group

when controlling for age, sex, history of seizures, and history of seizure medications. Patients who were treated with PR diazepam were still significantly more likely to have a seizure in the ED, require ED intubation, require oxygen at ED disposition, require anticonvulsants in the ED, require anticonvulsants in the ED to treat seizure activity, need hospital admission, and need PICU admission when compared with the IN-MAD midazolam group.

## DISCUSSION

We compared IN midazolam using the MAD with PR diazepam for the prehospital treatment of pediatric seizures. Our data demonstrate that IN-MAD midazolam is superior and has fewer side effects. This is the first study that looks at the use of MAD to administer IN midazolam for the treatment of pediatric seizures.

In our study, the 2 treatment groups were similar with regard to age, sex, history of seizures, and previous seizure medications. Yet, the patients treated with IN-MAD midazolam had significantly shorter total seizure time, shorter EMS-witnessed seizure time, and lower total hospital charges. Patients who received IN-MAD midazolam were also less likely to have recurrent seizures, respiratory complications, hospital admissions, or PICU admissions when compared with those receiving PR diazepam. Although not statistically significant, more patients were treated for their seizures after July 1, 2003, with the new IN-MAD midazolam protocol. We believe that this is secondary to the ease in administration.

Studies in other settings found IV diazepam and IN or IV midazolam to be equally effective in controlling seizures with no difference in side effects.<sup>7,8,10–18,20–23,26,27</sup> In 70 pediatric inpatients, Mahmoudian and Zadeh<sup>27</sup> showed that IN midazolam and IV diazepam had equal efficacy without

significant side effects. The mean time to seizure control (time from start of seizure to treatment) was significantly faster ( $P = 0.007$ ) in the midazolam group compared with the diazepam group.<sup>27</sup> One study limitation is that placement of an IV may have delayed treatment in the diazepam group. Another study compared IN midazolam to that of IV diazepam in the ED setting.<sup>16</sup> Intranasal midazolam controlled seizures in 23 of 26 patients, and IV diazepam controlled seizures in 24 of 26 patients.<sup>16</sup> They demonstrated no difference in side effects but showed that the mean time from arrival to the hospital to starting treatment and the mean time to control seizures was reduced by 2 minutes in the midazolam group.<sup>16</sup> Sample size may have limited the investigator's ability to show a difference in side effects between the 2 groups. Although our study also had a small sample size, we were able to show a difference in side effects (respiratory depression). Rainbow et al<sup>19</sup> demonstrated that IM or IV midazolam controls seizures as effectively as IV or PR diazepam in the prehospital setting. Here, patients treated with midazolam had less respiratory depression and decreased time to treatment.<sup>19</sup> This investigation did not distinguish the route of medication administration. All of these studies used IV diazepam for the treatment of seizures. Although these 3 studies demonstrate no difference in safety between midazolam and diazepam, placing an IV line in a patient with seizure activity can be difficult for even an experienced person and may delay treatment.

Intranasal midazolam has been shown to be as effective as PR diazepam in various community settings.<sup>10,13</sup> Fisgin et al<sup>13</sup> compared IN midazolam with PR diazepam for the treatment of pediatric seizures in the ED. Intranasal midazolam was more likely to treat seizure activity within the first 10 minutes (87%, 20/23 vs. 60%, 13/22;  $P < 0.05$ ).<sup>13</sup> In addition, more patients required a second anticonvulsant to stop seizures in the diazepam group ( $P < 0.05$ ).<sup>13</sup> Although the results of this study are encouraging, it was not conducted in the prehospital setting. Scheepers et al<sup>10</sup> describe using IN midazolam in adolescents and adults with severe epilepsy at an Inpatient Epilepsy Treatment Center. Of the 84 seizures in 22 patients, 79 of these were successfully treated.<sup>10</sup> Of the 5 treatment failures, 3 were thought to be secondary to poor technique delivering the medication.<sup>10</sup> Two treatment failures received the drug buccally; 1 patient was thought to have a psychogenic nonepileptic seizure, and the other patient responded initially but then had another seizure within an hour requiring further rescue treatment.<sup>10</sup> In these studies, midazolam was dripped into the nares with a syringe whereby it is more likely ingested. Our study used the MAD to effectively coat the nasal mucosa, which theoretically would achieve cerebral spinal fluid concentrations rapidly.

In community settings, several studies have described IN midazolam for the treatment of seizures, noting very few side effects.<sup>7,8,13</sup> Jeannet et al<sup>8</sup> used IN midazolam to control seizure activity in 26 patients (11 treated at home and 17 treated in the hospital). These 26 children had a total of 125 seizures; 122 seizures (98%) stopped within 10 minutes (average of 3.6 minutes) without serious side effects noted.<sup>8</sup>

Two of the hospitalized patients did not respond, and 3 patients had a seizure reoccur within 3 hours.<sup>8</sup> Fisgin et al<sup>12</sup> administered IN midazolam to 22 children for a total of 54 seizures that were stopped on 48 occasions (89%) without any respiratory compromise. Questionnaires were given to all those who used IN midazolam (30 parents, school assistants, and teachers).<sup>12</sup> Ninety percent had no difficulty giving the medication and of the 15 people who had also administered PR diazepam in the past, 14 preferred IN midazolam.<sup>12</sup> These 2 descriptive studies demonstrate that IN midazolam may be effective and safe for community use. However, community studies comparing IN midazolam to other anticonvulsants have not been performed.

The chief limitation of our study was the incomplete documentation, especially with regard to EMS data sheets. Seizure duration data were not uniformly available. Detailed dictated and written ED notes on all patients provided complete information on seizure in the ED, respiratory depression, medications needed to treat the seizure, and ED disposition. In addition, seizure time noted by EMS did not control for duration of transport to the hospital. Although there was no difference in etiology of seizure (Table 3), we did not compare the comorbidities of our patients. This might have confounded our results of seizure duration, complications, disposition, and total hospital charges. The protocol was gradually implemented across 50 agencies, whereas EMS personnel received training. Training may have varied. Lastly, the 2 treatments groups were not randomized, and the providers were not blinded to the medication used.

In summary, previous studies demonstrate IN midazolam to be equally or more effective than IV diazepam. However, IV placement may be difficult in a child with seizures and delay treatment. Rectal diazepam is an effective and popular anticonvulsant in the prehospital setting but is socially awkward to administer. In hospital settings, IN midazolam is as effective or more effective and associated with fewer complications than PR diazepam. Furthermore, descriptive studies demonstrated IN midazolam to be an effective and safe anticonvulsant for the community. Uniquely, our study used the MAD for administration of midazolam and compared IN-MAD midazolam to PR diazepam in the prehospital environment. Our study results demonstrate that IN-MAD midazolam is more effective and safe and had lower total hospital charges when compared with PR diazepam for the prehospital treatment of pediatric seizures.

Early treatment of seizures reduces reoccurrence of seizures and the morbidity and mortality associated with seizure activity.<sup>1-3,11</sup> We have shown IN-MAD midazolam controlled seizures better than PR diazepam in the prehospital setting with fewer respiratory complications, fewer hospital and PICU admissions, and lower total hospital charges. Given the ease of administration of IN-MAD midazolam and the results of our study, we recommend the use of IN-MAD midazolam for the prehospital treatment of pediatric seizures. Future studies should compare IN-MAD midazolam with PR diazepam for community and home use.

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