JOURNAL CLUB

Intranasal Midazolam vs Rectal Diazepam for the Home Treatment of Acute Seizures in Pediatric Patients With Epilepsy

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Objective: To compare intranasal midazolam, using a Mucosal Atomization Device (IN-MMAD), with rectal diazepam (RD) for the home treatment of seizures in children with epilepsy.

Design: Prospective randomized study.

Setting: Patients' homes and a freestanding children's hospital that serves as a referral center for 5 states.

Patients: A total of 358 pediatric patients who visited a pediatric neurology clinic from July 2006 through September 2008 and were prescribed a home rescue medication for their next seizure.

Intervention: Caretakers were randomized to use either 0.2 mg/kg of IN-MMAD (maximum, 10 mg) or 0.3 to 0.5 mg/kg of RD (maximum, 20 mg) at home for their child's next seizure if it lasted more than 5 minutes.

Outcome Measures: The primary outcome measure was total seizure time after medication administration. Our secondary outcome measures were total seizure time, time to medication administration, respiratory complications, emergency medical service support, emergency department visits, hospitalizations, and caretakers' ease of administration and satisfaction with the medication.

Results: A total of 92 caretakers gave the study medication during a child's seizure (50 IN-MMAD, 42 RD). The median time from medication administration to seizure cessation for IN-MMAD was 1.3 minutes less than for RD (95% confidence interval, 0.0-3.5 minutes; $P = .09$). The median time to medication administration was 5.0 minutes for each group. No differences in complications were found between treatment groups. Caretakers were more satisfied with IN-MMAD and report that it was easier to give than RD.

Conclusions: There was no detectable difference in efficacy between IN-MMAD and RD as a rescue medication for terminating seizures at home in pediatric patients with epilepsy. Ease of administration and overall satisfaction was higher with IN-MMAD compared with RD.

Trial Registration: clinicaltrials.gov Identifier: NCT00326612

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SEIZURES ARE THE MOST COMMON medical problem requiring emergency medical services (EMS) transport in pediatric patients, accounting for up to 25% of all pediatric EMS calls in the United States.[1] Seizures may also account for up to 15% of pediatric air transports.[2]

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Most seizures stop within 5 minutes and do not mandate immediate medical treatment.[3] Seizures that last longer than 5 to 10 minutes, however, are unlikely to stop without treatment and become more difficult to control with time.[3] Prolonged or recurrent seizure activity persisting for 30 minutes may result in significant morbidity and mortality that correlates directly with seizure duration.[3]

Benzodiazepines are currently used as the initial therapy for the treatment of acute seizure activity.[3-6] The administration of benzodiazepines in home and prehospital settings has proven to be safe and effective and may shorten seizure duration.[7,8] Diazepam and midazolam are 2 benzodiazepines commonly used as rescue medications for seizure activity.

In the United States, rectal diazepam (RD) is the most common rescue medication given to families for home treatment of seizures. It is not available intranasally or buccally. Its advantage is that

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no refrigeration or intravenous line is needed. Disadvantages of RD include the social awkwardness for patients and providers, potential for rejection, and its short half-life. Respiratory depression and need for ventilatory support has been reported in some patients who receive diazepam.[9,10] In the United States, the cost of RD (Diastat) is roughly $212 per dose.[11]

Midazolam is available for intranasal (IN) and buccal administration but has not been developed for rectal administration. Intranasal midazolam is also an effective rescue medication that can be given safely.[12-26] Midazolam is effective after buccal administration but has not been studied in the prehospital setting.[27-31] Midazolam is water-soluble but becomes fat-soluble at physiological pH, allowing it to cross the nasal mucosa into adjacent tissues including the cerebrospinal fluid, resulting in rapid onset of action.[32] 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. The cost of IN midazolam is $12 per dose.[11]

The Mucosal Atomization Device (Wolf Tory Medical Inc, Salt Lake City, Utah) is an applicator placed on the syringe hub that distributes liquid for nasal administration in a 30-μ particle size, coating the mucosa.[33] It is relatively inexpensive at $4 per applicator.[11] The Intranasal Midazolam Mucosal Atomization Device (IN-MMAD) should enhance rapid nasal absorption, achieving effective plasma and cerebrospinal fluid concentrations. A previous study at our institution demonstrated that IN-MMAD controlled seizures better than RD in the prehospital setting and resulted in fewer respiratory complications and admissions.[12] We sought to compare the effectiveness and complications of IN-MMAD with those of RD for the home treatment of childhood seizures by primary caretakers.

METHODS

The setting for this study was a freestanding children's hospital that serves as a referral center for 5 states. Patients were identified and recruited through the pediatric neurology clinic. Patients were eligible for the study if they had a known seizure disorder (of any type), were younger than 18 years, and were prescribed a rescue antiepileptic for home use by their neurologist. Patients were excluded from the study if their neurologist did not prescribe a home rescue medication, they were aged 18 years or older, or they were prescribed lorazepam as a home rescue medication.

A research assistant present in the pediatric neurology clinic helped identify potential patients. If a patient was eligible, the attending neurologist who was aware of the study would ask their patient and/or caretakers if they wanted information about a research study comparing home rescue medications. If verbal consent was obtained, a research assistant would explain the study and obtain written consent and assent. Randomization occurred in blocks of 6 using a computer program by a statistician. The sequence was inside a numbered folder and concealed until the intervention was assigned. A secretary assembled the randomized folders. Attending physicians, research assistants, and patients/caretakers were blinded to the rescue drug to be prescribed until after written consent was obtained.

Caretakers were then randomized to use either 0.2 mg/kg of IN-MMAD (maximum, 10 mg) or 0.3 to 0.5 mg/kg of RD (maximum, 20 mg) at home for their child's next seizure that lasted longer than 5 minutes. Caretakers who were present at the clinic visit watched a 5-minute instructional video on how to use their prescribed medication. They were instructed to only give 1 dose of study medication and call "911." If the seizure persisted, EMS could then give a second medication and transport the patient to an emergency department (ED) per their established protocol. Caretakers who gave the study medication recorded their observations using a stopwatch and timing sheets. Times of seizure initiation, medication administration, and seizure cessation were recorded, and sheets were mailed to the principal investigator.

Once the data sheets were received, a research assistant interviewed the caretaker by phone. Those who gave the rescue medication were then asked a series of questions to gauge their satisfaction with the medication. Caretakers answered questions regarding ease of administration and overall satisfaction with the study medication by rating them on an 11-point nominal scale (0, not satisfied and 10, greatly satisfied). Data for several other secondary outcomes were collected (need for additional medical support, hospitalization, length of stay, disposition, repeated seizures within 12 hours).

Recruited caretakers who did not spontaneously report use of the study medication were contacted by phone monthly to address any questions and to remind them of the study. Data was not collected on seizure type associated with study medication administration. If a caretaker reported use of study medication at the time of the phone call, information was obtained at that time.

When available, EMS, ED, and hospital medical records were reviewed for patients who were seen at the study hospital. If a patient was seen at an ED outside the study site, information was obtained from the caretaker by phone.

Our objective was to compare IN-MMAD with RD for the home treatment of seizures in children with epilepsy. Our primary outcome was total seizure time after study medication administration. Our hypothesis was that IN-MMAD would stop seizures faster than RD. Our secondary outcome measures were total seizure time, time to medication administration, respiratory complications, EMS support, ED visits, hospitalizations, and caretakers' ease of administration and satisfaction with the medication.

We conducted a power analysis based on a 10-minute difference in seizure time after administration of study medication. Our previous study found a difference of 19 minutes in seizure time after study medication.[12] To achieve 90% power, we estimated that we would need 61 patients in each group. We also estimated that we would need to enroll 350 patients to collect a total of 120 treated seizures. Once a patient used either study medication, their participation in the study was terminated.

We used Wilcoxon rank sum and Mann-Whitney *U* tests to compare times between the IN-MMAD and RD groups and to estimate 95% confidence intervals (CIs) for differences.[34,35] Treatment differences for categorical outcomes were estimated using exact odds ratios from logistic regression models. Analyses were performed using SAS/STAT software (version 9; SAS Institute Inc, Cary, North Carolina).

Approval for research with human subjects was obtained from the University of Utah Institutional Review Board. Investigational New Drug approval was obtained from the Food and Drug Administration. The project was registered with ClinicalTrials.gov. This research project was not sponsored or funded by a company. There is no relationship between the authors and the development, evaluation, and promotion of the IN-MMAD.

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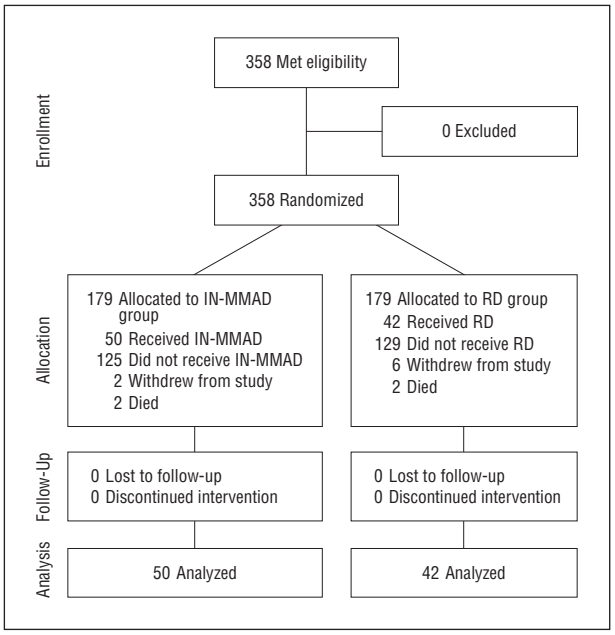

Figure 1. Patient enrollment flowchart. IN-MMAD indicates Intranasal-Midazolam Mucosal Atomization Device; RD, rectal diazepam.

RESULTS

Three hundred fifty-eight pediatric subjects with epilepsy were prospectively enrolled from July 2006 through September 2008 (**Figure 1**). Ninety-two caretakers gave study medication to a child during a seizure (50 IN-MMAD, 42 RD). Two hundred fifty-five patients remained in the study but did not receive study medication during enrollment. Eight patients/caretakers withdrew from the study, 6 of whom had been assigned to receive RD. Three withdrew because RD was too expensive and they wanted IN-MMAD, and 4 patients withdrew for no stated reason. Two patients randomized to IN-MMAD withdrew from the study for no stated reason. Four enrolled patients died during the study period but never used study medication. One patient had degenerative neurological disease and died of respiratory failure, and 3 with chronic medical problems died at home of unknown cause.

Table 1 presents the demographic data for the RD and IN-MMAD groups. Groups were similar with regard to age, sex, daily antiepileptic medication use, and percentage of caretakers' experience with RD. Satisfaction with RD was also similar among the 13 patients in the RD group and the 21 in the IN-MMAD group who had previously used RD. The mean dose was 0.41 mg/kg (95% CI, 0.37-0.45) for RD and 0.20 mg/kg (95% CI, 0.19-0.21) for IN-MMAD. In all 92 seizures treated with a study medication, either the child's mother, father, or both parents gave the medication.

Our primary outcome measure, time to seizure cessation from medication administration, is summarized by treatment group in **Figure 2**. The median time to seizure cessation from medication administration was shorter for the IN-MMAD group (median, 3.0 minutes; interquartile range [IQR], 1.0-10.0) compared with the RD group (median, 4.3 minutes; IQR, 2.0-14.5), with a difference of 1.3 minutes (95% CI, 0.0-3.5; $P=.09$).

Table 1. Demographic Data

Demographic Data	No. (%) IN-MMAD (n=50)	No. (%) RD (n=42)
Age, median (IQR), y	5.6 (2.5-0.7)	6.9 (3.8-10.8)
Male sex	24 (48)	22 (52)
Taking seizure medications	41 (82)	32 (76)
Caretakers who have previously given RD	21 (42)	13 (31)
Overall satisfaction with RD on enrollment median (IQR)[a]	6 (4-9)	8 (6-9)
Who missed dose(s) of daily seizure medications within 24 h of seizure	6 (12)	0 (0)
Dose, mg/kg, mean (SD)	0.20 (0.04)	0.41 (0.13)

Abbreviations: IN-MMAD, Intranasal-Midazolam Mucosal Atomization Device; IQR, interquartile range; RD, rectal diazepam.
[a] Scale, 0 to 10 points; 13 patients in the diazepam group and 21 patients in the midazolam group.

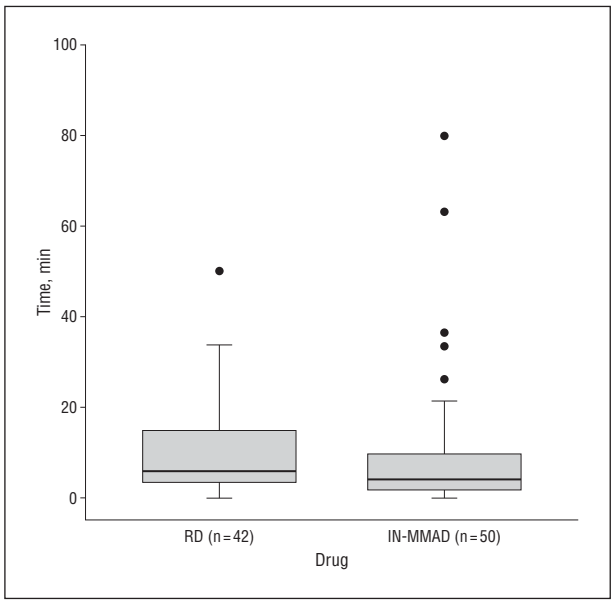

Figure 2. Time from medication use to seizure cessation (difference, 1.3 minutes; 95% confidence interval, 0.0-3.5; $P=.09$). Confidence intervals and P values were calculated using Wilcoxon rank sum tests and Mann-Whitney U tests. IN-MMAD indicates Intranasal-Midazolam Mucosal Atomization Device; RD, rectal diazepam.

Figure 3 shows total seizure time for the IN-MADD (median, 10.5 minutes; IQR, 7.0-18.0) and RD (median, 12.5 minutes; IQR, 7.0-30.0) groups, with a difference in median total seizure time of 2.0 minutes (95% CI, −1.0 to 5.7; $P=.25$). Time to rescue medication administration (**Figure 4**) did not differ between the IN-MADD (median, 5.0 minutes; IQR, 4.0-7.0) and RD (median, 5.0 minutes; IQR, 4.0-8.0) groups; the difference in median time to rescue medication administration was 0.0 minutes (95% CI, −1.0 to 1.0; $P=.57$).

No differences between groups were identified with respect to the other secondary outcome measures of repeated seizures, need for emergency services, respiratory depression, emergency department visits, or dispo-

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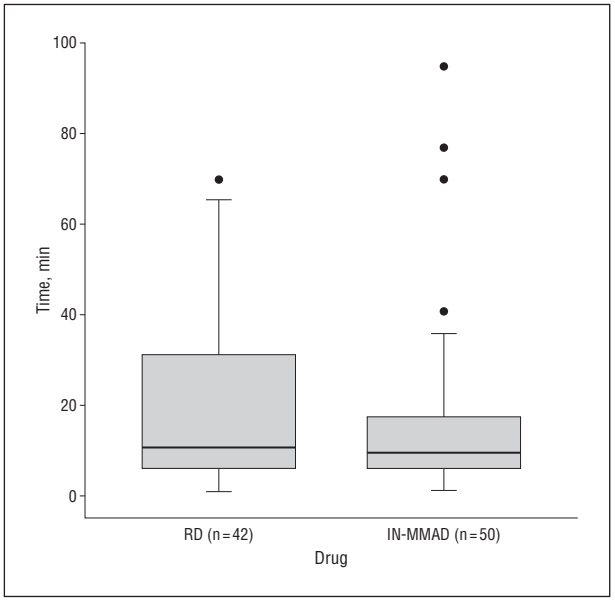

Figure 3. Witnessed total seizure time (difference, 2.0 minutes; 95% confidence interval, 1.0-5.7; *P*=.25). Confidence intervals and *P* values were calculated using Wilcoxon rank sum tests and Mann-Whitney *U* tests. IN-MMAD indicates Intranasal-Midazolam Mucosal Atomization Device; RD, rectal diazepam.

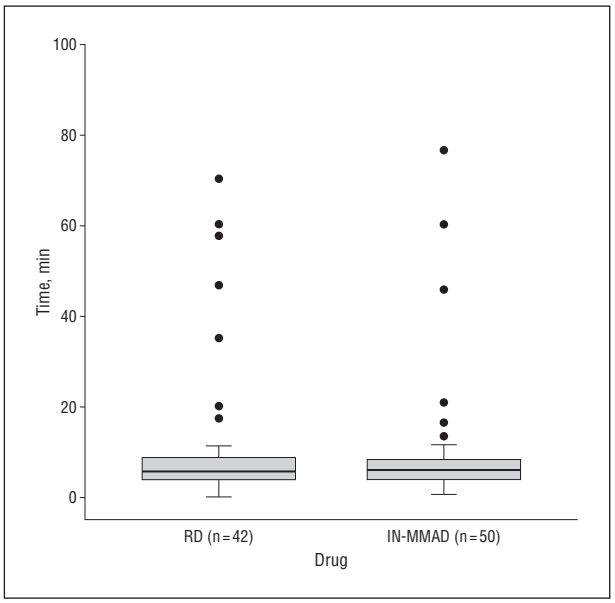

Figure 4. Witnessed time to medication administration (difference, 0.0 minutes; 95% confidence interval, −1.0 to 1.0; *P*=.57). Confidence intervals and *P* values were calculated using Wilcoxon rank sum tests and Mann-Whitney *U* tests. IN-MMAD indicates Intranasal-Midazolam Mucosal Atomization Device; RD, rectal diazepam.

sition (**Table 2**). One child in the IN-MMAD group required intubation compared with none in the RD group. In addition, the absolute numbers of patients who needed EMS and ED services was slightly higher in the IN-MMAD group.

Caretakers were asked about ease of administration and overall satisfaction with study medication (**Table 3**). They were asked to respond on an 11-point nominal scale with zero indicating not at all satisfied and 10, very satisfied. Caretakers reported that IN-MMAD was easier to give than RD (10 vs 9; 95% CI, 0-1; *P*=.02). Overall satisfaction with medication was also higher in the IN-MMAD group (9.3 vs 7.3; 95% CI, 0-2; *P*=.02).

Table 2. Secondary Outcome Results

Secondary Outcome Data	No. (%) IN-MMAD (n=50)	No. (%) RD (n=42)	OR (95% CI)
Prehospital			
Called 911	21 (42)	16 (38)	1.2 (0.5-3.0)
Seizure when EMS arrived	8 (16)	8 (19)	0.8 (0.2-2.8)
Seizure treated by EMS	2 (4)	4 (10)	0.4 (0.0-3.0)
Transport by ambulance	10 (20)	12 (29)	0.6 (0.2-1.8)
Emergency department			
ED visit	21 (42)	17 (40)	1.1 (0.4-2.7)
Seizure in the ED	5 (10)	4 (10)	1.1 (0.2-5.7)
Seizure treated in ED	5 (10)	5 (12)	0.8 (0.2-3.9)
Respiratory complications			
Intubation in ED	1 (2)	0 (0)	0.8 (0.0-Infinity)
Oxygen at ED disposition	3 (6)	1 (2)	2.6 (0.2-140.7)
Disposition from ED, inpatient	4 (8)	3 (7)	1.1 (0.2-8.2)
Repeat seizure within 12 h	1 (2)	1 (2)	0.8 (0.0-67.3)

Abbreviations: CI, confidence interval; ED, emergency department; EMS, emergency medical services; IN-MMAD, Intranasal-Midazolam Mucosal Atomization Device; OR, odds ratio; RD, rectal diazepam.

Table 3. Ease of Administration and Overall Satisfaction

Secondary Outcome Data	IN-MMAD (n=50)	RD (n=42)	Difference (95% CI)[a]
	Median (IQR)		
Ease/satisfaction			OR (95% CI)
Ease of administration	10 (9-10)	9 (7-10)	1 (0-1)[b]
Overall satisfaction	9.25 (8-10)	7.25 (5-10)	2 (0-2)[b]
	No. (%)		
Difficulties/complications			OR (95% CI)
Difficulties administering	6 (12)	3 (7)	1.8 (0.3-11.6)
Complications reported	16 (32)	15 (36)	0.8 (0.3-2.2)

Abbreviations: CI, confidence interval; IN-MMAD, Intranasal-Midazolam Mucosal Atomization Device; IQR, interquartile range; RD, rectal diazepam.
[a] Wilcoxon rank sum and Mann-Whitney U tests were used to calculate confidence intervals.
[b] Scale, 0 to 10 points.
[c] Statistically significant.

COMMENT

This is the first study that compares IN-MMAD with RD as a home rescue medication for pediatric epilepsy. Our study found no detectable difference in efficacy or adverse effects between IN-MMAD and RD when used as a rescue medication in children with a seizure disorder. However, our data suggest that there may be a trend toward faster seizure control in the IN-MMAD group. More patients in the IN-MMAD group required EMS and ED services, and 1 patient in the IN-MMAD group was intubated but the differences were not significant. Caretakers in our study were required to call EMS if they gave the study medication. More patients might have followed through on this instruction with a medication used for the first time,

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which may account for the increase in EMS and ED use in the IN-MMAD group. The ease of administration and overall satisfaction were higher in the IN-MMAD group compared with the RD group. Our results indicate that IN-MMAD may be a good alternative to RD for pediatric patients with epilepsy.

Rectal diazepam is approved for the home treatment of seizures and has facilitated earlier treatment of prolonged seizures in children, thereby preventing unnecessary ED visits.[6] With longer seizure duration, seizure control becomes increasingly difficult. An easily accessible home treatment can help limit seizure duration in children with epilepsy. However, RD may not be ideal in some cases. It can be socially awkward for some patients and caretakers, is expensive, and may cause respiratory adverse effects (especially if given in multiple doses or with other medications).[9,10] Of particular note, adolescents and their parents or caretakers may prefer IN-MMAD because of the social awkwardness associated with RD administration.

Midazolam, a water-soluble benzodiazepine, becomes lipophilic at physiological pH and readily crosses the blood-brain barrier into the central nervous system.[13,32,36] This mechanism of action allows for rapid delivery to the central nervous system to treat seizure activity.[32] Medications that are dripped into the nares, though, do not reliably coat the nasal mucosa because large droplets pass through the nasopharynx and are swallowed. Midazolam's clinical effects still occur if ingested orally but the availability of the drug directly into the central nervous system may be reduced. The Mucosal Atomization Device provides a mist of particle size (30 μ) that is too small to be aspirated but not large enough to be swallowed and, therefore, may allow more rapid penetration into the central nervous system.[32,33] Future studies should optimize the dose of IN-MMAD and compare IN-MMAD with that of buccal midazolam or intranasal lorazepam.[27-30,32,37,38]

Intranasal midazolam has been studied for the treatment of seizures. Studies performed in the ED and prehospital setting have demonstrated effectiveness of intranasal midazolam for the treatment of seizures.[14-16,28,39] Doses used have ranged from 0.2 to 0.5 mg/kg and, in these studies, the medication was simply dripped into the nares with a syringe,[14-16,28,39] subject to the concerns above.

A few studies have compared diazepam and midazolam in the prehospital or ED setting and have shown midazolam to be equally or more effective in treating seizure activity, sometimes with fewer adverse effects.[13,17-20,27,29,30,40,41] Some of those studies have also compared intranasal midazolam with rectal diazepam.[12,21,22] Fisgin et al[21] compared intranasal midazolam with RD in the ED setting. Intranasal midazolam was significantly more likely to successfully control seizure activity within the first 10 minutes (87%, 20 of 23 patients vs 60%, 13 of 22 patients).[21] Bhattacharyya et al[22] compared physician administration of intranasal midazolam or RD in 46 children (188 seizures) and found seizure control to be faster with intranasal midazolam, with fewer adverse effects. In both studies, study medication was given by a physician in an ED setting. Times documented as part of a research study are presumably done in a standard fashion and are thus more reliable than those of the parents in our study who may have given a medication to stop their child's seizure for the first time.

Holsti et al[12] also found that IN-MMAD controlled seizures better than RD in the prehospital setting, resulting in fewer respiratory complications and fewer admissions. In this study, historical RD controls were compared with a new IN-MMAD protocol used by EMS. We found that the mean seizure time with RD was 19 minutes longer than with IN-MMAD.[12] This study was conducted in a different setting and, owing to the study design, we were not able to collect data on time to administration of study medication, which may have contributed to longer seizure times in the RD group.[12]

In the community setting, midazolam dripped intranasally has been described as an effective rescue medication alternative for seizure activity.[15,23-26] Jeannet et al[23] used IN midazolam to control seizure activity in 26 patients for a total of 125 seizures. One hundred twenty-two seizures (98%) stopped within 10 minutes (mean, 3.6 minutes) without serious adverse effects noted.[23] Three patients had a seizure reoccur within 3 hours.[23] Fisgin et al[24] treated 54 seizures with IN midazolam (22 children). Seizure activity was controlled on 48 occasions (89%) without any respiratory compromise. Satisfaction questionnaires revealed that 90% had no difficulty giving the medication and 14 of 15 people with previous RD experience preferred IN midazolam.[24] Scheepers et al[15] also followed up adolescents and adults whose caretaker gave IN midazolam as a rescue medication for seizure activity. They found 79 of 84 seizures to be effectively treated, with no significant adverse effects.[15] Lastly, Harbord et al[26] prospectively followed up 22 children with 54 seizures and found IN midazolam to be effective in 48 of 54 seizures.[26] No respiratory arrests were reported, and 90% (27 of 30) of caretakers reported no difficulties in giving the medications.[26] These studies demonstrate that IN midazolam has gained widespread use and demonstrated efficacy and relative safety. However, none of the studies compared IN midazolam with RD in a community setting and none used the MAD for delivery.

The chief limitation of our study was the unblinding of study medication and possible selection bias. To keep this study blinded, caretakers would have had to give a study medication and placebo for their child's seizure, one intranasally and one rectally. We concluded that this would prove unacceptable to caretakers. We were able to blind research assistants, patients, and families before they agreed to enroll in the study. However, once enrolled, they were told which medication to use for their child's next seizure. Although some caretakers chose not to participate owing to their wish to receive IN midazolam, we did not separately track patients who were briefed about the study but then opted out because they wanted to choose their home rescue medication. Regardless, very few patients received IN-MMAD from participating neurologists outside of the study so we believe this is unlikely to have biased the outcome significantly. Lastly, some caretakers may have had more experience with a study medication or preference toward one treatment. Some parents, however, gave a medication to stop their child's seizure for the first time. The parent(s) present

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at the clinic visit received standardized formal training on how to give the medication. It is possible that the parent who gave the medication was not the one trained. No teachers or school nurses gave the medication. This variability in experience could have affected administration of study medication and recorded times.

It is certainly possible that seizure onset or exact time of seizure cessation may have been difficult to determine in every case. There may have been recall bias. Some start times may not have been witnessed, and caretakers may not have recognized when a seizure stopped or may have estimated the duration of seizure. We did, however, provide stopwatches, recording cards, and pens in the same container as the rescue medication in an effort to improve documentation and limit recall bias as much as possible. Additionally, research assistants contacted caretakers from both treatment groups with equal regularity to inquire about study medication usage. We only had full access to medical records at our own institution. The EMS and ED information for patients seen at other institutions was collected by phone from the caretaker. Of the patients admitted to the hospital, all were admitted to the study facility.

Our study was powered to detect a 10-minute difference in seizures between groups. We observed a 1.3-minute difference in the 92 patients who were finally enrolled. A conditional power analysis prompted termination of the study owing to a very low likelihood of showing a statistical difference in treatments unless a larger number of patients were enrolled than the expected 120. This study was not sufficiently powered to show equivalence between the 2 treatment modalities.

Early treatment of unremitting seizures reduces seizure duration and the morbidity and mortality associated with seizure activity. Use of IN-MMAD may be a less expensive alternative for the home treatment of seizures. To determine a true difference in overall expense, a cost analysis needs to be done.

We found no detectable difference in efficacy between IN-MMAD and RD as a rescue medication. However, our data suggest that there may be a trend toward faster seizure control in the IN-MMAD group. The published literature in the ED setting also suggests that IN midazolam may stop seizures more quickly than RD. Adverse effects appear to be minimal. Given the ease of administration/overall satisfaction, IN-MMAD may be considered an alternative to rectal diazepam as a rescue medication for the in-home treatment of prolonged seizures in children.

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Announcement

The *Archives* is introducing a rolling theme issue on comparative effectiveness research for the care of children and adolescents. We are interested in comparative effectiveness research across the spectrum of care that child health care providers deliver. Priority will be given to studies that use rigorous methodological designs, are generalizable well beyond an individual institution's walls, and are real-world effectiveness studies. Please consult our Web site at http://www.archpediatrics.com for instructions on manuscript preparation and submission.

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