Critical Review Form
Therapy

Bhattacharyya M, Kalra V, Gulati S. Intranasal midazolam vs rectal diazepam in acute childhood seizures. Pediatr Neurol. 2006 May;34(5):355-9.

Objective: **To compare the efficacy and side effects of intranasal midazolam and rectal diazepam in the treatment of acute childhood seizures.**

Methods: This randomized, controlled study was conducted in both the outpatient neurology department and the emergency department (ED) of the All India Institute of Medical Sciences in New Delhi, India. Children, aged 3 months to 12 years, without hypoglycemic seizures, hypocalcemic seizures, or upper respiratory infections were eligible for enrollment.

An equal number of sealed envelopes was created containing the name of the drug to be administered. These were randomized by "shuffling," and an envelope was chosen at random each time a child was enrolled. Patients received either diazepam (0.3 mg/kg administered rectally) or midazolam (0.2 mg/kg administered intranasally).

Outcomes included the duration of the seizure, with cessation defined as "cessation of visible epileptic phenomena or return of purposeful response to external stimuli" (p. 356), proportion of seizures that ceased within 10 minutes of drug administration, time to administration of drug, and recurrence of seizures within 60 minutes of drug administration. Investigators also assessed changes in respiratory rate, oxygen saturation, heart rate, and systolic blood pressure at 5 minutes, 10 minutes, and 30 minutes after drug administration.

A total of 188 seizure episodes were included in the analysis among 46 children. Diazepam was administered in 96 episodes and midazolam was administered in 92 episodes. The mean ages in the two groups were 74.5 months and 60.5 months respectively. Febrile seizures accounted for 11% of episodes, and 49% were simple partial seizures.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Sort of. Patients underwent a pseudorandomization in which envelopes containing the names of the two treatment options were "shuffled," and then an envelope was chosen at random each time a patient was enrolled.
2.	Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	No. The pseudorandomization method of shuffling envelopes could easily be subverted. In addition, the authors do not specify whether or not these envelopes were opaque.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. There was no crossover between groups.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Patients were similar with respect to age, gender, category of seizure (controlled, provoked, intractable), and perinatal history. A higher number of patients in the midazolam group had a family history of seizures compared to the diazepam group (27.8% vs. 7.1%), but this is unlikely to be of clinical importance.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	No. Patients were having seizures and hence would not be aware of group allocation.
2.	Were clinicians aware of group allocation?	Yes. While the authors mention that the study was "single masked," they provide no details on who was blinded or on how this blinding would have occurred. We must therefore assume that clinicians were aware of group allocation. This raises the possibility of performance bias on the part of the treating physicians and nurses.
3.	Were outcome assessors aware of group allocation?	Yes. While the authors mention that the study was "single masked," they provide no details on who was blinded or on how this blinding

		would have occurred. We must therefore assume that outcome assessors were not blinded to group allocation. This raises the possibility of observer bias.
4.	Was follow-up complete?	Yes. All outcomes were measured during the ED stay, and hence complete outcome data was available for all enrolled patients.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• It took significantly less time to prepare and administer the intranasal midazolam than to prepare and administer the rectal diazepam: mean 50.6 ± 14.1 seconds vs. 68.3 ± 55.1 seconds (p = 0.002). • The duration of time between drug administration and cessation of seizure activity was significantly shorter in the midazolam group than in the diazepam group: 116.7 ± 126.9 seconds vs. 178.6 ± 179.4 seconds (p = 0.005). • Seizures stopped within 10 minutes of drug administration in 96.7% of patients in the midazolam group and 88.5% of patients in the diazepam group: RR 1.1, 95% CI 1.0 to 1.2. • The mean oxygen saturation in the midazolam group did not vary at 5, 10, and 30 minutes after drug administration. In the diazepam group, there was a statistically significant decrease in the oxygen saturation at 5, 10, and 30 minutes after drug administration (p < 0.05). The authors do not provide values for oxygen saturation, but do note that hypoxia (which is never defined) occurred in one child receiving diazepam, necessitating oxygen supplementation for 7 hours. • Seizure recurrence occurred in 6.25% of cases in the diazepam group and 3% of cases in the midazolam group: RR1.9, 95% CI 0.50 to 7.4.
2.	How precise was the estimate of the treatment effect?	See above. This was a small study with wide 95% CIs. The CI nears 1 for the resolution of seizure activity within 10 minutes and crosses one for recurrence of seizures.
III.	**How can I apply the results to**	

	patient care (answer the questions posed below)?	
1.	Were the study patients similar to my patient?	No. This was a very small study conducted in India. Over 90% of enrolled patients had a history of birth asphyxia, 22% had a history of "degenerative brain disease," and 15% had a history of neurocysticercosis.
2.	Were all clinically important outcomes considered?	No. The authors did not evaluate other potentially patient-centered outcomes, such as the duration of sedation, ED length of stay, parent satisfaction or cost.
3.	Are the likely treatment benefits worth the potential harm and costs?	Likely yes. This was a small study with a poor randomization scheme and some poorly defined outcomes. While there were statistically significant decreases in time to drug administration and time to seizure cessation with IN midazolam, it is unclear if these differences were clinically significant. It does seem to suggest that at the very least, nasal midazolam is as safe and effective as rectal diazepam.

Limitations:

1. **The authors do not specify the time period over which the study was conducted, or whether consecutive patients or convenience sampling were used.**
2. **The authors utilized a poor randomization scheme that potentially introduced selection bias.**
3. **The authors note statistically significant decreases in time to drug administration and time to seizure cessation with IN midazolam, there is no discussion as to whether these differences are clinically significant.**
4. **The authors did not comply with several aspects of the CONSORT guidelines:**
    a. **There was no primary outcome prespecified.**
    b. **The authors report p-values without reporting measures of effect (such as relative risk or odds ratio) with their respective 95% confidence intervals.**

Bottom Line:

In this relatively small, semi-randomized, open-label study evaluating intranasal midazolam vs. rectal diazepam for the management of pediatric seizures, the authors

demonstrated that it took less time to prepare and administer intranasal midazolam, and that there was a shorter duration of time from drug administration to cessation of seizure activity. It is unclear, however, if these brief decreases in duration (mean 17.7 seconds and 61.9 seconds) are of any clinical significance. The authors also note that there was a statistically significant decrease in mean oxygen saturation in the diazepam group at 5, 10, and 30 minutes after drug administration, but do not provide any numbers to support this as clinically significant. It does seem from this study that intranasal midazolam is a safe and effective alternative to rectal diazepam in the management of pediatric seizures.