Critical Review Form
Therapy

Holsti M, Sill BL, Firth SD, Filloux FM, Joyce SM, Furnival RA. Prehospital intranasal midazolam for the treatment of pediatric seizures. Pediatr Emerg Care. 2007 Mar;23(3):148-53.

Objectives: **"to compare the effectiveness and complications of IN-MAD [intranasal mucosal atomization device] midazolam with that of PR [per rectal] diazepam for treatment of childhood seizures in the prehospital setting." (p. 149)**

Methods: **This before and after study was conducted within the EMS system that serves the Primary Children's Medical Center in Salt Lake City, Utah. A new protocol was enacted that directed EMT paramedics to treat seizure activity in children and adults with IN-MAD midazolam (0.2 mg/kg up to 10 mg). Patients less than 18 years of age treated with midazolam for seizures after July 1, 2003 were compared to historical controls treated with PR diazepam (0.3 to 0.5 mg/kg up to 20 mg). Inclusion required seizure in the presence of an EMS provider, and patients were excluded if they were transferred from another facility, received a rescue medication for seizures prior to EMS arrival, received more than one rescue medication by EMS, or had a seizure that was not witnessed by EMS.**

A seizure was defined as prolonged or recurrent if it persisted for 30 minutes or more, and duration of seizure was defined as the time from EMS arrival to seizure cessation or arrival to the hospital. The primary outcome was the presence of ongoing seizure in the emergency department (ED). Secondary outcomes included total seizure time, EMS seizure duration, respiratory complications, status epilepticus (> 30 minutes), anticonvulsants given in the ED, disposition, and total hospital charges.

Out of a total of 857 total patients brought to the ED by EMS for a chief complaint of seizure, 57 were eligible for inclusion (39 received IN-MAD midazolam and 18 received PR diazepam).

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?	No. This was a before and after study. EMS

		protocol after July 1, 2003 dictated the use of intranasal midazolam for the management of seizures. Patients treated after this date were compared to historical controls receiving PR diazepam.
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?	N/A. Patients were not randomized.
3.	Were patients analyzed in the groups to which they were randomized?	N/A. Patients were not randomized, but rather were treated according to EMS protocol, which changed on July 1, 2003. Patients were therefore assigned to groups according to the treatment actually received.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. The two groups were similar with respect to age, gender, seizure history, seizure medication history, and type of seizure.
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?	Yes. This was a non-blinded before and after study, and hence all participants were aware of treatment allocation.
2.	Were clinicians aware of group allocation?	Yes. This was a non-blinded before and after study, and hence all participants were aware of treatment allocation.
3.	Were outcome assessors aware of group allocation?	Yes. This was a non-blinded before and after study, and hence all participants were aware of treatment allocation.
4.	Was follow-up complete?	No. Data on EMS-witnessed seizure time was available in 25 (64%) of 39 patients in the midazolam group and 13 (72%) of 18 patients in the diazepam group. Data on total seizure time was available for 36 (92%) of 39 patients in the midazolam group and 17 (94%) of 18 patients in the diazepam group.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	The median EMS-witnessed seizure time was longer in the diazepam group compared to the midazolam group (30 minutes vs. 11 minutes, p =

		0.003). Total seizure time was also longer in the diazepam group compared to the midazolam group (45 minutes vs. 25 minutes, $p < 0.001$). Median hospital charges were lower in for patients in the midazolam group vs. the diazepam group ($1459 vs. $6980, $p < 0.0001$). Patients in the diazepam group were more likely to require bag-mask ventilation by EMS (OR 7.73, 95% CI 1.03-87.70), more likely to have seizure activity on arrival to the ED (OR 4.16, 95% CI 1.08-17.64), more likely to require intubation in the ED (OR 11.77, 95% CI 1.79-125.09), and were more likely to require hospital admission (OR 7.62, 95% CI 2.26-784.27).
2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes. These were pediatric patients with seizure being transported to a large, academic, pediatric ED by EMS around Salt Lake City Utah.
2.	Were all clinically important outcomes considered?	Yes. The authors evaluated EMS-witnessed seizure time, total seizure duration, need for additional interventions such as BVM, presence of seizure activity on arrival to the ED, need for hospital admission, and total cost. They did not evaluate ED length of stay or hospital length of stay.
3.	Are the likely treatment benefits worth the potential harm and costs?	Likely yes. While this was not a randomized controlled trial, and had very small enrollment numbers, the results suggest that use of intranasal midazolam resulted in decreased seizure duration, decresased need for advanced airway management (BVM, intubation), decreased need for hospital admission, and lower cost.

Limitations:

1. **This was a before and after study, with all of the inherent biases involved. Specifically, there is no way to control for other interventions that occurred with regards to seizure management in the interim.**

2. **The was a non-randomized, open-label (unblinded) study, open to several potential sources of bias as a result (selection bias, performance bias, recall bias, observer bias).**

3. **The authors do not provide any information regarding medical comorbidities or seizure etiology to allow an accurate comparison of the two groups.**

4. **There was a great deal of missing outcomes data from the EMS record**

Bottom Line:

While this before and after study comparing the use of rectal diazepam and intranasal midazolam for the management of pediatric seizures suggests that IN midazolam is preferable (decreased seizure duration, decreased hospitalization, decreased cost), the nature of the study leaves several potential areas for bias to be introduced leading to the observed effect. The study was not blinded, was not randomized, and used a before and after design which does not allow for adequate control of additional interventions.