

**Critical Review Form  
Therapy**

Fişgin T, Gurer Y, Teziç T, Senbil N, Zorlu P, Okuyaz C, Akgün D. Effects of intranasal midazolam and rectal diazepam on acute convulsions in children: prospective randomized study. J Child Neurol. 2002 Feb;17(2):123-6.

**Objectives:** To compare “the effects and side effects of rectal diazepam and intranasal midazolam...in the treatment of acute convulsions in children to develop a practical and safe treatment protocol.” (p. 123)

**Methods:** This prospective, randomized, open-label study was conducted between November 1997 and January 1999 in the emergency department (ED) of Dr. Sami Ulus Children’s Hospital in Ankara, Turkey. Patients aged 1 month to 13 years with a seizure that began within 5 minutes of enrollment, regardless of seizure type or etiology, were eligible for enrollment.

Patients in Group 1 were enrolled on odd days of the month and were given diazepam, 0.3 mg/kg, by the rectal route as the initial drug for the treatment of status epilepticus. Patients in Group 2 were enrolled on even days of the month and were given midazolam, 0.2 mg/kg, via the nasal route by a 30 second injection as the initial drug. A second drug was administered if the seizure persisted for 10 minutes after the initial drug. If the seizure persisted for one hour after the initial drug, a continuous infusion of intravenous midazolam was initiated and titrated until the seizure terminated.

A total of 45 patients were enrolled. There were 22 patients in Group 1 (11 girls and 11 boys) and 23 patients in Group 2 (15 girls and 8 boys). The average ages of the two groups were 2.02 and 3.80 years respectively.

<b>Guide</b>		<b>Comments</b>
I.	Are the results valid?	
A.	Did experimental and control groups begin the study with a	

	<b>similar prognosis (answer the questions posed below)?</b>	
1.	Were patients randomized?	Sort of. Group allocation occurred by the day of the month on which the patient presented. Patients presenting on odd days were assigned to the rectal diazepam group, while patients presenting on even days were assigned to the nasal midazolam group.
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. “Randomization” occurred according to the day of the month on which the patient presented. While it would not be possible to subvert such an allocation scheme, this is not true randomization.
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?	No. The mean age was significantly higher in the nasal midazolam group (3.80 years) compared to the rectal diazepam group (2.02 years). Patients were similar with respect to seizure type, gender, body temperature, or seizure duration prior to enrollment.
<b>B.</b>	<b>Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?</b>	
1.	Were patients aware of group allocation?	No. Patients were in status epilepticus and hence would not be aware of group allocation.
2.	Were clinicians aware of group allocation?	Yes. This was an open-label trial and all clinicians were aware of group allocation. This raises the possibility of <a href="#">performance bias</a> on the part of the treating physicians and nurses.
3.	Were outcome assessors aware of group allocation?	Yes. Outcomes were measured by the treating clinicians, who were not blinded to group allocation. This raises the possibility of <a href="#">observer bias</a> .
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.
<b>II.</b>	<b>What are the results (answer the questions posed below)?</b>	
1.	How large was the treatment effect?	<ul style="list-style-type: none"> <li>• <b>More patients in the nasal midazolam group had their seizure terminated within 10 minutes compared to the diazepam group: 20 (87%) vs.</b></li> </ul>

		<p><b>13 (60%); RR 1.5 (95% CI 1.0 to 2.2)</b></p> <ul style="list-style-type: none"> <li>• Overall, based on the duration of seizure following drug administration, nasal midazolam was found to be more effective (<math>p &lt; 0.05</math>).</li> <li>• More patients in the diazepam group needed a second drug to stop their seizure than in the midazolam group: <math>p &lt; 0.05</math>)</li> </ul>
2.	How precise was the estimate of the treatment effect?	See above. This was a small study with wide confidence intervals. However, the 95% CI did not cross one.
<b>III.</b>	<b>How can I apply the results to patient care (answer the questions posed below)?</b>	
1.	Were the study patients similar to my patient?	Uncertain. This was a very small study conducted in Turkey. There was very little information provided regarding pre-existing medical conditions, seizure etiology, duration of seizure prior to presentation, or hospital transport times.
2.	Were all clinically important outcomes considered?	No. The authors did not evaluate other potentially patient-centered outcomes, such as the incidence of hypoxia, duration of sedation, or ED length of stay.
3.	Are the likely treatment benefits worth the potential harm and costs?	Likely yes. This was a very small study with a poor randomization scheme. It does seem to suggest that at the very least, nasal midazolam is as safe and effective as rectal diazepam.

**Limitations:**

1. This was a very small study, enrolling a total of 45 patients.
2. The authors utilized a poor randomization scheme that potentially introduced [selection bias](#).
3. The authors did not comply with several aspects of the [CONSORT guidelines](#):
  - a. There was no [primary outcome](#) prespecified.
  - b. A [sample size analysis](#) was not conducted to justify the number of patients enrolled in the study.
  - c. No 95% Confidence Intervals were reported.

**Bottom Line:**

**This small, semi-randomized controlled trial in pediatric patients with status asthmaticus demonstrated a higher rate of seizure resolution in patients receiving nasal midazolam (87%) compared to rectal diazepam (60%). The study was small and had several important methodological flaws, but does suggest that nasal midazolam is a safe and effective alternative to rectal diazepam for the management of pediatric status epilepticus.**