

## Original Investigation

# Lorazepam vs Diazepam for Pediatric Status Epilepticus

## A Randomized Clinical Trial

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**IMPORTANCE** Benzodiazepines are considered first-line therapy for pediatric status epilepticus. Some studies suggest that lorazepam may be more effective or safer than diazepam, but lorazepam is not Food and Drug Administration approved for this indication.

**OBJECTIVE** To test the hypothesis that lorazepam has better efficacy and safety than diazepam for treating pediatric status epilepticus.

**DESIGN, SETTING, AND PARTICIPANTS** This double-blind, randomized clinical trial was conducted from March 1, 2008, to March 14, 2012. Patients aged 3 months to younger than 18 years with convulsive status epilepticus presenting to 1 of 11 US academic pediatric emergency departments were eligible. There were 273 patients; 140 randomized to diazepam and 133 to lorazepam.

**INTERVENTIONS** Patients received either 0.2 mg/kg of diazepam or 0.1 mg/kg of lorazepam intravenously, with half this dose repeated at 5 minutes if necessary. If status epilepticus continued at 12 minutes, fosphenytoin was administered.

**MAIN OUTCOMES AND MEASURES** The primary efficacy outcome was cessation of status epilepticus by 10 minutes without recurrence within 30 minutes. The primary safety outcome was the performance of assisted ventilation. Secondary outcomes included rates of seizure recurrence and sedation and times to cessation of status epilepticus and return to baseline mental status. Outcomes were measured 4 hours after study medication administration.

**RESULTS** Cessation of status epilepticus for 10 minutes without recurrence within 30 minutes occurred in 101 of 140 (72.1%) in the diazepam group and 97 of 133 (72.9%) in the lorazepam group, with an absolute efficacy difference of 0.8% (95% CI, -11.4% to 9.8%). Twenty-six patients in each group required assisted ventilation (16.0% given diazepam and 17.6% given lorazepam; absolute risk difference, 1.6%; 95% CI, -9.9% to 6.8%). There were no statistically significant differences in secondary outcomes except that lorazepam patients were more likely to be sedated (66.9% vs 50%, respectively; absolute risk difference, 16.9%; 95% CI, 6.1% to 27.7%).

**CONCLUSIONS AND RELEVANCE** Among pediatric patients with convulsive status epilepticus, treatment with lorazepam did not result in improved efficacy or safety compared with diazepam. These findings do not support the preferential use of lorazepam for this condition.

**TRIAL REGISTRATION** [clinicaltrials.gov](http://clinicaltrials.gov) Identifier: NCT00621478

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Status epilepticus occurs approximately 10 000 times in children annually in the United States,<sup>1</sup> and 4 to 8 children per 1000 have an episode of status epilepticus before age 15 years.<sup>2</sup> Rapid control of status epilepticus is desirable to avoid permanent neuronal injury and acute life-threatening complications such as respiratory failure. Benzodiazepines are widely used as first-line pharmacologic agents, achieving lasting seizure control in up to 80% of patients.<sup>3,4</sup> Respiratory depression and failure are the most common life-threatening complications of benzodiazepine treatment in status epilepticus; data on its safety in children are limited.<sup>5</sup>

Diazepam and lorazepam are both effective in treating pediatric status epilepticus.<sup>6</sup> The Food and Drug Administration (FDA) has approved diazepam for the treatment of status epilepticus in children. However, despite many experts advocating its use,<sup>5-9</sup> lorazepam is not yet FDA approved for this indication. Potential advantages proposed in some studies of lorazepam include improved effectiveness in terminating convulsions,<sup>10</sup> longer duration of action compared with diazepam,<sup>11</sup> and lower incidence of respiratory depression.<sup>4,12</sup> Specific pediatric data comparing diazepam with lorazepam suggest that lorazepam might be superior, but they are limited to reports from single institutions or retrospective studies with small sample sizes, thus limiting generalizability.<sup>12,13</sup> A registry study of childhood convulsive status epilepticus in North London found lorazepam more effective than diazepam in stopping status epilepticus, but these data are difficult to interpret because lorazepam was administered intravenously while diazepam was administered rectally.<sup>14</sup> Other pediatric studies have found that the 2 medications are similar in efficacy<sup>15,16</sup> but there may be differences in safety.<sup>12,16</sup> Thus, there is no conclusive evidence to support lorazepam as a superior treatment and there is little consensus as to which is the preferred agent.<sup>17</sup>

The Best Pharmaceuticals for Children Act was enacted to enhance pediatric clinical studies, leading to new pediatric labeling in accordance with FDA regulations. Lorazepam as a therapy for pediatric status epilepticus was chosen as a priority off-patent medication for which pediatric studies are needed. The purpose of this study was to test the hypothesis that lorazepam is superior in efficacy (primary efficacy hypothesis) and safety (primary safety hypothesis) to diazepam for the treatment of pediatric status epilepticus.

## Methods

We conducted a double-blind, randomized clinical trial to compare the efficacy and safety of intravenous lorazepam with diazepam in children presenting to the emergency department (ED) with generalized convulsive status epilepticus.

### Setting

We enrolled patients at 11 large academic pediatric hospitals in the United States. Initial recruitment of sites was from the Pediatric Emergency Care Applied Research Network

(PECARN); subsequently, we included 3 additional sites to enhance enrollment.

### Study Participants

Children aged 3 months to younger than 18 years were eligible for inclusion if they exhibited generalized tonic-clonic status epilepticus. Status epilepticus was defined as either (1) 3 or more convulsions within the preceding hour and currently experiencing a convulsion; (2) 2 or more convulsions in succession with no recovery of consciousness and currently experiencing a convulsion; or (3) a current single convulsion of at least 5 minutes' duration. Seizures may have started focally and then generalized; however, to be included, the patients had to have loss of consciousness and generalized tonic-clonic seizures. These definitions are consistent with current standards for therapy.<sup>7,18,19</sup>

Patients were excluded if they met any of the following criteria prior to medication administration: known pregnancy; hypotension; significant cardiac dysrhythmia; need for emergent surgical intervention and general anesthesia; known contraindication to benzodiazepine use; or benzodiazepine use within the preceding 7 days, including use of anticonvulsant medications by ambulance personnel. Patients were terminated from the study (early terminators) if the investigators discovered 1 of the exclusionary criteria after receiving study medication or if the family refused participation in the study. Efficacy and safety data were retained from early terminators in accordance with FDA regulations.

### Informed Consent

Recognizing the need to include status epilepticus in patients with previously undiagnosed seizure disorders, patients were enrolled using the Exception from Informed Consent for Emergency Research, 21 CFR 50.24. This federal regulation allows emergency research without prior consent under limited conditions and requires additional safeguards to protect the well-being of patients.<sup>20</sup> Thus, patients were randomized and treated prior to consent. After stabilization of the patient's clinical condition in conjunction with family support through the period of crisis, we approached families to discuss the study and obtain written consent for continued participation and collection of blood specimens for pharmacokinetic analyses. Patients from neurology practices with a known history of epilepsy were approached to obtain prospective informed consent prior to an actual episode of status epilepticus whenever possible. The FDA, the study sponsor (Eunice Kennedy Shriver National Institute of Child Health and Human Development), an external expert ethics advisory panel, and the institutional research review boards of the participating centers approved the Exception from Informed Consent for Emergency Research plan for the study.

### Randomization and Study Medication Administration

An age-stratified, permuted block randomization (1:1) scheme with block sizes of 4 in 3 age groups—3 months to younger than 3 years, 3 years to younger than 13 years, and

13 years to younger than 18 years—was incorporated. These age groups were chosen at the request of an expert panel of the FDA, which commissioned this trial. A medication nurse or pharmacist selected a vial of study medication from the medication-dispensing system sequentially based on the patient's age group. The medication nurse or pharmacist, independent of the treating team at the patient's bedside, used a dosing card to prepare the study medication based on estimated patient weight to deliver a final dose of 0.2 mg/kg of diazepam (maximum dose, 8 mg) or 0.1 mg/kg of lorazepam (maximum dose, 4 mg). To maintain blinding of the bedside clinicians, diluent was added to lorazepam so that the final medication volume was the same for both medications. Opaque syringe cylinders were used to prevent visualizing the medication. The medication was handed to the treating team, who administered it by slow intravenous (IV) push for 1 minute. The end of the IV push was defined as time 0. If a second dose was required for ongoing convulsions at 5 minutes, the dispensing and administration processes were repeated using half the initial dose.<sup>21</sup> If the patient had ongoing status epilepticus at 12 minutes, IV fosphenytoin or phenytoin, 15 to 20 mg/kg, was administered; phenobarbital, 15 to 20 mg/kg, was used if the patient was allergic to phenytoin. At 20 minutes, open-label treatment with anticonvulsants of choice based on clinician preference was allowed.

### Determination of Study Outcomes

#### Efficacy

The primary efficacy outcome was defined as cessation of status epilepticus within 10 minutes of the initial dose of study medication and a sustained absence of convulsions for 30 minutes. The end of status epilepticus was defined as the time when generalized convulsive activity stopped, provided that it was followed by return of consciousness within the 4-hour follow-up period. Recurrence of generalized convulsions without return of consciousness was considered ongoing status. Secondary efficacy end points included response latency (time to cessation of convulsions), need for a second dose of study medication, need for additional anticonvulsant medications for ongoing status, and sustained absence of convulsions for 60 minutes and 4 hours after receiving the study medication.

#### Safety

The primary safety outcome was severe respiratory depression within 4 hours of initial medication, which was defined as the need for assisted ventilation (bag-valve-mask ventilation or endotracheal intubation). Secondary safety end points included aspiration pneumonia, any degree of respiratory depression, time to return to baseline mental status, and sedation or agitation, as measured by the Riker Sedation-Agitation Scale.<sup>22</sup> The Riker scale ranges from 1 (deeply sedated, no response to stimuli) to 7 (dangerously agitated), with 4 representing normal baseline mental status (neither sedated nor agitated). The Riker scale was modified for use in preverbal children (eTable in Supplement) and demonstrated internal and external validity prior to this study (data available on re-

quest). Patients were followed up for adverse events for up to 24 hours or until hospital discharge, whichever came first. A follow-up phone call was performed at 30 days to determine whether adverse events occurred after hospital discharge.

All study outcomes were determined by the treating attending physician and were reviewed by the site principal investigator and the study principal investigator.

### Statistical Analyses

The primary efficacy outcome included all patients who were randomized and met the definition of generalized convulsive status epilepticus. This group was defined because some patients received study medication but were not in generalized status. For patients who were enrolled more than once, only the first visit was included. For the primary safety outcome, an intention-to-treat analysis, including all randomized patients, was used. Additionally, per-protocol analyses of efficacy outcomes to account for 64 patients with significant protocol deviations were performed. Predefined protocol deviations included study medication dose administration outside a margin of  $\pm 30\%$  of the desired dose, a second dose of study medication more than 9 minutes after the first dose, administration of a secondary anticonvulsant before 10 minutes, benzodiazepines within 2 hours prior to enrollment, and IV extravasation. Protocol violations also included 15 patients who were systematically randomized incorrectly because of a pharmacy error at a single site.

Time to cessation of convulsions, time to new seizure activity, and time to recovery to baseline mental status are reported as median and interquartile range. Cox proportional hazards regression models for time-to-event analyses were developed for these secondary outcomes. The assumptions for proportional hazards models were met for all time-to-event outcomes. Patients who received second-line or third-line medications, paralytic agents, or coma induction were censored at the time of these medications. Independent factors in the Cox proportional hazards regression model included treatment assignment and treatment hospital; treatment hospital had no effect. Kaplan-Meier survival curves were constructed for each treatment group. All analyses were performed for the overall treatment groups and for each age stratum.

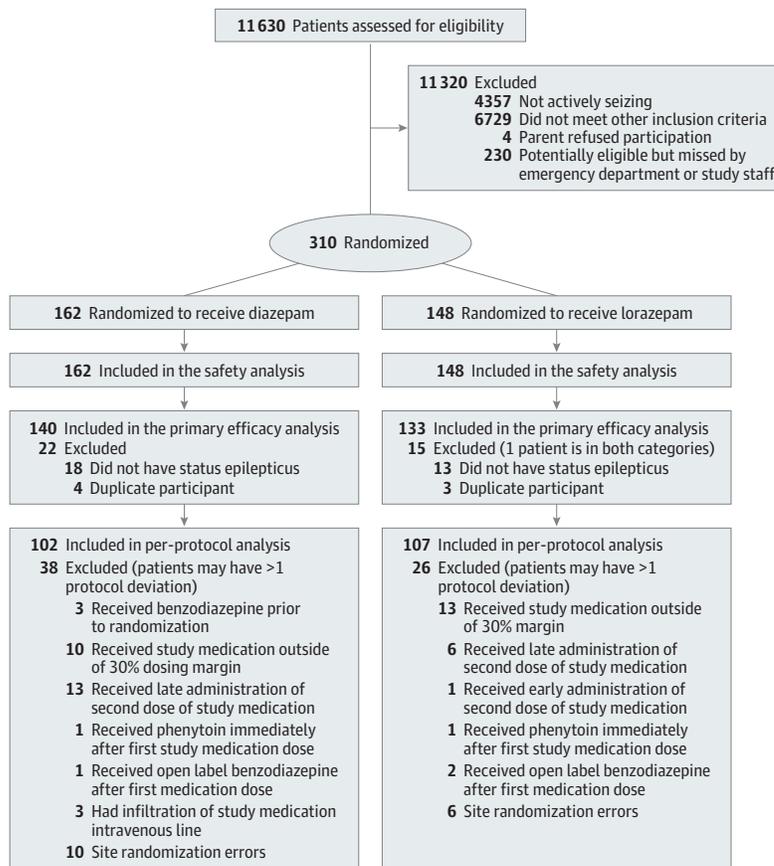
Sample-size estimates were based on the primary efficacy outcome and an expected efficacy of diazepam of 60% based on previous literature.<sup>15,16</sup> With a 2-sided alpha of .05, the study had 80% power to detect an absolute difference in efficacy of at least 17% with 120 patients in each group.<sup>23</sup> Based on a planned interim analysis after enrollment of 50%, the independent data monitoring committee recommended increasing the sample size to 131 in each group.<sup>24</sup>

All analyses were performed using SAS version 9.2 (SAS Institute Inc).

## Results

A total of 310 patients were randomized, of whom 273 patients met the definition of generalized convulsive status epi-

Figure. CONSORT Diagram of Participants in the Pediatric Seizure Study



lepticus (140 taking diazepam and 133 taking lorazepam). The Figure depicts the CONSORT diagram for all patients. Table 1 displays the patient characteristics of the randomized patients and Table 2 shows the seizure etiologies in the 2 treatment groups. There were no significant baseline differences in patient characteristics or the distribution of seizure etiologies between the treatment groups.

There were no significant differences in the primary efficacy and safety outcomes. Cessation of status epilepticus within 10 minutes without recurrence within 30 minutes occurred in 101 patients (72.1%) in the diazepam group compared with 97 patients (72.9%) in the lorazepam group (Table 3; absolute efficacy difference, 0.8%; 95% CI, -11.4% to 9.8%). Twenty-six patients in each group required assisted ventilation (16.0% in the diazepam vs 17.6% in the lorazepam groups; absolute risk difference, 1.6%; 95% CI, -9.9% to 6.8%). These findings were consistent in per-protocol analyses after excluding 64 additional patients with significant protocol deviations, also shown in Table 3. The most common protocol violations were study medication dose outside the 30% margin ( $n = 27$ ), late administration of the second dose of study medication ( $n = 21$ ), incorrect randomization ( $n = 15$ ), receipt of a benzodiazepine within 2 hours prior to enrollment ( $n = 4$ ), IV extravasation ( $n = 3$ ), and early administration of secondary medications ( $n = 3$ ).

Secondary study outcomes are shown in Table 3. The rates of recurrent generalized convulsions within 60 minutes, excluding patients who failed the primary outcome, were 10.9% for diazepam and 10.3% for lorazepam and the rates of recurrence within 4 hours were 38.6% and 39.2%, respectively. Data on the precise time of cessation of status epilepticus were available in 266 of 273 patients (97.4%). The median time to termination of status epilepticus was 2.5 minutes (interquartile range, 1.0-12.5 minutes) in the diazepam group and 2.0 minutes (interquartile range, 1.0-11.0 minutes) in the lorazepam group ( $P = .80$ ). The only statistically significant difference between treatment groups in any of the secondary outcomes was in the incidence of sedation, which occurred in 81 of 162 diazepam patients (50%) and 99 of 148 lorazepam patients (66.9%) (absolute risk difference, 16.9%; 95% CI, 6.1%-27.7%). Survival analyses showed no statistically significant differences between groups in response latency (hazard ratio, 0.99; 95% CI, 0.75-1.29;  $P = .92$ ; eFigure 1 in Supplement) or time to recurrence of seizures (hazard ratio, 1.04; 95% CI, 0.77-1.4;  $P = .81$ ; eFigure 2 in Supplement). There was a significant difference favoring the diazepam arm in time to return to baseline mental status (hazard ratio, 1.96; 95% CI, 1.35-2.84;  $P = .0004$ ; eFigure 3 in Supplement). There were no significant differences in efficacy between treatments when com-

Table 1. Characteristics of Randomized Patients<sup>a</sup>

Characteristic	Age 3 mo to <3 y		Age 3 to <13 y		Age ≥13 y		Overall	
	Diazepam (n = 77)	Lorazepam (n = 71)	Diazepam (n = 68)	Lorazepam (n = 63)	Diazepam (n = 17)	Lorazepam (n = 14)	Diazepam (n = 162)	Lorazepam (n = 148)
Age, mean (SD), y	1.4 (0.7)	1.4 (0.7)	6.1 (2.5)	6.3 (2.6)	15.9 (3.7)	15.5 (1.6)	4.9 (4.9)	4.8 (4.6)
Median (range)	1.3 (0.3-2.9)	1.3 (0.3-2.9)	5.2 (3.0-11.7)	5.8 (3.0-12.0)	14.6 (13.1-28.0)	15.9 (13.0-17.8)	3.2 (0.3-28.0)	3.1 (0.3-17.8)
Male, No. (%)	41 (53.2)	33 (46.5)	35 (51.5)	30 (47.6)	11 (64.7)	5 (35.7)	87 (53.7)	68 (45.9)
Ethnicity, No. (%)								
Hispanic/Latino	30 (39.0)	20 (28.2)	19 (27.9)	21 (33.3)	2 (11.8)	3 (21.4)	51 (31.5)	44 (29.7)
Not reported	2 (2.6)	1 (1.4)	3 (4.4)	2 (3.2)	2 (11.8)	1 (7.1)	7 (4.3)	4 (2.7)
Race/ethnicity, No. (%)								
American Indian/Alaska Native	0	0	0	1 (1.6)	1 (5.9)	0	1 (0.6)	1 (0.7)
Asian	3 (3.9)	1 (1.4)	1 (1.5)	2 (3.2)	0	0	4 (2.5)	3 (2.0)
Black/African American	26 (33.8)	27 (38.0)	23 (33.8)	23 (36.5)	5 (29.4)	7 (50.0)	54 (33.3)	57 (38.5)
Native Hawaiian/Pacific Islander	1 (1.3)	0	1 (1.5)	0	0	1 (7.1)	2 (1.2)	1 (0.7)
White	38 (49.4)	31 (43.7)	34 (50.0)	33 (52.4)	9 (52.9)	4 (28.6)	81 (50.0)	68 (45.9)
More than 1 race	5 (6.5)	8 (11.3)	3 (4.4)	2 (3.2)	0	0	8 (4.9)	10 (6.8)
Other	4 (5.2)	2 (2.8)	4 (5.9)	1 (1.6)	2 (11.8)	1 (7.1)	10 (6.2)	4 (2.7)
Not reported	0	2 (2.8)	2 (2.9)	1 (1.6)	0	1 (7.1)	2 (1.2)	4 (2.7)

<sup>a</sup> None of the differences were statistically significant.

paring subgroups of primary etiology. The point estimate for overall efficacy for febrile seizures was lower than for other etiologies but was not statistically significant (65.2% vs 76.1%; absolute efficacy difference, -10.9%; 95% CI, -22.6% to 0.74%).

## Discussion

The results of this randomized clinical trial do not support the hypothesis that lorazepam is superior to diazepam for the treatment of pediatric status epilepticus of at least 5 minutes' duration. Both medications were effective in stopping status epilepticus in more than 70% of cases and had rates of severe respiratory depression of less than 20%. There were no statistically significant differences in either primary or secondary efficacy and safety outcomes, with the exception of higher rates and duration of sedation for lorazepam.

Our results are similar to several previous studies of benzodiazepines for status epilepticus in children. In a single-site quasirandomized study<sup>16</sup> of IV lorazepam compared with diazepam in 61 children, efficacy was 70% and 65%, respectively, similar to our results. Qureshi et al<sup>15</sup> performed a pediatric medical record audit after a protocol change from IV diazepam to IV lorazepam and found a success rate of 65% in both groups. While a randomized trial (RAMPART [Rapid Anticonvulsant Medication Prior to Arrival Trial])<sup>25</sup> of adults and children found, overall, that intramuscular midazolam initiated in the prehospital setting stopped more seizures at arrival to the ED than intrave-

nous lorazepam (73% vs 63%), subgroup analysis of the 149 children enrolled showed similar results (70% vs 68%, respectively) for the 2 medications. The overall rate of intubation (14% in each group) was also similar to the overall rates of severe respiratory depression in our study (17%).

Previous studies of adults with status epilepticus have found consistent, but statistically nonsignificant, trends toward superiority of lorazepam over diazepam with respect to efficacy. Treiman et al<sup>26</sup> enrolled 518 adults with both overt and subtle status; in the subgroup of patients with overt status epilepticus, success rates were 65% for the lorazepam group and 56% for the diazepam plus phenytoin group. Alldredge et al<sup>23</sup> enrolled 205 adults with status epilepticus in the prehospital setting and found success rates for lorazepam and diazepam of 59% and 43%, respectively. In this study, both medications were superior to placebo for both efficacy and safety. Similarly, a smaller study of 78 adults found success rates for lorazepam and diazepam of 89% and 76%, respectively.<sup>10</sup> These trials found similar safety rates for both medications.<sup>10,23,26</sup>

Our study's results contrast with several retrospective studies in children, which suggested that lorazepam was more effective in stopping convulsions or had lower rates of respiratory depression.<sup>12,13</sup> This study was designed to improve on the limitations of previous studies. First, it was a randomized clinical trial rather than a retrospective review or quasi-experimental trial. Second, a second dose was administered, when needed, at half the initial dose based on pharmacokinetic models derived in a previous study.<sup>21</sup> Finally, medications were administered as a slow IV

Table 2. Seizure Etiology by Treatment Group<sup>a</sup>

Variable	No. (%)							
	Age 3 mo to <3 y		Age 3 to <13 y		Age ≥13 y		Overall	
	Diazepam (n = 72)	Lorazepam (n = 62)	Diazepam (n = 55)	Lorazepam (n = 60)	Diazepam (n = 13)	Lorazepam (n = 11)	Diazepam (n = 140)	Lorazepam (n = 133)
Febrile	36 (50.0)	32 (51.6)	13 (23.6)	8 (13.3)	0	0	49 (35.0)	40 (30.1)
Low levels of anti-epileptic drugs	2 (2.8)	4 (6.5)	8 (14.5)	9 (15.0)	2 (15.4)	0	12 (8.6)	13 (9.8)
Acute symptomatic	13 (18.1)	7 (11.3)	8 (14.5)	8 (13.3)	2 (15.4)	0	23 (16.4)	15 (11.3)
Head injury	3 (4.2)	1 (1.6)	0	2 (3.3)	0	0	3 (2.1)	3 (2.3)
CNS infection	1 (1.4)	1 (1.6)	3 (5.5)	1 (1.7)	0	0	4 (2.9)	2 (1.5)
Acute hypoxic/ischemic insult	2 (2.8)	0	0	0	0	0	2 (1.4)	0
Hypoglycemia	0	0	0	0	0	0	0	0
Electrolyte abnormality	0	2 (3.2)	0	0	0	0	0	2 (1.5)
Brain tumor	1 (1.4)	0	1 (1.8)	0	1 (7.7)	0	3 (2.1)	0
Acute vascular event	0	1 (1.6)	0	0	0	0	0	1 (0.8)
Alcohol or other drug toxicity	1 (1.4)	0	0	0	0	0	1 (0.7)	0
Other	5 (6.9)	2 (3.2)	4 (7.3)	5 (8.3)	1 (7.7)	0	10 (7.1)	7 (5.3)
Remote symptomatic	5 (6.9)	6 (9.7)	7 (12.7)	6 (10.0)	1 (7.7)	2 (18.2)	13 (9.3)	14 (10.5)
Past hypoxic/ischemic insult	2 (2.8)	0	1 (1.8)	1 (1.7)	0	1 (9.1)	3 (2.1)	2 (1.5)
Past head injury	0	1 (1.6)	1 (1.8)	0	0	0	1 (0.7)	1 (0.8)
Past brain surgery	0	1 (1.6)	0	1 (1.7)	0	0	0	2 (1.5)
Other	3 (4.2)	4 (6.5)	5 (9.1)	4 (6.7)	1 (7.7)	1 (9.1)	9 (6.4)	9 (6.8)
Idiopathic	14 (19.4)	13 (21.0)	15 (27.3)	24 (40.0)	8 (61.5)	7 (63.6)	37 (26.4)	44 (33.1)
Other	2 (2.8)	0	4 (7.3)	4 (6.7)	0	2 (18.2)	6 (4.3)	6 (4.5)

Abbreviation: CNS, central nervous system

<sup>a</sup> None of the differences were statistically significant.

push for 1 minute. In contrast, retrospective studies cannot ensure that dosing was given in such a standardized manner. Our study results are also different than the population-based study by Chin et al.<sup>14</sup> They showed that lorazepam was far more effective than diazepam; however, lorazepam was administered intravenously and diazepam rectally, making a direct comparison difficult.

Compared with previous studies of status epilepticus in children, this study was larger and is further strengthened by the multicenter design across 11 geographically diverse pediatric academic hospitals. Furthermore, the use of Exception from Informed Consent for Emergency Research helped prevent selection bias by allowing the inclusion of patients without previous seizures. Prior prehospital care was controlled for by excluding all patients who had received a benzodiazepine in the previous 7 days, including ambulance administration, allowing for an uncontaminated examination of efficacy and safety. The methods used incorporated a standardized assessment of sedation, using the validated Riker scale, and are a strength of this study as compared with previous studies.

The study results have important implications for both prehospital and ED care. Diazepam can be stored without refrig-

eration and thus has been used as the treatment of choice in many prehospital systems. The results of this study do not support the superiority of lorazepam over diazepam as a first-line agent for pediatric status epilepticus. Taken together with the results of the RAMPART trial,<sup>25</sup> it would appear that either diazepam, lorazepam, or midazolam could be chosen as a reasonable first-line therapy.

The study has several potential limitations. First, electroencephalogram monitoring was not used to determine the termination of status epilepticus. Instead, clinical criteria were used, which is consistent with previous studies.<sup>10,12,13,23</sup> Electroencephalogram monitoring is not readily available in most EDs and is not clinically useful except in rare circumstances or unusual forms of status epilepticus. Second, this study was designed as a superiority trial rather than a noninferiority trial. Therefore, failure to demonstrate a difference between treatment groups should not be construed to mean that lorazepam is statistically equivalent to diazepam. Although the point estimates for both efficacy and safety outcomes are similar in the 2 groups, the confidence intervals suggest that one medication could be superior in efficacy by as much as approximately 10% to 11% and in safety by approximately 7% to

Table 3. Primary and Secondary Efficacy and Safety Outcomes<sup>a</sup>

Outcome	No./Total No. (%)							
	Age 3 mo to <3 y		Age 3 to <13 y		Age ≥13 y		Overall	
	Diazepam	Lorazepam	Diazepam	Lorazepam	Diazepam	Lorazepam	Diazepam	Lorazepam
<b>Primary Outcomes</b>								
Efficacy	48/72 (66.7)	38/62 (61.3)	44/55 (80.0)	49/60 (81.7)	9/13 (69.2)	10/11 (90.9)	101/140 (72.1)	97/133 (72.9)
Efficacy (per-protocol population)	35/48 (72.9)	32/48 (66.7)	36/43 (83.7)	44/50 (88.0)	7/11 (63.6)	9/9 (100.0)	78/102 (76.5)	85/107 (79.4)
Need for assisted ventilation (all randomized patients)	11/77 (14.3)	16/71 (22.5)	12/68 (17.6)	10/63 (15.9)	3/17 (17.6)	0/14	26/162 (16.0)	26/148 (17.6)
<b>Secondary Outcomes</b>								
Patients requiring only a single dose of study medication	41/72 (56.9)	34/62 (54.8)	37/55 (67.3)	38/60 (63.3)	9/13 (69.2)	8/11 (72.7)	87/140 (62.1)	80/133 (60.2)
Patients requiring a second dose of study medication	27/72 (37.5)	25/62 (40.3)	14/55 (25.5)	17/60 (28.3)	1/13 (7.7)	2/11 (18.2)	42/140 (30.0)	44/133 (33.1)
Patients requiring study medication plus additional anticonvulsant medication(s)	15/72 (20.8)	15/62 (24.2)	4/55 (7.3)	6/60 (10.0)	2/13 (15.4)	0/11	21/140 (15.0)	21/133 (15.8)
Patients responding to fosphenytoin or phenytoin within 10 min	6/15 (40.0)	2/15 (13.3)	0/4	1/6 (16.7)	0/2	NA	6/21 (28.6)	3/21 (14.3)
Recurrence within 1 h	6/48 (12.5)	3/38 (7.9)	5/44 (11.4)	6/49 (12.2)	0/9	1/10 (10.0)	11/101 (10.9)	10/97 (10.3)
Recurrence within 4 h	23/48 (47.9)	25/38 (65.8)	11/44 (25.0)	12/49 (24.5)	5/9 (55.6)	1/10 (10.0)	39/101 (38.6)	38/97 (39.2)
Any respiratory depression (all severities)	38/77 (49.4)	32/71 (45.1)	33/68 (48.5)	21/63 (33.3)	3/17 (17.6)	1/14 (7.1)	74/162 (45.7)	54/148 (36.5)
Sedation (Riker score <3)	35/77 (45.5)	44/71 (62.0) <sup>b</sup>	38/68 (55.9)	47/63 (74.6) <sup>b</sup>	8/17 (47.1)	8/14 (57.1)	81/162 (50.0)	99/148 (66.9) <sup>b</sup>
Aspiration pneumonia	0/77	1/71 (1.4)	1/68 (1.5)	1/63 (1.6)	1/17 (5.9)	0/14	2/162 (1.2)	2/148 (1.4)
<b>Secondary Time Outcomes, Median (IQR), min</b>								
No. of noncensored patients	51	42	46	53	11	11	108	106
Time to status epilepticus cessation	3.0 (1.0-9.0)	4.0 (1.0-10.0)	2.0 (1.0-7.0)	2.0 (1.0-6.5)	3.0 (1.0-5.0)	1.0 (0.0-2.0)	2.5 (1.0-12.5)	2.0 (1.0-11.0)
Time to recovery from sedation	114.0 (60.0-121.0)	60.0 (49.0-176.0)	120.0 (55.0-174.0)	136.0 (111.5-180.0)	10.5 (4.5-25.0)	5.0 (1.0-35.0)	104.5 (60.0-125.0)	120.0 (53.0-174.5)

Abbreviations: IQR, interquartile range; NA, not applicable.

<sup>a</sup> Efficacy analysis includes all patients who received study medication and were experiencing generalized convulsive SE. Patients who were enrolled more

than once were only included for the first visit. The per-protocol analysis excludes patients with significant protocol deviations (see Methods section).

<sup>b</sup> *P* < .05.

10%. Third, prehospital treatment by paramedics is an effective therapy<sup>25</sup> and is becoming more common. While excluding patients receiving benzodiazepines in the previous 7 days permitted a cleaner analysis of efficacy, we did not study the efficacy or safety of lorazepam or diazepam for patients requiring additional benzodiazepine treatment in the ED after receiving prehospital treatment. Fourth, the duration of status epilepticus prior to treatment in the cohort was not characterized because duration of status epilepticus prior to hospital arrival is often not avail-

able or reliable by historical report. Finally, protocol deviations were common in this study and reflect the often unpredictable practice of emergency medicine, including incomplete or inaccurate initial information available in emergency situations, incorrect weight estimation, and IV infiltration during infusion. However, it is reassuring that the results of the per-protocol analysis are consistent with overall results.

The results suggest future research opportunities. For example, more efforts are required to ensure patient safety

and the prevention of adverse events, especially in the emergency care setting.<sup>27,28</sup> Failure of efficacy was observed in approximately 1 in 4 children and severe respiratory depression rate in approximately 1 in 6. Future trials should consider newer medications and novel interventions targeting those at highest risk for medication failure or respiratory depression.

## Conclusions

Among pediatric patients with convulsive status epilepticus, treatment with lorazepam did not result in improved efficacy or safety compared with diazepam. These findings do not support the preferential use of lorazepam for this condition.

### ARTICLE INFORMATION

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### REFERENCES

1. US Department of Health and Human Services. 2010 national statistics. <http://hcupnet.ahrq.gov/Hcupnet.jsp>. Accessed July 5, 2013.
2. Shinnar S, Berg AT, Moshe SL, et al. The risk of seizure recurrence after a first unprovoked afebrile seizure in childhood: an extended follow-up. *Pediatrics*. 1996;98(2, pt 1):216-225.
3. De Negri M, Baglietto MG. Treatment of status epilepticus in children. *Paediatr Drugs*. 2001;3(6):411-420.
4. Treiman DM. The role of benzodiazepines in the management of status epilepticus. *Neurology*. 1990;40(5)(suppl 2):32-42.
5. Mitchell WG. Status epilepticus and acute repetitive seizures in children, adolescents, and young adults: etiology, outcome, and treatment. *Epilepsia*. 1996;37(suppl 1):S74-S80.
6. Appleton R, Choonara I, Martland T, Phillips B, Scott R, Whitehouse W. The treatment of convulsive status epilepticus in children: The Status Epilepticus Working Party, Members of the Status Epilepticus Working Party. *Arch Dis Child*. 2000;83(5):415-419.
7. Manno EM. New management strategies in the treatment of status epilepticus. *Mayo Clin Proc*. 2003;78(4):508-518.
8. Bleck TP. Management approaches to prolonged seizures and status epilepticus. *Epilepsia*. 1999;40(suppl 1):S59-S63, discussion S64-S66.
9. Sabo-Graham T, Seay AR. Management of status epilepticus in children. *Pediatr Rev*. 1998;19(9):306-309, quiz 310.

10. Leppik IE, Derivan AT, Homan RW, Walker J, Ramsay RE, Patrick B. Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA*. 1983;249(11):1452-1454.
11. Cock HR, Schapira AHV. A comparison of lorazepam and diazepam as initial therapy in convulsive status epilepticus. *QJM*. 2002;95(4):225-231.
12. Chiulli DA, Terndrup TE, Kanter RK. The influence of diazepam or lorazepam on the frequency of endotracheal intubation in childhood status epilepticus. *J Emerg Med*. 1991;9(1-2):13-17.
13. Giang DW, McBride MC. Lorazepam versus diazepam for the treatment of status epilepticus. *Pediatr Neurol*. 1988;4(6):358-361.
14. Chin RF, Neville BG, Peckham C, Wade A, Bedford H, Scott RC. Treatment of community-onset, childhood convulsive status epilepticus: a prospective, population-based study [published correction appears in *Lancet Neurol*. 2008;7(9):771]. *Lancet Neurol*. 2008;7(8):696-703.
15. Qureshi A, Wassmer E, Davies P, Berry K, Whitehouse WP. Comparative audit of intravenous lorazepam and diazepam in the emergency treatment of convulsive status epilepticus in children. *Seizure*. 2002;11(3):141-144.
16. Appleton R, Sweeney A, Choonara I, Robson J, Molyneux E. Lorazepam versus diazepam in the acute treatment of epileptic seizures and status epilepticus. *Dev Med Child Neurol*. 1995;37(8):682-688.
17. Martland T, Baxter P, Rittey C. Is there an agreed treatment for children in status epilepticus? *Dev Med Child Neurol*. 1998;40(4):286-287.
18. Lowenstein DH. Status epilepticus: an overview of the clinical problem. *Epilepsia*. 1999;40(suppl 1):S3-S8, discussion S21-S22.
19. Appleton R, Choonara I, Martland T, Phillips B, Scott R, Whitehouse W. The treatment of convulsive status epilepticus in children: The Status Epilepticus Working Party. *Arch Dis Child*. 2000;83(5):415-419.
20. Food and Drug Administration. Guidance for institutional review boards, clinical investigators, and sponsors: Exception from Informed Consent Requirements for Emergency Research. March 2011. <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf>. Accessed April 13, 2012.
21. Chamberlain JM, Capparelli EV, Brown KM, et al; Pediatric Emergency Care Applied Research Network (PECARN). Pharmacokinetics of intravenous lorazepam in pediatric patients with and without status epilepticus. *J Pediatr*. 2012;160(4):667-672, e2.
22. Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. *Crit Care Med*. 1999;27(7):1325-1329.
23. Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med*. 2001;345(9):631-637.
24. Chen YHJ, DeMets DL, Lan KKG. Increasing the sample size when the unblinded interim result is promising. *Stat Med*. 2004;23(7):1023-1038.
25. Silbergleit R, Durkalski V, Lowenstein D, et al; NETT Investigators. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med*. 2012;366(7):591-600.
26. Treiman DM, Meyers PD, Walton NY, et al; Veterans Affairs Status Epilepticus Cooperative Study Group. A comparison of four treatments for generalized convulsive status epilepticus. *N Engl J Med*. 1998;339(12):792-798.
27. Woods D, Thomas E, Holl J, Altman S, Brennan T. Adverse events and preventable adverse events in children. *Pediatrics*. 2005;115(1):155-160.
28. Krug SE, Frush K; Committee on Pediatric Emergency Medicine, American Academy of Pediatrics. Patient safety in the pediatric emergency care setting. *Pediatrics*. 2007;120(6):1367-1375.