CJEM Journal Club

Lorazepam v. diazepam for pediatric status epilepticus

Reviewed by: Rovina Fiona Pinto, BBA, MD*; Jennifer Turnbull, MD†

Clinical question
Is intravenous (IV) lorazepam superior to IV diazepam in the treatment of pediatric status epilepticus?
Article chosen
Chamberlain JM, Okada P, Holsti M, et al. Lorazepam v. diazepam for pediatric status epilepticus: a randomized clinical trial. *JAMA* 2014;311(16):1652-60.
Objective
To determine whether lorazepam has better efficacy and safety than diazepam for treating pediatric status epilepticus.

Keywords: pediatric, status epilepticus, Lorazepam, Diazepam

BACKGROUND

Status epilepticus is a neurological emergency defined as continuous generalized tonic-clonic seizure activity, with loss of consciousness for longer than 30 minutes, or two or more discrete seizures without return to baseline mental status.[1] "Early" or "impending" status epilepticus is a continuous or intermittent seizure lasting longer than 5 minutes without full recovery of consciousness between seizures.[1] The annual incidence of status epilepticus is about 10 to 75 per 100,000[2] in developed countries. If not managed appropriately, status epilepticus can result in permanent neuronal cell injury and cell loss, in addition to systemic problems such as impaired ventilation, pulmonary aspiration, and metabolic complications.[3] However, early cessation of seizures has been shown, by animal models and observational studies to result in improved morbidity and mortality.[4-6] Benzodiazepines are the most commonly used first-line agent for the management of status epilepticus.[7] Diazepam, lorazepam, and midazolam have been used in the treatment of status epilepticus,[8] though intravenous (IV) lorazepam has been recommended by the Canadian Pediatric Society (CPS) as the first-line treatment in the hospital.[9,10] Lorazepam is thought to cause less hypotension and respiratory depression, compared to diazepam, and be less sedating. [11] Some non-randomized controlled trial (RCT) pediatric studies also suggested that lorazepam may be more effective at terminating seizures.[12-14] Lorazepam is not currently Food and Drug Administration (FDA) approved in the United States for the treatment of seizures. This study was designed to evaluate whether lorazepam is more efficacious and safer than diazepam for the purpose of gaining FDA approval.

STUDY DESIGN

The study was a large RCT involving 11 academic pediatric hospitals in the United States, 8 of which were part of the Pediatric Emergency Care Applied Research Network (PECARN). Both participants and clinicians were blinded to the intervention received. The study was designed as a superiority trial and powered to detect an absolute difference in efficacy of at least 17% between the two groups, based on previous literature (80% power, $n = 262$).

The study population was children age 3 months to less than 18 years in generalized tonic-clonic status epilepticus.

Participants were recruited between March 2008 and March 2012. They were stratified into three age groups with a 1:1 permuted block randomization and block

From the *McGill Emergency Medicine Residency Program, McGill University, Montreal, QC; and †Division of Pediatric Emergency Medicine, Montreal Children's Hospital, McGill University Health Centre, Montreal, QC.

Correspondence to: Dr. Rovina Fiona Pinto, 1634 Selkirk Ave, Apt. 4, Montreal, QC, H3H1C8; Email: rovina.pinto@mail.mcgill.ca

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sizes of four subjects. The age groups were 3 months to less than 3 years, 3 years to less than 13 years, and 13 years to less than 18 years. Opaque syringes with equal medication volumes were provided to the clinicians so that they were blinded to medication that they were administering.

STUDY OUTCOMES

The primary efficacy outcome was determined to be the cessation of status epilepticus within 10 minutes and a sustained absence of convulsions for 30 minutes.

Primary safety outcome was the need for assisted ventilation (bag-valve-mask ventilation or endotracheal intubation) within 4 hours of initial medication.

Secondary efficacy outcomes were time to cessation of convulsions, need for second dose of medication, need for second- or third-line anticonvulsants, and sustained absence of convulsions at 1 and 4 hours. Secondary safety outcomes were incidence of aspiration pneumonia, any degree of respiratory depression, time to return to baseline mental status, and degree of sedation or agitation.

RESULTS

A total of 310 patients were enrolled in the study. All 310 randomized patients were included in the safety analysis; however, 37 patients were excluded from the primary efficacy analysis (22 diazepam, 15 lorazepam). Patients were excluded because they did not have status epilepticus ($n=31$) or they were duplicate participants ($n=7$). One of the excluded patients met both criteria. Primary efficacy analysis was therefore performed on 273 patients only. The results were analysed using an intention-to-treat analysis; however, a per-protocol analysis was conducted for the efficacy outcome to account for 64 patients with significant protocol deviations (38 diazepam, 26 lorazepam). Protocol violations included a medication dose outside of the 30% margin ($n=27$), late administration of second dose ($n=21$), incorrect randomization ($n=15$), receipt of a benzodiazepine prior to enrolment ($n=4$), IV extravasation ($n=3$), and early administration of secondary medications ($n=3$).

There was no significant difference between diazepam and lorazepam with respect to the primary outcomes. Specifically, there was no difference between groups in the cessation of seizures at 10 minutes and the absence of seizures at 30 minutes, with an absolute efficacy difference of 0.8% (95% confidence interval [CI]: −11.4% to 9.8%). This was true on both intention-to-treat ($n=273$) and per-protocol analysis ($n=209$). Likewise, the absolute risk difference for the primary safety outcome, the need for assisted ventilation within 4 hours of initial medication, was not significant at 1.6% (95% CI: −9.9% to 6.8%). Approximately 72% of seizures were arrested with either medication, and there was a 16%-17% incidence of respiratory depression requiring assisted ventilation in both groups. In terms of secondary outcomes, the only statistically significant difference was in the incidence of sedation, which occurred in 50% of diazepam-treated patients and 66.9% in lorazepam-treated patients, with an absolute risk difference of 16.9% (95% CI: 6.1%-27.7%). All other secondary outcomes were not significantly different. Despite age stratification, statistical difference between groups within age groups was not analysed.

COMMENTARY

This study is the first pediatric-specific multicentre RCT looking at IV lorazepam versus IV diazepam for the treatment of status epilepticus. Previous studies have shown varying results, but existing data combined with consensus opinion led to the recommendation of IV lorazepam as first-line treatment in the hospital.[6]

The results of the current study do not support the hypothesis that IV lorazepam is superior to IV diazepam for pediatric status epilepticus. IV lorazepam did not result in a decrease in the cessation of the number of seizures or in the number of patients requiring assisted ventilation, such as bag-valve-mask ventilation or intubation. It should be noted that lorazepam and diazepam should not be considered equivalent to each other, because this trial was designed as a superiority trial and not a non-inferiority or equivalency trial. It is interesting that the authors chose this trial design, when most trials seeking federal approval of a medication use a non-inferiority design. A considerably larger sample size would have been required to determine the non-inferiority of lorazepam versus diazepam. The conclusion that lorazepam is non-inferior to diazepam for pediatric status epilepticus, therefore, cannot be drawn from the current results.

There were significant protocol deviations in this study, and 12%-20% of patients were excluded at different levels of the analysis. Appropriately, an intention-to-treat analysis was performed; however, the

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patient population analysed differed between the two primary outcomes of efficacy and safety. Intention-to-treat analysis should include all patients randomized, yet 37 patients were excluded from the primary efficacy analysis. The primary efficacy analysis is therefore a modified intention-to-treat as the patients were excluded because they did not met inclusion criteria. Baseline characteristics were compared for the original 310 randomized patients only. We are unable to determine whether the exclusion of these patients introduced bias or differences between groups. A per-protocol analysis was performed for the primary efficacy analysis. Unfortunately, due to 64 exclusions, the sample size in this analysis was smaller than that required by the power calculation. It would strengthen the results if the study were powered for the per-protocol analysis.

Another notable point is the dose regimen selected. In the study, the lorazepam dose was 0.1 mg/kg, and the second dose was half that amount. This dose regimen was selected based on a previous study conducted by the authors looking at the pharmacokinetics of lorazepam in the treatment of status epilepticus.[15] This regimen differs from common practice and the CPS Guidelines where the second dose is generally recommended to be the same as the initial dose.[10] The amount of respiratory depression and sedation may in fact be higher in these patients than what was determined in the study. The duration of sedation was already longer for the lorazepam group and may be even higher if common practice protocols are used.

FUTURE STUDIES

An additional area of interest is the possibility of differential effects among the age groups. Although lorazepam and diazepam had similar results in primary outcomes for children ages 3 months to <3 years and 3 to <13 years, lorazepam seemed superior for the > 13 years population. Lorazepam had improved efficacy (90.9% v. 69.2%) and decreased the need for assisted ventilation (0% v. 17.6%) compared to diazepam. This suggests that each benzodiazepine may not be equally efficacious in all age groups. This study was not powered to detect differences between the various age stratifications, so firm conclusions cannot be drawn. Nonetheless, this is an area of interest and can be explored with further research.

Future similarly designed studies comparing IV midazolam with lorazepam or diazepam would further add to the literature of the treatment of pediatric status epilepticus.

Finally, at least 30% of patients failed either treatment. This efficacy is similar to that found in other studies of lorazepam and diazepam. The researchers suggested that future trials should look into different medication and novel procedures for patients who do not respond to benzodiazepines. Thus, future studies should look at identifying and targeting those at highest risk for medication failure or respiratory depression.

CONCLUSION

This was a well-designed RCT comparing IV lorazepam to IV diazepam. This study is important because it highlighted that, although IV lorazepam was suggested by other non-RCTs to be the superior medication for the treatment of seizures, this did not appear to be true. The current study improved on the limitations of previous studies because it was a pediatric-specific RCT, and there was standardized dosing across the study population. Its results were in contrast to previous literature and the CPS guidelines, which currently suggest the superiority of lorazepam.

Although this study was not designed to determine non-inferiority or equivalency, it is likely that, clinically, both IV lorazepam and IV diazepam can be used to effectively treat pediatric status epilepticus. These results, combined with the results of the RAMPART (rapid anticonvulsant medication prior to arrival) trial that found both intramuscular midazolam and IV lorazepam were equally efficacious in the treatment of seizures in children,[16] indicate that midazolam, diazepam, or lorazepam can likely be used interchangeably for pediatric seizure management. The medication selected can be based on physician comfort and the protocol derived at the institution of practice. Each medication has advantages and disadvantages related to route of administration and need for refrigeration, and lorazepam need not be preferentially selected as the medication of choice for the treatment of pediatric status epilepticus.

Competing interests: None declared.

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