

# WHERE IN THE WORLD ARE WE? GENERALIZING THE RESULTS OF STATUS EPILEPTICUS TRIALS

**Comparison of Buccal Midazolam with Rectal Diazepam in the Treatment of Prolonged Seizures in Ugandan Children: A Randomized Clinical Trial.** Mpimbaza A, Ndeezi G, Staedke S, Rosenthal PJ, Byarugaba J. *Pediatrics* 2008; 121(1):e58–64. **OBJECTIVE:** Our goal was to compare the efficacy and safety of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children. **METHODS:** This was a single-blind, randomized clinical trial in which 330 patients were randomly assigned to receive buccal midazolam or rectal diazepam. The trial was conducted in the pediatric emergency unit of the national referral hospital of Uganda. Consecutive patients who were aged 3 months to 12 years and presented while convulsing or who experienced a seizure that lasted >5 minutes were randomly assigned to receive buccal midazolam plus rectal placebo or rectal diazepam plus buccal placebo. The primary outcome of this study was cessation of visible seizure activity within 10 minutes without recurrence in the subsequent hour. **RESULTS:** Treatment failures occurred in 71 (43.0%) of 165 patients who received rectal diazepam compared with 50 (30.3%) of 165 patients who received buccal midazolam. Malaria was the most common underlying diagnosis (67.3%), although the risk for failure of treatment for malaria-related seizures was similar: 35.8% for rectal diazepam compared with 31.8% for buccal midazolam. For children without malaria, buccal midazolam was superior (55.9% vs 26.5%). Respiratory depression occurred uncommonly in both of the treatment arms. **CONCLUSION:** Buccal midazolam was as safe as and more effective than rectal diazepam for the treatment of seizures in Ugandan children, although benefits were limited to children without malaria.

## COMMENTARY

Convulsive status epilepticus (SE), continuous or recurrent epileptic seizures without full recovery between seizures, is a neurological emergency requiring rapid diagnosis and treatment to prevent morbidity and mortality. Since early treatment is more efficacious, the duration of seizures required to diagnose SE has been progressively shortened, from 30 to 10 or even 5 minutes (1). In adults, intravenous lorazepam has been identified as the most effective initial treatment but controls SE only two-thirds of the time (2,3). Treatment for SE in children has been less well studied than in adults. A recent Cochrane review of four studies of prolonged convulsive seizures in children concluded that 1) intravenous lorazepam is at least as effective as intravenous diazepam and is associated with fewer adverse

events, and 2) buccal midazolam is the treatment of choice when intravenous access is not available (4). In a randomized, controlled, unblinded study of prolonged seizures among patients in the United Kingdom, buccal midazolam stopped seizures within 10 minutes and prevented recurrence in the next hour in 56 percent of subjects, compared with 27 percent for rectal diazepam (5). Respiratory depression (i.e., a fall in oxygen saturation or decrease in respiratory rate necessitating assisted breathing with face-mask inflation or intubation) was seen in approximately 5.5 percent of patients in both groups.

Should SE treatment be the same in developed and developing countries, which have markedly different etiologies of SE? In developed countries, febrile seizures and low antiepileptic drug (AED) levels cause most cases of SE in children. In developing countries, acute symptomatic etiologies, most often CNS infections, account for 28 to 67 percent of cases of SE (6). In malaria-endemic areas, falciparum malaria is the leading

cause of presentation to the emergency department for seizures (6). While some seizures associated with malaria may be simple febrile seizures, seizures are more common for patients with high parasitemia and in children under age 5. About a third of patients with malaria and seizures have cerebral malaria, manifesting as seizures, confusion, or coma. In these cases, *Plasmodium falciparum*-infected erythrocytes sequester in deep capillary beds in the cerebral microvasculature, causing local ischemia and hypoxia. Prolonged convulsions with malaria are associated with a high risk of mortality and neurologic sequelae in survivors, such as behavioral abnormalities, focal neurologic deficits, and epilepsy.

Countries with limited healthcare resources face particular challenges in the treatment of SE. Equipment for intravenous administration or refrigeration of AEDs may be limited or unavailable. Many centers lack the infrastructure to provide ventilatory support, so respiratory depression by AEDs is associated with increased mortality. Because of these limitations, diazepam is the first-line treatment for seizures in most of sub-Saharan Africa. Rectal diazepam is inexpensive, readily available, well absorbed, and fairly efficacious. Onset of action is rapid, but peak levels are variable. Diazepam is rapidly redistributed from brain to body fat, so seizures may recur early after administration. Accumulation with repeated doses carries an increased risk of respiratory depression. Buccal midazolam is also inexpensive, well absorbed, easily administered, and rapidly effective. Because of more prolonged duration of activity, seizures are less likely to recur early after treatment.

The current study by Mpimbaza et al. is a large, well-designed trial comparing buccal midazolam to rectal diazepam for treatment of prolonged seizures in pediatric patients in Uganda. The primary outcome measures of combined initial efficacy and sustained efficacy are appropriate ones for SE trials. Rapid cessation of seizures is essential, and early recurrence can necessitate additional doses of AEDs, increasing the risk for respiratory depression. Dose was determined by age range, for approximate doses of 0.5 mg/kg. To blind the study team, patients received two simultaneous treatments, colored to match. Although the inclusion criteria specified an age range of 3 months to 12 years, 95 percent of enrolled children were under age 5.

In the overall analysis, buccal midazolam was significantly superior to rectal diazepam. Two-thirds of each treatment group had severe or cerebral malaria. A subgroup analysis of those patients without malaria found buccal midazolam was superior to diazepam—a difference similar to that reported by McIntyre et al. in the United Kingdom (5). The subgroup analysis of those with malaria found no significant difference in efficacy between the two treatments. Most of the efficacy difference was due to lower recurrence of seizures in the midazolam group, which translates in clinical practice into fewer required doses and lower risk of respiratory depression. The median time to re-

currence within 24 hours was 1.8 hours for rectal diazepam and 5.11 hours for midazolam, even for individuals with malaria.

The main determinants of mortality and morbidity after SE are age, etiology, and duration of SE. The 6 percent mortality rate in this study is higher than the 0 to 3 percent typically reported in children. This finding is likely secondary to the high prevalence of severe and cerebral malaria, which accounted for 50 percent of the deaths. Acute symptomatic SE, within 1 week of an acute medical or neurologic insult is associated with higher mortality than remote symptomatic or cryptogenic SE.

One potential confounder not explored in this study was the impact of the duration of SE on treatment efficacy. Treatment was initiated when seizures lasted for more than 5 minutes, but the total duration of seizure activity was not reported. In developing countries, there may be significant delay between onset of seizures and arrival in an emergency department. One study in India found only 23 percent of patients presented to the emergency department within 3 hours of onset of seizures, and the mean duration before admission was 18 hours (7). It is not clear if a similar delay in treatment occurred in this Ugandan patient population.

Another limitation of this study was reliance on clinical evidence of seizure cessation. Several studies have demonstrated that electrographic seizures continue in nearly a quarter of patients with SE after clinical manifestations have ended. One EEG study of childhood cerebral malaria found seizures in 40 of 65 children, with subtle or purely electrographic seizures in 15 (37%) of all those with seizures (8). Since continuous EEG resources are unlikely to be available in developing countries, clinical cessation of motor movements is the most useful outcome measure.

The global treatment gap with epilepsy and seizures remains large. As new treatments for epilepsy and SE become more available in developing countries, it will be important to reexamine the efficacy and adverse effect profiles of AEDs, particularly when seizure types or underlying etiologies differ greatly from those in industrialized countries. This study demonstrates that well-designed clinical trials are being performed in countries with limited resources. The study group enrolled their 330 patients in just 8 months from a single center, and the procedures and blinding were equal to or better than trials in countries with more organized health systems.

The results of the study by Mpimbaza and colleagues suggest that buccal midazolam should be encouraged as first-line therapy for convulsive SE in developing countries. When transportation to an emergency department is delayed, use of midazolam by community physicians, paramedics, and perhaps even caregivers may shorten the duration of SE and reduce morbidity and mortality. Because midazolam was less effective for treatment of SE associated with malaria, it raises the question of

whether an AED with a different mechanism of action would be more efficacious in this group of patients.

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## References

1. Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. *Epilepsia* 1999;40:120–122.
2. Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, Gottwald MD, O'Neil N, Neuhaus JM, Segal MR, Lowenstein DH. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med* 2001;345:631–637.
3. Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, Handforth A, Faught E, Calabrese VP, Uthman BM, Ramsay RE, Mamdani MB. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med* 1998;339:792–798.
4. Appleton R, Macleod S, Martland T. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. *Cochrane Database of Systematic Reviews* 2008;3:CD001905. DOI: 10.1002/14651858.CD001905.pub2.
5. McIntyre J, Robertson S, Norris E, Appleton R, Whitehouse WP, Phillips B, Martland T, Berry K, Collier J, Smith S, Choonara I. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. *Lancet* 2005;366:205–210.
6. Idro R, Gwer S, Kahindi M, Gatakaa H, Kazungu T, Ndiritu M, Maitland K, Neville BG, Kager PA, Newton CR. The incidence, aetiology and outcome of acute seizures in children admitted to a rural Kenyan district hospital. *BMC Pediatr* 2008;8:5–16.
7. Murthy JM, Jayalaxmi SS, Kanikannan MA. Convulsive Status Epilepticus: Clinical Profile in a Developing Country. *Epilepsia* 2007;48:2217–2223.
8. Crawley J, Smith S, Muthinji P, Marsh K, Kirkham F. Electroencephalographic and clinical features of cerebral malaria. *Arch Dis Child* 2001;84:247–253.