A Shot in the Arm for Prehospital Status Epilepticus: The RAMPART Study

Intramuscular Versus Intravenous Therapy for Prehospital Status Epilepticus.

Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, Barsan W; NETT Investigators. *N Engl J Med* 2012;366(7):591–600.

BACKGROUND: Early termination of prolonged seizures with intravenous administration of benzodiazepines improves outcomes. For faster and more reliable administration, paramedics increasingly use an intramuscular route. METHODS: This double-blind, randomized, noninferiority trial compared the efficacy of intramuscular midazolam with that of intravenous lorazepam for children and adults in status epilepticus treated by paramedics. Subjects whose convulsions had persisted for more than 5 minutes and who were still convulsing after paramedics arrived were given the study medication by either intramuscular autoinjector or intravenous infusion. The primary outcome was absence of seizures at the time of arrival in the emergency department without the need for rescue therapy. Secondary outcomes included endotracheal intubation, recurrent seizures, and timing of treatment relative to the cessation of convulsive seizures. This trial tested the hypothesis that intramuscular midazolam was noninferior to intravenous lorazepam by a margin of 10 percentage points. RESULTS: At the time of arrival in the emergency department, seizures were absent without rescue therapy in 329 of 448 subjects (73.4%) in the intramuscular-midazolam group and in 282 of 445 (63.4%) in the intravenous-lorazepam group (absolute difference, 10 percentage points; 95% confidence interval, 4.0 to 16.1; P<0.001 for both noninferiority and superiority). The two treatment groups were similar with respect to need for endotracheal intubation (14.1% of subjects with intramuscular midazolam and 14.4% with intravenous lorazepam) and recurrence of seizures (11.4% and 10.6%, respectively). Among subjects whose seizures ceased before arrival in the emergency department, the median times to active treatment were 1.2 minutes in the intramuscular-midazolam group and 4.8 minutes in the intravenous-lorazepam group, with corresponding median times from active treatment to cessation of convulsions of 3.3 minutes and 1.6 minutes. Adverse-event rates were similar in the two groups. CONCLUSIONS: For subjects in status epilepticus, intramuscular midazolam is at least as safe and effective as intravenous lorazepam for prehospital seizure cessation. (Funded by the National Institute of Neurological Disorders and Stroke and others; ClinicalTrials.gov number, ClinicalTrials.gov NCT00809146.)

Commentary

Being a paramedic caring for a person in status epilepticus is a tough job. Emergency services are not called by the patient, the one who needs help; even a caregiver familiar with the medical history may not be readily available in some situations. The patient is actively convulsing, sometimes violently, and therefore attempting to put in an intravenous (IV) line may be a challenge. Hospitals with neurologic services may be a considerable distance away.

Recognizing these challenges, guidance was provided over a decade ago through the PHTSE (Prehospital Treatment of Status Epilepticus) trial, which compared IV diazepam, lorazepam, and placebo given by paramedics for subjects in status epilepticus (1). The results demonstrated that lorazepam was superior to diazepam (59.1 vs 42.6% without seizures upon arrival in the emergency department), and both were better than placebo (21.1%). However, both of these drugs are intravenously administered, and lorazepam requires refrigeration, not always available on ambulances (2). For busy paramedics with limited time to spare, clearly alternatives are desired.

Over the past several years, many emergency services groups have been using intramuscular (IM) midazolam as such an alternative. It does not require refrigeration and can be administered very quickly and reliably. Sporadic small studies have backed up the efficacy of this approach, but none formally (3). To resolve this uncertainty, a randomized, double-blind, phase-3, noninferiority trial was designed (4). Entitled "RAMPART" (Rapid Anticonvulsant Medication Prior to Arrival Trial), this large study was funded by the National Institute of Neurologic Disorders and Stroke and included over 4,000 paramedics and nearly 80 hospitals in the United States.

Similar to the PHTSE trial, the study design used a novel exception from informed consent allowed for emergency

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research (with patients and caregivers notified as soon as possible after drug administration). Subjects included both children and adults having active convulsions for at least 5 minutes. Adults, and those over 40-kg body weight, were then randomized by the paramedics to receive IM injections of either 10 mg midazolam with IV or IM placebo followed by 4 mg IV diazepam. The active doses were halved for children under 40 kg. These were certainly appropriate doses. Auto-injectors were supplied by the Department of Defense, who undoubtedly saw some potential use in the field for such a product, especially in very warm climates, but they did provide material support for this study. Although the primary goal was obviously termination of seizures prior to arrival at the emergency department (similar to the PHTSE trial), the investigators added some interesting secondary outcomes. These included time from study box-opening to termination of convulsions (which also accounts for ease of use), intensive care unit admission rate, and need for endotracheal intubation.

At completion, 893 subjects were randomized and assigned to one of the two study arms. Although equal numbers were assigned, as would be expected a large number (148 of 445) of the IV lorazepam group did not actually receive the medication as planned, often because of unsuccessful IV line access or the because the convulsions stopped before access was obtained. Results demonstrated noninferiority, supporting the hypothesis of this study. Either using an intent-to-treat analysis or accounting for subjects in which the protocol was not followed correctly due to dosing or administration errors (reducing the study population by about 15%), there was no statistical difference between seizure termination by IM midazolam (~74%) or IV lorazepam (~64%). One might argue that the differences in the size of the study groups, with fewer patients in the IV lorazepam group, could have led to the slightly lower rate of response. On a practical level, however, if the paramedics in the field, who were trained to be involved in this study, still had difficulty with providing IV medications, one can only imagine the problems the average paramedics are having in our communities.

Examining the secondary outcomes, there was also an overall similarity; with the exception of lower hospital admission rates with IM midazolam. Midazolam could be given quicker, but it worked a bit slower, usually by 2 to 3 minutes for each respective delay. The authors mention in their discussion that the time saved in administration would "offset" the delay in action, which seems reasonable. The equivalence data does back up its use and should make paramedics more comfortable using IM midazolam from here onward.

Now that we have these two *New England Journal of Medicine* trials, is there a need for any further investigation into prehospital treatment of status epilepticus? I believe so, especially as one-quarter of patients in this study did not stop seizing despite the "superior" IM midazolam, and half were still hospitalized. We still have some work to do. In children, many parents will administer rectal diazepam prior to calling paramedics (4). Would this provide additional benefit with IM midazolam or perhaps make it less effective due to benzodiazepine tolerance? There are also alternative means of administration being investigated such as intranasal and buccal midazolam (4, 5). The authors state in their discussion that these approaches are inferior to IM approaches because of these drugs being "blown or spat out by the convulsing patient." Obviously, that remains to be demonstrated in a comparative clinical trial. Lastly, different doses and injection devices may provide superior treatment effect.

by Eric H. Kossoff, MD

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