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Lessons from the RAMPART study – and which is the best route of administration of benzodiazepines in status epilepticus

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Summary

Early treatment of prolonged seizures with benzodiazepines given intravenously by paramedics in the prehospital setting had been shown to be associated with improved outcomes, but the comparative efficacy and safety of an intramuscular (IM) route, which is faster and consistently achievable, was previously unknown. RAMPART (Rapid Anticonvulsant Medication Prior to Arrival Trial) was a double-blind randomized clinical trial to determine if the efficacy of IM midazolam is noninferior by a margin of 10% to that of intravenous (IV) lorazepam in patients treated by paramedics for status epilepticus (SE). In children and adults with >5 min of convulsions and who are still seizing at paramedic arrival, midazolam administered by IM autoinjector was non-inferior to IV lorazepam on the primary efficacy outcome with comparable safety. Patients treated with IM midazolam were more likely to have stopped seizing at emergency department (ED) arrival, without EMS rescue therapy, and were less likely to require any hospitalization or admission to an intensive care unit. Lessons from the RAMPART study's findings and potential implications on clinical practice, on the potential role of other routes of administration, on the effect of timing of interventions, and on future clinical trials are discussed.

Keywords

Midazolam; Lorazepam; Comparative efficacy; emergency medical services; intramuscular

Early treatment of SE by paramedics reduces the number of patients with persistent seizures on ED arrival and the number admitted to the intensive care unit (ICU) for refractory status (Alldredge et al., 2001) Traditionally, diazepam has been the agent used most frequently by Emergency Medical Services (EMS) to treat patients with seizures despite evidence that intravenous lorazepam may be more effective. Lorazepam has proven impractical for EMS use because of its short shelf life without refrigeration. More recently, midazolam has been

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adopted in a limited number of EMS systems because it is more rapidly absorbed by intramuscular and transmucosal routes than diazepam or lorazepam, and has excellent stability (Warden & Frederick, 2006) The safety and efficacy of intramuscular midazolam, however, had not until recently been studied in a randomized controlled trial, and the optimal agent for prehospital treatment of SE was unknown. In RAMPART (the Rapid Anticonvulsant Medication Prior to Arrival Trial) we hypothesized that in the prehospital treatment of SE, the efficacy of IM midazolam would be non-inferior to that of intravenous (IV) lorazepam, as determined by the proportion of subjects with termination of clinically evident seizure at arrival in the ED after a single dose of study medication and without use of rescue medication (Silbergleit et al., 2012a)

Methods

RAMPART was a double-blind randomized noninferiority clinical trial of the efficacy of IM midazolam versus IVlorazepam in the prehospital treatment of SE by paramedics (Silbergleit et al., 2012a; Durkalski et al., 20114) The trial was conducted in the Neurological Emergencies Treatment Trials (NETT) network, a multidisciplinary clinical trials infrastructure funded by the National Institute of Neurological Disorders and Stroke (NINDS). RAMPART involved more than 4,314 paramedics, 33 EMS agencies, and 79 receiving hospitals across the United States.

Subjects enrolled in RAMPART were all administered study medication by IM autoinjector followed by rapid placement of a venous catheter and IV study medication. All subjects received active treatment. In half of the subjects the active treatment was in the IM study medication and in half active treatment was in the IV study medication. Children over 40 kg and all adults randomized to active IM therapy were treated with 10 mg midazolam IM followed by IV placebo. Children over 40 kg and all adults randomized to IV active therapy were treated with IM placebo followed by 4 mg lorazepam IV. The weight of children was estimated from their length using a length-based weight-estimation tape. Active therapy in children estimated to be <40 kg was either 5 mg midazolam IM or 2 mg lorazepam IV. Children estimated to be <13 kg were not enrolled.

A specially designed study box incorporated a voice recorder activated by opening the box. Study personnel used the device to identify the following events: IM treatment, IV access obtained, IV administered, administration of any rescue treatments, when and if convulsions are observed to stop, and whether the subject is seizing on arrival at the ED. The recorders' time code allowed each event to be time-stamped. When starting an IV was difficult, medics attempted placement for at least 10 minutes, or were allowed to place an intraosseous (IO) line in lieu of IV access. Rescue therapy, as dictated by local EMS protocol, was used in subjects who were still convulsing 10 min after the last study medication was administered.

The study was conducted under 21 CFR 50.24, U.S. Food and Drug Administration (FDA) regulations governing emergency clinical research performed with exception from informed consent (EFIC)(U.S. Government Printing Office, 2005) The Institutional Review Board (IRB) at the coordinating center and at each site reviewed and approved the trial. Each site IRB reviewed local community consultation and public disclosure activities. Subjects or their legally authorized representatives were notified about enrollment in the trial by the study team as soon as possible, usually while the subject was still in the ED, and were asked for their consent for continued data collection through the subject's end of study (Silbergleit et al., 2012b)

Results

Eight hundred ninety three subjects were enrolled over 19 months (Silbergleit et al., 2012a) Subjects were well balanced between treatment groups on demographic and clinical characteristics, dose tier, prior history of epilepsy, accuracy in diagnosis of status epilepticus (versus a discharge diagnosis of seizure mimic or pseudoseizure), and in the diagnosis of the underlying cause of status epilepticus. Among subjects with a prior history of epilepsy, status epilepticus was most commonly from noncompliance with, or withdrawal from, anticonvulsant medication, but idiopathic precipitants and other breakthrough seizures were also common. Status epilepticus resulting from lowering of the seizure threshold by identifiable acute co-morbidities was much less common.

Seizures were absent without rescue therapy at ED arrival in 329 of 448 (73.4%) subjects allocated to active IM treatment and in 282 of 445 (63.4%) allocated to active IV treatment (difference: 10.1%, 95% CI: 4.0%, 16.1%; $p<0.001$ for non-inferiority and $p<0.001$ for superiority). Among the 119 subjects in the IM group and the 163 in the IV group that failed the primary outcome, 47 (39.5%) and 57 (35.0%) respectively received rescue medications and were not seizing on arrival, and 22 (18.5%) and 42 (25.8%) received rescue medications and were still seizing on arrival.

The secondary and safety outcomes were consistent with and reinforced the finding of non-inferiority for the primary outcome. In IM and IV treatment groups, the frequency of endotracheal intubation (14.1% v. 14.4%), recurrent seizures (11.4% v. 10.6%), and other predefined safety outcomes were similar by group. In those admitted, the ICU and hospital length of stay did not vary with treatment group, but the proportion of subjects admitted was significantly lower in the IM group (57.6%) as compared to the IV group (65.6, $p=0.01$).

Time interval data included those subjects meeting the primary outcome in whom time of active treatment and seizure cessation were captured (n=317). Time to administration of drug by the IM route was significantly shorter than by the IV route, but the onset of action (seizure termination) after IV administration was shorter than after IM administration. The overall interval until seizure termination was similar in both groups.

Intramuscular midazolam is the best option for the prehospital treatment of status epilepticus

The superiority of IM midazolam over IV lorazepam in RAMPART indicates that early administration of IM midazolam is the best option for the prehospital treatment of SE by paramedics. While early administration of adequate doses of IV lorazepam is the preferred initial treatment for SE in the emergency department and other controlled clinical environments, it has limitations that make it less preferable for use by EMS. The need to rapidly establish IV access in a convulsing patient may delay benzodiazepine administration in the prehospital environment, and lorazepam's short shelf life out of refrigeration is not pragmatic for EMS use (McMullan et al. 2013) The ability to use an IM route with midazolam allowed more reliable and rapid administration and ultimately led to better clinical outcomes as reflected in lower rates of hospital admission, and lower rates of ICU admission.

Implications for other non-intravenous routes of administration

Some EMS systems that use midazolam for the prehospital treatment of SE use transmucosal routes of administration (buccal, nasal, or rectal) as an alternative to IM administration. Such routes are less invasive and are potentially similarly rapid (McMullan et al., 2010) Advocates for these routes were disappointed that RAMPART did directly compare alternative non-intravenous routes of midazolam administration to each other and

to intravenous lorazepam. Based upon what is known about the pharmacodynamics of transmucosal midazolam, the RAMPART investigators feel that the differences among various non-intravenous routes are likely to be small, and that the trial successfully answered the key question: whether a non-IV route can be non-inferior to an IV route. In the context of status epilepticus, the clinical importance of avoiding the invasiveness of an IM injection per se is unclear, and there are potential limitations to each non-intravenous route. These include the relatively low concentrations of midazolam that are commercially available for atomized administration, and that have most often been studied in nasal administration, as well as the occasional problem of seizing patients spitting or blowing out medication during adminstration. However, we feel that the RAMPART results should be taken to be generally supportive of non-intravenous midazolam administration.

Implications for the timing of interventions for status epilepticus

With regard to mechanism, the time interval data in RAMPART are consistent with the expectation that the medication given by the IM route is administered more rapidly after arrival than medication given IV, but that the onset of action after IV administration is more rapid than after IM administration. The administration time saved by using the IM route appears to more than offset the delay in onset of action. It is interesting to speculate that the earlier administration in the IM group, of just a few minutes, may have been enough of a difference to drive the slight superiority of IM seen in the primary outcomes.

Implications for future clinical trials in the emergency treatment of status epilepticus

While RAMPART definitively identified the best route of administration and optimal benzodiazepine for initial treatment of seizures and status epilepticus, it also suggests many opportunities and questions for future investigation. Primary among these is recognition that 26.5% had SE that remained refractory to benzodiazepines at emergency department arrival. Identification of the most effective second line anticonvulsant therapy for this population is thus a research priority. Furthermore these clinical data indicating that earlier treatment may work synergistically to improve anticonvulsant efficacy, taken in combination with pre-clinical animal data, suggest that future clinical trials should examine collapsing or accelerating the traditional serial progression of emergency treatments of SE, including the possible use of additional agents in prehospital treatment.

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