Intramuscular vs. Intravenous Therapy for Prehospital Status Epilepticus (RAMPART Trial)

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At the time of this trial, it was clear that early, pre-hospital termination of prolonged seizures via IV benzodiazepines improved long-term outcomes. However, IM therapies had gained popularity by EMS personnel in the out-of-hospital setting, due to the ease of administration of IM vs. IV therapies. Further, the Prehospital Treatment of Status Epilepticus trial (PHTSE, 2001) had shown that IV lorazepam and IM diazepam were equally effective in terminating prolonged convulsive seizures in the pre-hospital setting, at least as compared to placebo. As such, given the higher ease of use of IM vs. IV therapies, the goal of this trial was to directly determine if IM midazolam was at least as safe and effective as IV lorazepam for the pre-hospital management of convulsive seizures.

Experimental design and statistics: This study was designed as a randomized, double-blind, phase 3, noninferiority trial, involving 4314 paramedics, 33 EMS agencies, and 79 receiving hospitals across the US. The rationale for employing a non-inferiority design was to show that IM midazolam was at least as safe and effective as IV lorazepam for pre-hospital convulsive seizure termination, without the need for a placebo group. Enrolled participants included both children and adults who were found to be with convulsive seizures at the time of EMS arrival to a scene, and if such convulsions were 1) >5min, or 2) repetitive without return to baseline for >5min. Additional exclusion criteria are noted below.[1] The treatment protocol itself was activated by paramedics upon arrival to the scene after identifying eligible patients. Specifically, paramedics used drug study kits to begin treatment. Each drug kit contained both an IM autoinjector and an IV syringe, and all patients received 1 of 2 study treatments: 10mg of IM midazolam followed by IV placebo OR IM placebo followed by 4mg of IV lorazepam[2]. If IV access was unsuccessful after 10min, paramedics were able to obtain IO access instead. Added rescue therapies were available per local EMS protocols if needed. The primary outcome was the % of patients who achieved seizure termination, without the need for more rescue therapy, before arrival to the nearest ED. Major secondary outcomes included 1) the time of drug box opening to active treatment, and 2) the time of active treatment to cessation of convulsions. Other secondary outcomes included the frequency of hospitalizations, intubation, ICU admission, and seizure recurrence. Statistically, the primary outcome was compared between the two treatment groups using a non-inferiority design. Specifically, the null hypothesis of non-inferiority was assessed via a one-sided Z-statistic with a non-inferiority margin of 10 percentage points. Secondary analyses were compared between the two treatment groups using a superiority framework analysis, with two-sided tests. Analyses were conducted via the intention-to-treat protocol and sensitivity analyses were conducted with the per-protocol population, which excluded patients that were found to have violated the study protocol.

Results: A total of 893 patients were enrolled in the study, with 448 patients randomized to obtain treatment with IM midazolam and 445 to IV lorazepam. Baseline characteristics between the treatment groups were similar (Table 1). In terms of the primary outcome, the % of patients who achieved seizure termination without rescue therapy was 73.4% in the midazolam group vs. 63.4% in the IV lorazepam group, leading to a 10 percentage point difference and statistical significance for non-inferiority ($p<$ 0.001, Figure 2); results were similar in the per-protocol analysis (Table 2). In addition to this similarity in efficacy, patients who obtained IM midazolam were also LESS likely to have continued seizure activity

[1] Exclusion criteria: cause for SE was due to trauma, hypoglycemia, cardiac arrest, or bradycardia (as all would require alternate treatment); known allergy to midazolam or lorazepam, pregnancy, prisoner status.

[2] In patients weighing 13-40kg, 5mg of IM midazolam and 2mg of IV lorazepam were used instead of the above dosages.

after arrival to the ER vs. the IV lorazepam group; the primary reason behind a failure to achieve seizure termination with IV lorazepam was difficulty in obtaining IV access. The time from active treatment to convulsion cessation was faster with IV lorazepam (1.6min IV vs. 3.3min IM), but the time to treatment administration was faster with IM midazolam due to the ease of IM access (1.2min vs. 4.8min for IV, Figure 3). Finally, secondary outcomes were similar, if not better, in the IM group vs. the IV group: the % of patients requiring an eventual hospitalization/ICU admission was LOWER in the IM midazolam vs. IV lorazepam group.

Conclusions: Overall, this study confirmed that IM midazolam was at least as safe and effective as IV lorazepam in the pre-hospital treatment of convulsive seizures. Specifically, cessation of seizure activity (without the need for rescue) occurred with equal prevalence following the use of IM midazolam and IV lorazepam. Further, patient outcomes were equivalent following IM vs. IV therapy. Notably, though seizure cessation occurred faster with IV lorazepam than with IM midazolam, the time needed to administer IM midazolam was shorter and easier, offsetting the difference in treatment effect. For this reason, this study supported the use of IM midazolam by EMS and paramedics as an alternate to IV lorazepam for convulsive seizure management in the pre-hospital setting.

Associated reading, if interested:

Allredge, BK et. al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus, NEJM (2001): 345: 631-637.

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