Randomized Trial of Three Different Anticonvulsant Medications for Status Epilepticus

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Early termination of status epilepticus (SE) reduces the risk of cardiac and respiratory complications and ICU admissions in adults and mortality in children. A large body of evidence supports the use of IV benzodiazepines for the early termination of SE, though up to 1/3rd of SE is refractory to IV benzodiazepines. At the time of this trial fosphenytoin was the only FDA-approved medication for benzodiazepine-refractory SE, though fosphenytoin, valproate, and levetiracetam were still commonly used for benzodiazepine-refractory SE. As such, the goal of this trial was to assess the superiority or inferiority of fosphenytoin, valproate, and levetiracetam for the successful treatment of benzodiazepine-refractory SE.

Experimental design and statistics: This trial was an investigator-initiated, multicenter, randomized and blinded, comparative-effectiveness trial conducted across 57 hospital EDs throughout the US; adults and children were included. The study was completed under the exception from informed consent requirements for emergency research. Eligibility for trial enrollment included the following: 2yrs of age or older and treatment with an IV benzodiazepine[1] after >5min of initial generalized convulsive seizures but with recurrent/persistent convulsions for at least 5 min after IV benzodiazepine use. Exclusion criteria is noted below.[2] Patients were deemed eligible for enrollment after they presented to a participating ED, and eligible patients were treated via a medication box containing one of the trial drugs. Use of medication boxes activated the trial protocol and contained a weight-based infusion dose for IV administration over 10min. The three study drugs were administered at the following loading doses: levetiracetam at 60mg/kg (max 4500mg), fosphenytoin at 20mgPE/kg (max 1500mgPE), valproate at 40mg/kg (max 3000mg). Following initial treatment, rescue therapy could be provided if convulsions continued after 20min of trial drug administration. The primary outcome was the absence of clinical seizure activity and improved responsiveness[3] at 60min following trial drug initiation, without the need for additional medications. Secondary outcomes included time to seizure termination, admission to the ICU, and length of hospitalization. Primary safety outcomes included hypotension, cardiac arrhythmias, or intubation within 60min of trial drug initiation. Statistically, data were analyzed via a response-adaptive, comparative-effectiveness design, which used a Bayesian probability analysis. Essentially, before trial data was collected, all trial drugs were considered as equally likely to be the most or least effective treatment. As response rates were analyzed, the study authors determined the probability that one of the trial drugs was the most or least effective at achieving the primary outcome, and the criterion for declaring a drug to be the most or least effective option was a probability of >0.975; only 1 treatment drug could be considered the "best" option. These probabilities were calculated at planned interim analyses to determine if the trial could be stopped early due to either success or futility.

Results: A total of 400 patients were enrolled in the study, as trial enrollment was discontinued by Nov 2017 after a monitoring board found that there was a <1% chance that one of the treatment drugs would meet criteria for the best or worst treatment option, per predefined criteria. Otherwise, of those enrolled, baseline patient characteristics were similar in the three treatment groups (Table 1). A total of

[1] Accepted doses: 4mg of lorazepam, 10mg of diazepam or midazolam if ≥32kg OR 0.3mg/kg of diazepam, 0.1mg/kg of lorazepam, or 0.2 – 0.3mg/kg of midazolam for children <32kg

[2]Exclusion criteria: seizures due to trauma, hypo/hyperglycemia, anoxia, cardiac arrest; pregnancy/incarceration; prior treatment with an AED after an IV benzodiazepine, presentation with intubation; known allergies to the 3 treatment drugs

[3] Clinical seizure activity was defined as tonic-clonic activity, nystagmoid/rhythmic eye movements, or myoclonus; improved responsiveness was defined as withdrawal to noxious stimuli, following of commands, or verbalization.

108 enrollments did have deviations from trial eligibility criteria[4], but their data was still included in the intention-to treat analysis. Regarding the primary outcome, this was achieved in 47% of patients in the levetiracetam group, 45% in the fosphenytoin group, and 46% in the valproate group in the intention-to-treat analysis.[5] In addition, the probabilities that one treatment drug was better than any of the other treatment drugs were all <0.975 (Table 2, Fig 2), and all results were similar in the per-protocol analyses. Finally, comparisons of secondary outcomes between treatment groups were also without statistical significance (Table 2), as were the frequencies of life-threatening hypotension, arrhythmias, or endotracheal intubation (Table 3).

Conclusions: Overall, this trial showed that levetiracetam, fosphenytoin, and valproate were all equally effective at terminating benzodiazepine-refractory SE. Major strengths of the study included a relatively large sample size, weight-based anti-convulsant medication dosing, and the statistical design used, which increased the likelihood of identifying a true difference between study drugs, if one existed. Otherwise, limitations of the study included the use of clinical judgement rather than EEG data to determine seizure cessation, rendering it difficult to identify non-convulsive status vs. a sedation effect/post-ictal state as the cause for continued, reduced responsiveness at 60min post treatment. Further, specific to fosphenytoin, the loading dose was limited to a maximum of 1500mgPE, making it submaximal in patients >75kg. However, despite these limitations, this trial ultimately suggested that all three of the study drugs tested carry equal efficacy and safety in terms of seizure termination following IV benzodiazepine use, and all can be used as first line treatment for benzodiazepine-refractory SE.

Additional resources, if interested:

AAN Podcasts on management of status epilepticus:
- Part 1: https://neurology.libsyn.com/website/managing-status-epilepticus-part-1
- Part 2: https://neurology.libsyn.com/website/managing-status-epilepticus-part-2

Summary completed by Elaine Sinclair, DO/PhD

[4] Inadequate benzo dosing, improper timing of benzo administration, enrollment of patients w/out SE, including patients with PNES

[5] In those who did not achieve the primary outcome of seizure cessation, 70% were treated with a 2nd anti-convulsant.