Randomized Trial of Three Different Anticonvulsant Medications for Status Epilepticus (ESETT trial)

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Early termination of status epilepticus (SE) reduces both the risk of cardiac and respiratory complications + ICU admissions in adults as well as mortality in children. While IV benzodiazepines are first line for the early termination of SE, 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, in practice, fosphenytoin, valproate, and levetiracetam were 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 treatment of benzodiazepine-refractory SE.

Experimental design and statistics: This 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 age $\geq$ 2yrs and treatment with an IV benzodiazepine[1] after >5 min of generalized convulsive seizures, but with persistent convulsions for at least 5 min after IV benzodiazepine use. Exclusion criteria is noted below.[2] Patients were eligible for enrollment after they presented to a participating ED. Eligible patients were treated using a medication box which contained one of the three study drugs (weight-based infusion, dosing for IV administration over 10min) and which activated the trial protocol. The three study drugs were administered at the following loading doses: levetiracetam at 60mg/kg (max 4500mg), fosphenytoin at 20mgPE/kg (max 1500mgPE), and valproate at 40mg/kg (max 3000mg). Following initial treatment, rescue therapy could be provided if convulsions continued after 20 min of trial drug administration. The primary outcome was the absence of clinical seizure activity and improved responsiveness at 60 min following trial drug initiation, without the need for additional medications.[3] 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 60 min of trial drug initiation. Statistically, data were analyzed via a response-adaptive, comparative-effectiveness design, which used a Bayesian probability analysis. 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. 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. 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. Trial enrollment was discontinued early (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 pre-defined criteria. Otherwise, of those enrolled, baseline patient characteristics were similar in the three treatment groups (**Table 1**). A total of 108 enrollments did have deviations from trial eligibility criteria, 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-

[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: tonic-clonic activity, nystagmoid/rhythmic eye movements, or myoclonus; improved responsiveness: (+) withdrawal to noxious stimuli, following of commands, or verbalization.

treat analysis. The probabilities that any one treatment drug was better than any of the other treatment drugs were all less than the pre-specified probability of 0.975, suggesting no significant differences in efficacy (**Fig 2**). All results were similar in the per-protocol analyses. 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 60 min post treatment with the study drugs. Further, specific to fosphenytoin, the loading dose was limited to a maximum of 1500mgPE due to ASE risk, making it submaximal in patients >75kg. However, despite these limitations, this trial ultimately suggested that all three of the anti-seizure medications used here carry equal efficacy and safety for seizure termination following IV benzodiazepine use, and supported the use of all three as first line treatment for benzodiazepine-refractory SE.

Additional resources, if interested:

Alvarez, V. et al., Second-line status epilepticus treatment: comparison of phenytoin, valproate, and levetiracetam. Epilepsia (2011), 53 (7): 1292-1296.

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