Published in final edited form as:
Epilepsia. 2013 September ; 54(0 6): 89–92. doi:10.1111/epi.12288.

The Established Status Epilepticus Trial 2013

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Summary

Benzodiazepine-refractory status epilepticus (established status epilepticus, ESE) is a relatively common emergency condition with several widely used treatments. There are no controlled, randomized, blinded clinical trials to compare the efficacy and tolerability of currently available

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Disclosure

The authors have no conflict of interest to declare in relation to this article. The authors confirm that they have read the Journal's position on issues involved in ethical publication and affirms that this report is consistent with those guidelines.

treatments for ESE. The ESE treatment trial is designed to determine the most effective and/or the least effective treatment of ESE among patients older than 2 years by comparing three arms: fosphenytoin (fPHT) levetiracetam (LVT), and valproic acid (VPA). This is a multicenter, randomized, double-blind, Bayesian adaptive, phase III comparative effectiveness trial. Up to 795 patients will be randomized initially 1:1:1, and response-adaptive randomization will occur after 300 patients have been recruited. Randomization will be stratified by three age groups, 2–18, 19–65, and 66 and older. The primary outcome measure is cessation of clinical seizure activity and improving mental status, without serious adverse effects or further intervention at 60 min after administration of study drug. Each subject will be followed until discharge or 30 days from enrollment. This trial will include interim analyses for early success and futility. This trial will be considered a success if the probability that a treatment is the most effective is >0.975 or the probability that a treatment is the least effective is >0.975 for any treatment. Proposed total sample size is 795, which provides 90% power to identify the most effective and/or the least effective treatment when one treatment arm has a true response rate of 65% and the true response rate is 50% in the other two arms.

Keywords

Comparative efficacy; Bayesian design; Fosphenytoin; Levetiracetam; Valproic acid

Objectives

There are approximately 120,000–180,000 episodes of convulsive status epilepticus (SE) each year in the United States, affecting individuals of all ages from very young to the elderly (DeLorenzo et al., 1995, 1996; Shinnar et al., 1997; Towne, 2007). The primary goal of status epilepticus (SE) treatment is prompt termination of seizures because rates of adverse consequences of SE, including mortality, systemic complications, neurologic injury, and refractoriness, increase with increasing seizure duration (DeLorenzo et al., 1996; Neligan & Shorvon, 2010; Nordli et al., 2012; Shinnar et al., 2012). Initial SE treatment with benzodiazepines is based on evidence from three double-blind, randomized, controlled clinical trials (Treiman et al., 1998; Alldredge et al., 2001; Silbergleit et al., 2012). Approximately one third of SE patients continue to have seizures despite administration of adequate doses of benzodiazepines; they are considered to have established SE (ESE). There are no class I clinical trials comparing the efficacy of currently available medications for the treatment of ESE: phenytoin (PHT)/fos-phenytion (fPHT), valproic (VPA), and levetiracetam (LVT). A large-scale, retrospective analysis of protocol-driven treatment of ESE suggested superiority of VPA over LVT; PHT was not statistically significantly different from other two agents but was numerically poorer than VPA (Alvarez et al., 2011). Fosphenytoin (fPHT) is the most commonly preferred treatment and is recommended by current guidelines (Meierkord et al., 2010; Loddenkemper & Goodkin, 2011; Brophy et al., 2012). Experts, guideline writers, Cochrane reviews, and professional associations have recommended a prospective randomized trial to determine the best available treatment of ESE.

The primary objective of the Established Status Epilepticus Trial (ESETT) is to determine the most effective and/or the least effective treatment of benzodiazepine-refractory SE among patients older than 2 years. There are three active treatment arms: fPHT, LVT, and VPA. Primary outcome is clinical cessation of status epilepticus, without recurrent seizures, life-threatening hypotension or cardiac arrhythmia, or the use of additional antiseizure medications within 60 min of the start of study drug infusion. Clinical cessation of SE is defined as the absence of clinical seizures and improving mental status. The mortality and etiology of SE vary with age, as do the incidence of some side effects such as hypotension. Therefore, the secondary objective is a subgroup analysis to determine the most effective and/or the least effective treatment for benzodiazepine-refractory SE in children. The final objective is a comparison of three drugs with respect to secondary outcomes: time to termination of clinical seizures (i.e., response latency), and rates of intubation, admission to intensive care unit (ICU), and mortality. Cessation of SE and occurrence of serious adverse effects will be analyzed separately.

Methods

This is a multicenter, randomized, allocation-concealed, Bayesian adaptive, phase III comparative effectiveness trial of three active treatments in patients with benzodiazepine-refractory status epilepticus (ESE). Response-adaptive randomization will be used to allocate patients to fPHT, LVT, or VPA for the treatment of SE in the emergency department (ED), with the goal of focusing randomization preferentially on the treatment arms with the highest response rates. Initial randomization will be 1:1:1 and response-adaptive randomization will occur after 300 patients have been recruited. Randomization will be stratified by three age groups, 2–18, 19–65, and 66 and older. Each subject will be followed until hospital discharge or 30 days from enrollment if still hospitalized.

We expect to enroll up to 795 patients over 4 years, an accrual rate of approximately 16.5 patients per month. Patients will be enrolled by two national networks of emergency departments: Neurology Emergency Treatment Trials network (NETT) and Pediatric Emergency Care and Applied Research Network (PECARN). Each network has successfully undertaken a SE treatment trial under Exception from Informed Consent (EFIC) rules.

Inclusion

We will include patients older than 2 years of age with witnessed, clinically apparent seizures in the ED for at least 5 min after receiving an adequate dose of benzodiazepines for generalized, tonic–clonic convulsion(s). Adequate doses of benzodiazepines for this study are: diazepam 10 mg intravenous (IV), lorazepam 4 mg IV, or midazolam 10 mg IV or intramuscular (IM) for subjects >40 kg; and diazepam 0.3 mg/kg IV, lorazepam 0.0.1 mg/kg IV, or midazolam 0.3 mg/kg IV or IM for subjects between 10 and 40 kg. These drugs may have been administered in two or more divided doses, including in the out-of-hospital setting.

Interventions and Duration

The study drugs will be formulated in the following strengths: fPHT 16.66 mg/ml, VPA 33.33 mg/ml, and LVT 50 mg/ml so as to allow identical infusion times in order to maintain blinding. The drug will be produced, packaged, and labeled by the University of California, Davis, and shipped to the study sites. Medications will be placed in prerandomized study boxes kept in an ED medication refrigerator. Each study box will contain a device for real-time recording of medication allocation, study procedure times, and outcomes. The iPOD (Apple, Cupertino, CA, U.S.A.) will also provide alarms to remind staff of upcoming study procedures. Any patient with witnessed seizures in the ED will be evaluated for enrollment based on inclusion and exclusion criteria. Enrollment will occur using the EFIC for Emergency Research because of the emergent and life-threatening nature of SE. Randomization will be stratified by age groups: 2–18, 19–65, and 66 years and older.

This is an intention-to-treat study. Enrollment occurs when the infusion pump connected to study drug vial and patient's IV catheter is switched on and the time of enrollment is recorded on the study device. The assigned treatment dose (fPHT 20 mg/kg, LVT 60 mg/kg, or VPA 40 mg/kg) will be infused over 10 min. The patients will be observed for 20 min, at which time the duration of clinical seizures and response to verbal or painful stimuli will be recorded. At 60 min from enrollment, a study team member will record whether a clinically apparent seizure requiring intervention has occurred, whether there has been improvement in mental status since the last observation, and whether life-threatening hypotension or arrhythmias requiring intervention have occurred. Based on response to these questions, the primary outcome will be determined and recorded at this time. A subsequent chart review will determine duration of clinical seizures, admission to ICU or floor, whether patient was intubated, and final disposition.

Sample Size and Analysis

Based on a recent study (Alvarez V et al., 2011) and expert evaluation of all currently published data on the treatment of ESE, we assumed that the worst drug will be effective in 50% of the patients. The recently completed Rapid Anticonvulsant Medications Prior to Arrival Trial (RAMPART) study for the initial treatment of SE was conducted designed with the assumption that an absolute difference of 10% or less would be considered nonclinically significant (i.e., the noninferiority margin). There is broad consensus among experts that a difference of 15% would indicate superiority of one of the drugs over others, and will be sufficient to change clinical practice; therefore, the study is powered to detect a 15% difference on the whole study population in response rates.

The posterior probabilities that each treatment is the most and least effective treatment will be calculated using Bayesian methods based on a uniform prior for each treatment's success rate, and a conjugate beta-binomial model (Connor et al., 2013). This trial will be considered a success if the probability that a treatment is the most effective is >0.975 or the probability that a treatment is the least effective is >0.975 for any treatment. A sample size of 795 provides 90% power to identify the most effective and/or the least effective treatment when one treatment arm has a true response rate of 65% and the true response rate is 50% in the

other two arms. The false-positive rate of this trial is the probability of identifying either the most or the least effective treatment, when in truth there is no difference between the arms. Under simulation, the false-positive rate was determined to be <0.05 under a variety of scenarios. The simulation details have been published elsewhere (Connor et al., 2013).

Randomization will be stratified by the following age groups: 2–18, 19–65, and 66 and older. Midway through the trial after 300 patients are enrolled, the randomization of future patients will also depend on the responses of patients randomized earlier. Future patients will be more likely to be randomizaed to the treatment that has the highest success rate, has imprecise effect estimates, or has fewer patients randomized to it thus far. The posterior probabilities that each treatment is the most and least effective treatment will be calculated using Bayesian methods based on a uniform prior for each treatment's success rate, and a conjugate beta-binomial model.

Early stopping may occur at interim analyses conducted after 400, 500, 600, and 700 patients are enrolled. At an interim look, if the probability a single therapy offers the highest success rate is >97.5% then the trial will be stopped early for success. At an interim look, if the predictive probability of trial succcess is <5%, the trial will be stopped for futility.

This trial will be considered a success if the probability that a treatment is the most effective is >0.975 or the probability that a treatment is the least effective is >0.975 for any treatment. When the total sample size is 795, there will be 90% power to identify the most effective and/or the least effective treatment when one treatment arm has a true response rate of 65% and the true response rate is 50% in the other two arms (as determined by simulation). The secondary goal is to detect an absolute difference in proportions as small as 20% between treatments in children with at least 80% power. To detect this difference, a sample size of 336 children is required.

Early stopping may occur at interim analyses at 400, 500, or 600 patients. If ever the probability a single therapy offers the highest success rate is >97.5% then the trial stops early for success. If ever the predictive probability of trial succcess is <5%, the trial stops for futility.

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