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Neonatal Status Epilepticus Treatment Trial

(N-SETs Trial)

Research Question: This is a multi-center, randomized controlled trial to determine whether second line seizure treatment with midazolam infusion reduces time to seizure cessation compared to standard of care in neonates with status epilepticus.

Study Design: Cluster randomized non-inferiority trial.

Phenobarbital is most frequently employed as first-line seizure treatment in neonates with seizures. Among eight participating centers, four centers will be randomly allocated to second line seizure treatment with midazolam infusion and the other four centers will be allocated to standard of care treatment, which generally includes reloading with phenobarbital, followed by stepwise addition of fosphenytoin and then levetiracetam if seizures persist. In addition, after 2.5 years, clusters will crossover to the alternative treatment arm after a 1 month washout period. In this way, centers initially assigned to treat patients with midazolam will switch to treating patients with standard of care treatment after 2.5 years of study initiation. This design will allow us to measure and account for variations between centers.

Subjects:

Target Population: All neonates with status epilepticus

Accessible Population: Neonates admitted to the eight participating centers and diagnosed with status epilepticus.

Inclusion Criteria: Neonates (28 days or younger) who have already received first line seizure treatment of 20 mg/kg IV of phenobarbital and continue to seize on electroencephalogram (EEG) for more than 5 minutes after phenobarbital dose.

Exclusion Criteria: None.

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Measurements:

Predictor Variable: Second line seizure treatment with midazolam infusion

Primary Outcomes:

- Time to seizure cessation on EEG after initiation of second line seizure treatment
- Total electrographic seizure burden (in minutes)

Secondary Outcomes:

- Development of status epilepticus defined as continuous seizure lasting 30 minutes or a series of seizures whose total duration exceeds 50% of a given epoch or both (Dichotomous)
- Death (Dichotomous) and date and time of death
- All antiepileptic medications along with timing and doses given inpatient and outpatient (Categorical, Continuous)
- Discharged on antiepileptic medications (Dichotomous)
- ICN length of stay (Continuous)
- Neurodevelopmental outcomes at ICN discharge, 6 months, 12 months, and 18 months of age (Continous on standardized scale)
- Diagnosis of epilepsy (Dichotomous) and age of diagnosis
- Medication side effects
- Time to seizure treatment (minutes)
- Seizure etiology (categorical)

Control group

The control group will include subjects who receive standard of care treatment. It would be unethical to include a placebo group as status epilepticus is known to be deadly.

Intervention

Experimental Intervention

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After enrollment in the study, subjects will receive midazolam 0.2 mg/kg IV bolus (max 10 mg) and infusion at 0.1 mg/kg/hr. If seizure persists 5 minutes after the bolus, repeat the bolus at 0.2 mg/kg IV and titrate up every 5 minutes by 0.1 mg/kg/hr (max 2mg/kg/hr) until seizure cessation on EEG. If seizure persists despite maximum midazolam infusion, initiate pentobarbital and wean midazolam. Continue the pharmacologic coma until 24 hours after the last seizure on EEG. Wean midazolam infusion by 0.05 mg/kg/hr every 3 hours with frequent EEG reviews. Continue EEG until 24 hours after the end of the infusion.

Control Intervention

After enrollment in the study, subjects will receive a second loading dose of phenobarbital 20 mg/kg IV to a maximal loading dose of 40 mg/kg IV. Start a maintenance dose of phenobarbital at 2.5 mg/kg IV every 12 hours. If seizures on EEG continue, add fosphenytoin at 20 mg/kg/day IV divided TID. If seizures continue, add levetiracetam 40 mg/kg IV load. Repeat 20 mg/kg to a maximal total loading does of 60 mg/kg IV if seizures persist. A levetiracetam maintenance dose of 5 mg/kg IV every 12 hours should be added to the treatment schedule. Consider weaning maintenance anti-epileptic drugs once subject is seizure-free on EEG for 48-72 hours. Drug levels should be checked daily, as well as albumin.

Methods for randomization and blinding

Of the eight participating centers, four centers will be selected based on computer randomization to receive the experimental intervention and the other four centers will receive the control intervention. It would be impossible to blind physicians and nurses to the treatment intervention, but biases will be minimized as a result of the following: researchers performing analyses and electrophysiologists reading the EEGs will be blinded to treatment and subjects (neonates) will be unaware of the research study. Furthermore, the cluster design decreases risk for within-hospital intervention bias.

Methods for maximizing adherence

All interventions will take place within a hospital setting and each hospital will be given a detailed treatment protocol. All participating physicians will be required to complete a

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short, 15 minute online protocol training at the initiation of the study and at any point at which there are amendments to the protocol (e.g. at crossover). In addition the protocol will be posted in visible locations in the emergency department and on pediatric floors where neonates receive treatment. A simplified protocol checklist will also be used for each subject enrolled to adherence to the treatment protocol.

Measurement of Adverse Effects & Side Effects

Prior to discharge from the hospital and at each follow-up visit, an investigator will evaluate the subject's medical record for adverse effects and side effects using a checklist. Serious adverse effects such as death, disability, organ dysfunction, and future hospitalizations will be the focus but the checklist will also screen for varying levels of irritability, neuromotor development, and growth. Parents or guardians will also have the opportunity to answer pre-determined and scripted open-ended questions about other adverse effects and side effects that may not have been covered in the checklist.

Interim Monitoring

A data safety and monitoring board (DSMB) will be organized to serve as an independent body to monitor trial safety, efficacy, ethical issues, and progress. Individuals selected for the DSMB must be free of conflicts of interest and will be comprised of experts in the field of neonatal status epilepticus and clinical trials, ethicists, and statisticians. Over the course of the five year trial, interim monitoring will take place at regular six month intervals. Lan-DeMets statistical methods will be used to determine statistical significance for multiple interim analyses.

Potential Ethical Issues

The largest ethical issue that this trial raises is the method of consent for this population of vulnerable subjects. Status epilepticus is considered an emergent, life-threatening condition, which requires rapid response and management. For this reason, it would be unethical to withhold treatment while consent is obtained prior to enrollment in the study. In addition, since this is a cluster randomized trial, all subjects admitted to a particular participating center would receive the same treat whether or not he or she is enrolled in

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the study. Thus we suggest using deferred informed consent. In other words, all eligible subjects will be enrolled in the study without consent initially; then prior to discharge from the hospital, a parent or guardian will have the option of opting out of participation in the entire study or the follow-up portion of the study only.