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Neonatal Seizures: Providing Care With Evidence, Not Just Experience

Safety of early discontinuation of antiseizure medication after acute symptomatic neonatal seizures

Glass HC, Soul JS, Chang T, et al. *JAMA Neurol*, 78(7): 817-825, 2021

Importance: Antiseizure medication (ASM) treatment duration for acute symptomatic neonatal seizures is variable. A randomized clinical trial of phenobarbital compared with placebo after resolution of acute symptomatic seizures closed early owing to low enrollment. Objective: To assess whether ASM discontinuation after resolution of acute symptomatic neonatal seizures and before hospital discharge is associated with functional neurodevelopment or risk of epilepsy at age 24 months. Design, setting, and participants: This comparative effectiveness study included 303 neonates with acute symptomatic seizures (282 with follow-up data and 270 with the primary outcome measure) from 9 US Neonatal Seizure Registry centers, born from July 2015 to March 2018. The centers all had level IV neonatal intensive care units and comprehensive pediatric epilepsy programs. Data were analyzed from June 2020 to February 2021. Exposures: The primary exposure was duration of ASM treatment dichotomized as ASM discontinued vs ASM maintained at the time of discharge from the neonatal seizure admission. To enhance causal association, each outcome risk was adjusted for propensity to receive ASM at discharge. Propensity for ASM maintenance was defined by a logistic regression model including seizure cause, gestational age, therapeutic hypothermia, worst electroencephalogram background, days of electroencephalogram seizures, and discharge examination (all $P \leq .10$ in a joint model except cause, which was included for face validity). Main outcomes and measures: Functional neurodevelopment was assessed by the Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA-FS) at 24 months powered for propensity-adjusted noninferiority of early ASM discontinuation. Postneonatal epilepsy, a prespecified secondary outcome, was defined per International League Against Epilepsy criteria, determined by parent interview, and corroborated by medical records. Results: Most neonates (194 of 303 [64%]) had ASM maintained at the time of hospital discharge. Among 270 children evaluated at 24 months (mean [SD], 23.8 [0.7] months; 147 [54%] were male), the WIDEA-FS score was similar for the infants whose ASMs were discontinued (101 of 270 [37%]) compared with the infants with ASMs maintained (169 of 270 [63%]) at discharge (median score, 165 [interquartile range, 150–175] vs 161 [interquartile range, 129–174]; $P = .09$). The propensity-adjusted average difference was 4 points (90% CI, −3 to 11 points), which met the a priori noninferiority limit of −12 points. The epilepsy risk was similar (11% vs 14%; $P = .49$), with a propensity-adjusted odds ratio of 1.5 (95% CI, 0.7–3.4; $P = .32$). Conclusions and relevance: In this comparative effectiveness study, no difference was found in functional neurodevelopment or epilepsy at age 24 months among children whose ASM was discontinued vs maintained at hospital discharge after resolution of acute symptomatic neonatal seizures. These results support discontinuation of ASM prior to hospital discharge for most infants with acute symptomatic neonatal seizures.

Commentary

Having a baby, even a healthy newborn, is an overwhelming experience. Now imagine being told your newborn is having seizures—and there are minimal guidelines for best treatment. This has been the reality for many of our patients' families.

The neonatal brain is particularly susceptible to seizures due to age-dependent physiology that leads to increased excitation and decreased inhibition.[1] Seizures occur in 1–5 per 1000 live births and are the most common neurological emergency in the neonatal period.[2] The majority of seizures in neonates occur in response to a brain insult—acute provoked seizures.[2] Treatment of neonatal seizures has been riddled with controversy: whether continuous EEG recording is needed, whether to treat electrographic-only seizures, which antiseizure medications (ASM) to use, and what duration of medication treatment.[3] Primarily through the help of the ILAE Task Force on Neonatal Seizures and the Neonatal Seizure Registry, we are now finding answers to these questions.

Question #1: Do We Need EEG?

The immature state of the motor pathways in neonates leads to difficulties in differentiating seizures from nonepileptic events.

Health care professionals are able to accurately identify only 50% of seizures, with poor inter-observer agreement.[2] Furthermore, electrographic-only seizures are common.[2] In the recent position paper by the ILAE Task Force on Neonatal Seizures, only clonic seizures could be reliably diagnosed clinically. Diagnosis of other clinical seizure types, including automatisms, epileptic spasms, myoclonic, tonic, autonomic, behavioral arrest, and sequential, was unreliable without EEG.[2]

Question #2: Do We Need to Treat Electrographic-Only Seizures?

Payne et al[4] showed seizure burden per hour, rather than duration of individual seizures, was associated with a significantly higher likelihood of neurological decline. This was most evident in those with acute seizures and systemic disease. In neonates with acute provoked seizures, the seizures may exacerbate the underlying injury.[5] A seizure burden of >30–60 seconds per hour is an indication for initiating treatment, regardless of presence or absence of clinical signs.[2]

Question #3: Which Medications Should We Use?

Phenobarbital is the most used ASM to treat neonatal seizures. A single loading dose of 20 mg/kg is effective at controlling seizures in approximately half of patients.[3,5] However, we should not use phenobarbital simply because it is the medication most used. It is important to use the most effective and best tolerated ASM.

There has been concern that ASMs, especially phenobarbital, are associated with neuronal apoptosis in neonatal animal models, as well as cognitive decline in older children and adults, prompting the use of newer ASMs to treat neonatal seizures.[6] A study of 280 infants with comparable seizure etiology demonstrated an 8-point decrease in Bayley Scale of Infant Development (BSID) scores per 100 mg/kg phenobarbital exposure. By comparison, levetiracetam was associated with a 2.2-point decrease per 300 mg/kg, making levetiracetam an attractive alternative.[6]

However, the recent multicenter, randomized, blinded, controlled study comparing phenobarbital and levetiracetam as first-line treatment of acute provoked neonatal seizures (NEOLEV2) found that 80% of neonates randomized to phenobarbital 20 mg/kg loading dose (with an additional 20 mg/kg dose if seizures persisted) as the first medication remained seizure-free for 24 hours. By comparison, only 28% of neonates showed a similar response to levetiracetam 40 mg/kg loading dose (with an additional 20 mg/kg dose if seizures persisted). Increasing from 40 to 60 mg/kg of levetiracetam increased the response only by 7.5%.[5] Therefore, phenobarbital is not the most used ASM just because it is one of the oldest—it is also the most effective.

Furthermore, it is also important to understand the etiology of the neonatal seizures and differentiate those with acute provoked seizures from those with neonatal-onset genetic epilepsy. When infants with genetic epilepsies were compared to term neonates with acute provoked seizures, those with genetic epilepsies responded poorly to phenobarbital—it was ineffective in 93%. In contrast, the majority of infants with tonic seizures and suspected or known channelopathies became seizure-free with carbamazepine.[7] Fortunately, this study also demonstrated significant differences in seizure types between the two groups. Infants with acute provoked seizures often present with clonic or electrographic seizures, and the clinical onset of seizures was approximately 30 seconds after electrographic onset.[7] Those with genetic epilepsies presented with tonic seizures and clinical onset coincided with electrographic onset.[7] This aids the clinician in distinguishing genetic epilepsy from provoked seizures, even when infants are too ill to undergo neuroimaging.

Question #4: How Long Should We Continue ASMs in Neonates With Acute Provoked Seizures?

While it is necessary to treat seizures, the ASMs are not benign. Parents, while already worried about the long-term effects of seizures and the underlying cause, also have significant concerns about the treatment. Nearly two-third of interviewed parents expressed fears about adverse drug events.[8] Furthermore, 86% of parents reported adverse effects, including sedation and abnormal behavior. Most importantly, approximately half reported substantial effects on the child's daily life and negative impact on development.[8]

What can we do to mitigate these concerns? We know there is concern that phenobarbital may impact long-term neurologic outcomes. Lacking an effective ASM that is without such potential risks, the next best option is to limit the treatment duration. Fortunately, recent studies have shown this is a possibility for neonates with acute provoked seizures.

Acute provoke seizures typically arise within the first 48 hours of life, continue for 48-96 hours, and then dissipate, although there is up to 25% risk of postneonatal epilepsy.[9] The Neonatal Seizure Registry found ASMs were continued at discharge in 73% of survivors of acute provoked seizures.[9] However, only study site and etiology were significantly associated with continuing ASMs.[9] Therefore, Glass and colleagues[10] analyzed seizure and developmental outcomes of this prospectively enrolled cohort of neonates with acute provoked seizures, comparing those maintaining ASMs vs discontinued ASMs at hospital discharge across 9 centers. Overall, there were no differences in childhood development or risk of epilepsy at 24 months between children who had ASMs maintained and those in whom ASM was discontinued at hospital discharge. Furthermore, all 11 children with epilepsy onset prior to age 4 months had ASMs maintained.

This provides the last piece to our puzzle. We now have evidence to support how to treat neonatal seizures, especially acute provoked seizures. We need EEG to accurately detect all seizure activities and know that it is important to treat all seizures, including those without clinical accompaniment.

Phenobarbital is the most effective medication and should be used first unless we suspect neonatal-onset epilepsy due to channelopathy. We should try to discontinue ASMs prior to hospital discharge. We can give parents the peace of mind that comes from both experience and evidence.

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