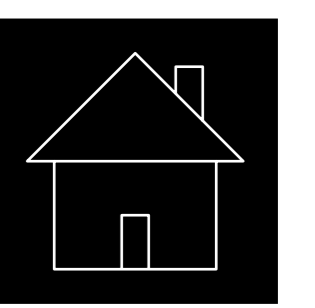


# Efficacy of Fosphenytoin as First-line Anti-epileptic for Neonatal Seizures as Compared to Phenobarbital

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## Abstract

- OBJECTIVE: To compare the efficacy of fosphenytoin and phenobarbital as first-line anti-epileptic drug (AED) for neonatal seizures treatment and to assess neurodevelopmental outcomes at 18 months of age.
- METHODS
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- Neonatal seizures are common in both term and preterm infants, often indicative of an underlying pathological process and associated with high morbidity and mortality.
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RESULTS: Infants in both groups had similar baseline characteristics for neonatal variables (gestational age, birth weight, gender, mode of delivery and 5-minute APGAR score) as well as maternal antenatal complications. For outcome variables there was no difference in EEG/neuroimaging findings, time to seizure control, recurrence of seizures, need for a second-line AED, and discharge home on AED. However, we did find significantly fewer infants in the fosphenytoin group vs phenobarbital group (4.8% vs 30%,  $p=0.02$ ) with moderate to severe neurodevelopmental delay at 18-month assessments.

CONCLUSIONS: Fosphenytoin as well as phenobarbital are equally efficacious as first-line AED in neonatal seizure control but neonates treated with fosphenytoin have significantly better neurodevelopmental outcomes at 18 months of age. Further multicenter studies are recommended to confirm our findings.

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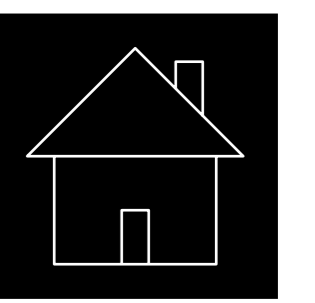


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Neonatal seizures are common in both term and preterm infants, ranging with a risk of seizures being highest in the neonatal period (1.8 to 3.5/1000 live births in the United States). They are often indicative of an underlying pathological process such as hypoxic ischemic encephalopathy, intracranial hemorrhage, stroke or sepsis. Neonatal seizures are associated with high morbidity and mortality. While outcome is strongly influenced by etiology, there is evidence that uncontrolled seizures can exacerbate brain injury and have a negative impact on neurodevelopment. The question of which therapy to initiate is highly disputed, as some AEDs may have negative effects on the developing brain.

Currently the most commonly used first line treatment in new onset neonatal seizures is phenobarbital in most clinical settings, despite known negative impact on the developing neonatal brain. Phenobarbital binds to the GABA receptor, improving the effect of GABA by extending the duration of chloride channel openings and allows increased flow of chloride ions across the membrane. This causes neuronal hyperpolarization and is in fact excitatory in nature in neonates. When neuronal activity is abnormally suppressed, the timing and sequence of synaptic connections can be disrupted and it causes nerve cells to receive signals to self- destruct resulting in apoptosis. Fosphenytoin, a phosphate ester prodrug, is equally efficacious with no known neurocognitive side effects, though cardiac side effects are well known.

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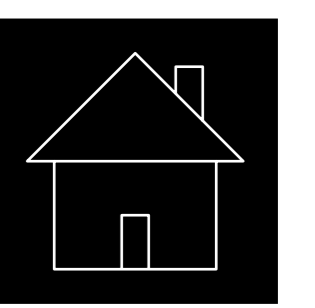


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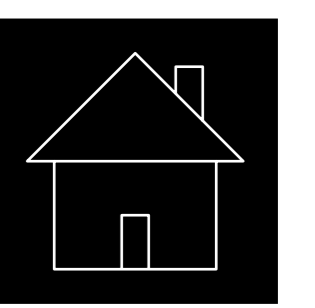


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- For outcome variables there was no difference in EEG, neuroimaging findings, recurrence of seizures, need for a second-line AED, time to seizure control and discharge home on AED as shown in **Table 2** and **Figure 1**.
- However, we did find significantly fewer infants in the fosphenytoin group vs phenobarbital group (4.8% vs 30%,  $p=0.02$ ) with moderate to severe neurodevelopmental delay at 18-month assessments as demonstrated in **Figure 2**.

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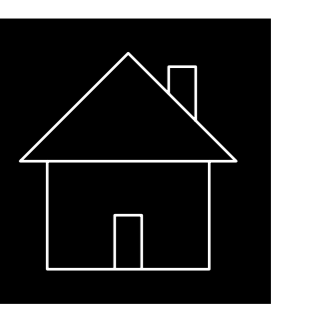
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### Clinical Characteristics for First line Anti-Epileptic Drugs

Variable	Level	Fosphenytoin Total N = 23 N (%)	Phenobarbital Total N = 80 N (%)	P-value
Gestational Age, weeks (Mean, SD)		38.4 (± 2.3)	38.8 (± 2.7)	0.57
Gender	Male	9 (39.1)	47 (58.8)	0.10
Birth weight, grams (Mean, SD)		3144.3 (630.6)	3298.5 (631.6)	0.31
Antenatal Complication	Maternal Abruptio Maternal Uterine Rupture Maternal Chorioamnionitis Fetal Cord Prolapse Fetal Shoulder Dystocia Other	1 (8.3) 0 (0) 1 (8.3) 0 (0) 0 (0) 10 (83.3)	4 (7) 1 (1.8) 10 (17.5) 1 (1.8) 1 (1.8) 40 (70.2)	0.92
Mode of Delivery	C-section	9 (39.1)	38 (47.5)	0.64
5 – minute APGAR score median (IQR)		9.0 (3.0, 9.0)	8.0 (5.0, 9.0)	0.76
Clinical Diagnosis	HIE IVH Infarct Hemorrhage Hypoglycemia Sepsis Drug Withdrawal Syndrome Other (Metabolic, Genetic)	9 (40.9) 0 (0) 3 (13.6) 2 (9.1) 1 (4.5) 1 (4.5) 1 (4.5) 5 (22.7)	28 (38.4) 1 (1.4) 10 (13.7) 9 (12.3) 1 (1.4) 1 (1.4) 2 (2.7) 21 (28.8)	0.82

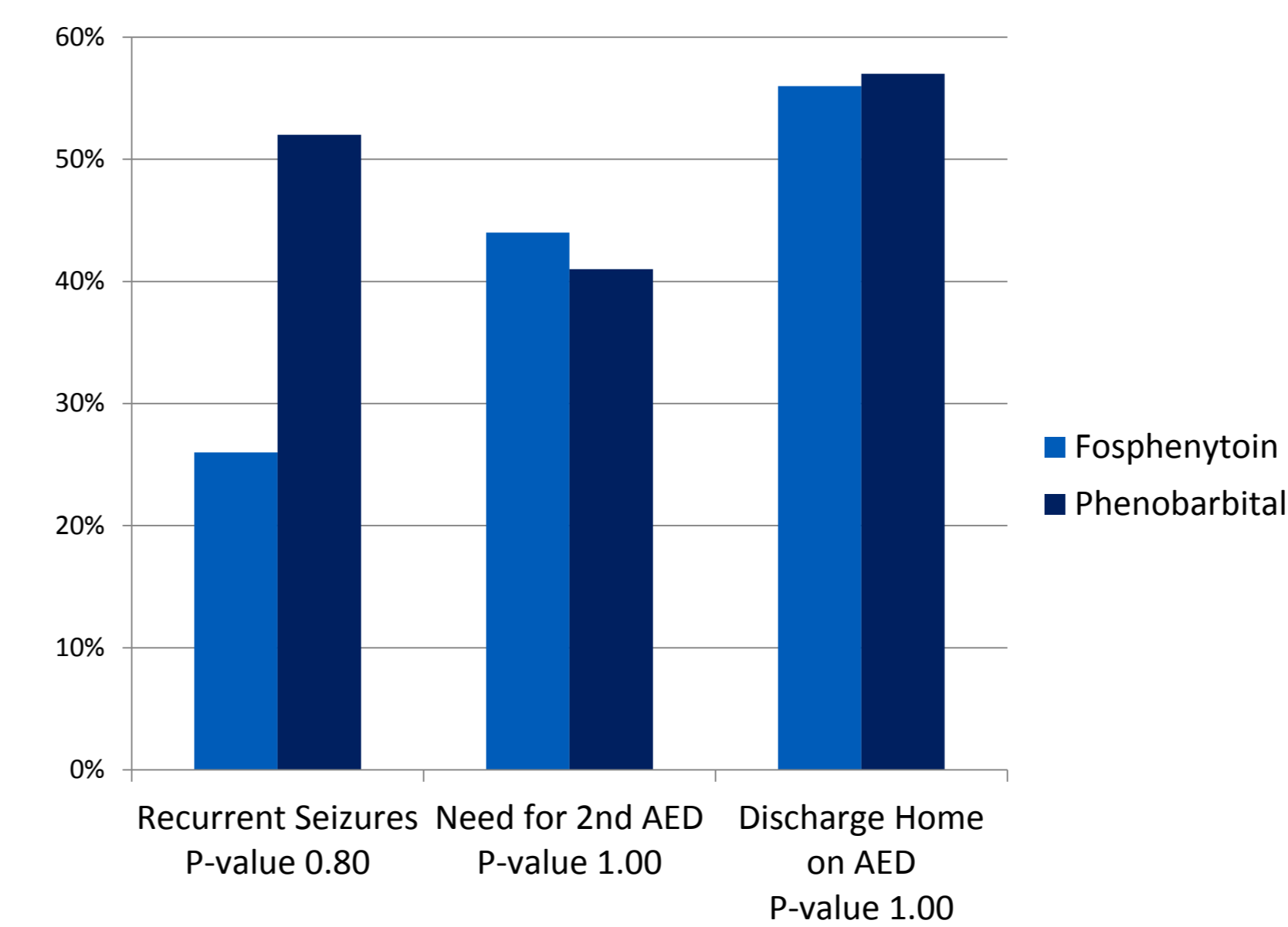
**Table 1.** Infants in both groups had similar baseline characteristics for neonatal variables as well as maternal antenatal complications

### Outcome Variables for First line Anti-Epileptic Drugs

Variable	Level	Fosphenytoin Total N = 23 N (%)	Phenobarbital Total N = 80 N (%)	P-value
aEEG	Yes	21 (95.5)	47 (61)	0.001
Full complement EEG	Yes	21 (100)	75 (96.2)	1.00
EEG Seizure Focus ( Side)	Right Left Bilateral	7 (46.7) 5 (33.3) 3 (20)	12 (26.7) 22 (48.9) 11 (24.4)	0.35
EEG Seizure Focus ( Site)	Frontal Temporal Occipital Multifocal	1 (9.1) 8 (72.7) 0 (0) 2 (18.2)	6 (15.8) 22 (57.9) 4 (10.5) 6 (15.8)	0.76
Head US	IVH Infarct Other	0 (0) 1 (33.3) 2 (66.7)	6 (13.6) 1 (2.3) 37 (84.1)	0.16
MRI Prior to discharge	HIE IVH Infarct Other	4 (25.0) 1 (6.3) 5 (31.3) 6 (37.5)	20 (31.3) 9 (14.1) 14 (21.9) 21 (32.8)	0.77
MRI Post Discharge	HIE IVH Resolved Other	1 (16.7) 0 (0) 3 (50) 2 (33.3)	2 (4.5) 4 (9.1) 10 (22.7) 28 (63.6)	0.18
Time to seizure control (Hours) (Median, IQR)		1 (0, 16)	1 (0, 13)	0.97

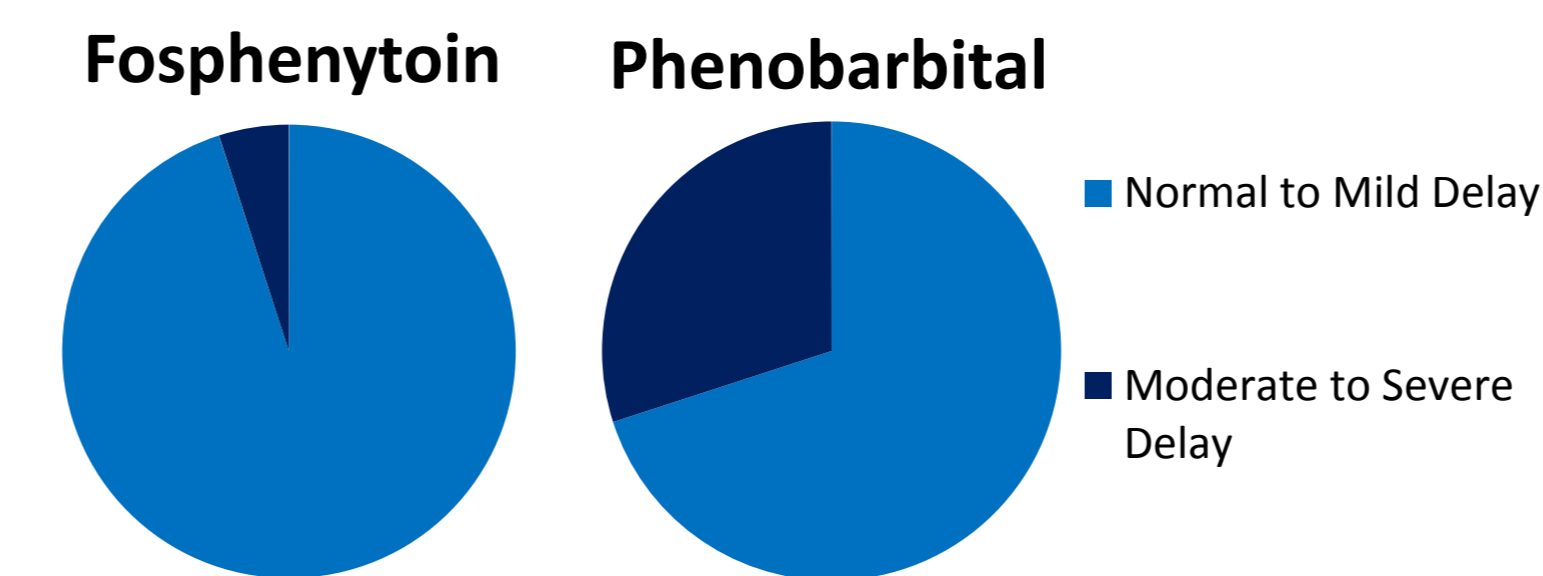
**Table 2.** There was no difference in EEG, neuroimaging findings, recurrence of seizures, or time to seizure control.

### Comparative effectiveness of Fosphenytoin and phenobarbital



**Figure 1.** Though 52% of neonates treated with phenobarbital had recurrent seizures while only 26% of neonates treated with fosphenytoin had recurrent seizures, this was not statistically significant. There was also no statistical significance between both drugs in the need for a second anti-epileptic drug (AED) or if the neonate was discharged home on an AED.

### 18 Month Neurological Outcome



**Figure 2.** At neurodevelopmental or neurology follow ups at 18 months, 30% of infants treated with phenobarbital had a moderate to severe delay while 5% of infants treated with fosphenytoin had a moderate to severe developmental delay

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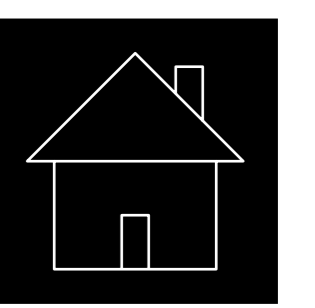


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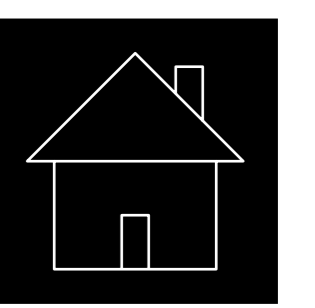


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