

## Phenobarbitone versus Phenytoin for Treatment of Neonatal Seizures: An Open-label Randomized Controlled Trial

GARIMA PATHAK, AMIT UPADHYAY, UMESH PATHAK, \*DEEPAK CHAWLA AND †SNEH P GOEL

From the Department of Pediatrics, LLRM Medical College, Meerut; \*Department of Pediatrics, Government Medical College, Chandigarh; and †Department of Pediatrics, Subharti Medical College, Meerut, UP, India.

Correspondence to: Dr Amit Upadhyay, Department of Pediatrics, LLRM Medical College, Meerut, India.

anuamit7@rediffmail.com

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**Objective:** To compare the efficacy of phenobarbitone and phenytoin for treatment of neonatal seizures in term and near-term neonates.

**Design:** Open labeled randomized controlled trial.

**Setting:** Neonatal intensive care unit of a level II unit from India, from November 2008 to September 2009.

**Participants:** All term and late pre-term neonates admitted with clinically apparent seizures and not having any transient metabolic disorders (hypoglycemia or hypocalcemia) were randomly assigned.

**Intervention:** Phenobarbitone ( $n=54$ ) or phenytoin ( $n=55$ ) intravenously 20 mg/kg/dose over 20-30 min. Neonates whose seizures were not controlled by the assigned drug were then crossed over to be treated with other drug in same dose.

**Primary outcome variable:** Clinical control of seizures (seizure free period of 24 hours after giving anticonvulsant).

**Results:** Baseline characteristics including mean birthweight, gestation age and sex were comparable in both groups. Seizures were controlled in 8 of the 55 (14.5%) neonates who received phenytoin, as compared to 39 of 54 (72.2%) neonates who received phenobarbitone ( $P<0.001$ ). In babies not responding to assigned drugs, after cross-over to the other drug, seizure control was achieved in 44/55 (80%) of the neonates assigned to receive phenytoin first as compared to 49/54 (91%) of those assigned to receive phenobarbitone first ( $P=0.014$ ). After maximum dose of phenobarbitone seizures were controlled in 49/55(89%) in phenytoin group and 52/54 (96%) in phenobarbitone group ( $P<0.05$ ).

**Conclusion:** Phenobarbitone is more efficacious than phenytoin in control of clinical seizures in term or near-term neonates, irrespective of etiology.

**Key words:** Convulsion, Phenobarbitone, Phenytoin, EEG.

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Neonatal seizures are often treated with phenobarbitone or phenytoin [1-6], equally but incompletely. Efficacy of both the drugs in neonates is reported to be (30-50%) for abolition of electrical seizures [4]. However, in developing countries, most units have no access to electroencephalogram (EEG) monitoring in NICU. We intended to compare efficacy of phenobarbitone and phenytoin in the treatment of clinically apparent seizures in term and late pre-term neonates.

### METHODS

This open-label randomized controlled trial was conducted at a Level II neonatal unit of a government medical college in India.

**Inclusion criteria:** All term or near term neonates ( $\geq 35$  weeks of gestation) admitted with clinically apparent seizures not responding to treatment of hypoglycemia, hypocalcemia and other metabolic disorders. Clinical criteria for diagnosis of neonatal seizures were: (i) clonic

movement which could be unifocal, multifocal or generalized (ii) tonic posturing with or without abnormal gaze (iii) subtle seizures and spontaneous paroxysmal, repetitive motor or autonomic phenomenon like lip smacking, chewing, paddling, cyclic movements or respiratory irregularities. Three resident doctors posted in NICU were taught diagnosis and classification of seizures with an educational video and they recorded all seizures (with time) on a pre-designed proforma. Seizures responding to correction of hypoglycemia, hypocalcemia or any other metabolic disorder, and babies with major congenital malformation or myoclonic jerks were excluded.

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**Randomization, allocation concealment and blinding:** Block randomization of 112 numbers in blocks of 4 was done by using computer generated random numbers. They were put in serially numbered opaque envelopes and sealed. This was done by a person not involved in

study. These pre-numbered sealed envelopes were opened to determine the anticonvulsant to be given to the baby. Our trial was an open label trial, so the doctors and nursing staff were aware of the treatment assignments. However, the EEG technicians and neurologist reporting the EEG were blinded to the intervention.

*Protocol for giving anticonvulsants:* Details of name, age, sex, weight, head circumference and length were recorded on a pre structured proforma. Patency of airway, breathing and circulation was ensured based on standard guidelines [7]. After a cannula was secured, blood sugar, serum calcium and blood for other tests was drawn. Hypoglycemia was defined as blood sugar <45mg/dL [7]. Hypocalcemia was defined as ionized calcium <4 mg/dL (1mmol/L) in late preterm and less than 1.2 mmol/L (ionic) in term neonates [7]. If seizures persisted even after correction of hypoglycemia and hypocalcemia, babies were randomized to either phenytoin (plan A) or phenobarbitone (plan B). In plan A, baby was loaded with injection phenytoin at 20mg/kg slow IV infusion over 30 min at a rate of 1mg/kg/min. Cardiac rate, rhythm and blood pressure was monitored during the infusion. If seizure persisted, the babies were crossed over to IV phenobarbitone. In Plan B, babies were loaded with injection phenobarbitone at 20 mg/kg slow IV infusion over 30 min under cardiorespiratory monitoring. If seizure persisted, baby crossed over to receive IV phenytoin in above dose. If seizure persisted after two drugs, baby was reloaded with IV phenobarbitone @ 10 mg/kg each to a maximum of 40 mg/kg and then a third line drug like midazolam was used i.v at 0.1mg/kg/dose. Administration of the drug was discontinued if respiratory depression (cessation of respiration for more than 20 seconds, or less than 20 seconds associated with cyanosis or bradycardia), hypotension (mean blood pressure less than 35 mm of Hg) or bradycardia (heart rate <80/minute) developed after use of either of the drugs.

Once the baby was seizure-free for five days, anticonvulsants were stopped in the same order as they were started except phenobarbitone. IV phenobarbitone was changed to oral once baby was on 50% of enteral feeds. Phenobarbitone was stopped last at discharge if neurological examination was normal and EEG demonstrated no electrical seizures. If neurological examination or EEG was not normal or not done then phenobarbitone was continued after discharge, and baby was re-evaluated at age of 1 month and baby managed according to unit protocol [7] in consultation with a neurologist. However, weaning or discontinuation of anticonvulsants was the prerogative of the unit in which the baby was admitted. EEG was recorded after control

of all clinical seizures for 48-72 hours (when baby was hemodynamically stable) after transporting the baby to the EEG room.

Cessation of clinical seizure activity was primary outcome variable of this study. Secondary outcome variables were (i) survival at discharge, (ii) neurodevelopment outcome at 3 months (Amiel-Tieson method), (iii) time taken to control seizures, and (iv) EEG control of seizures. Neurological examination was done in all babies at discharge. It included examination of overall activity, response to stimuli, ability to suck and swallow, active and passive tone of neck and trunk muscles and neonatal reflexes ( Moro, traction ,and habituation). Examination at 3 months was done by examination of tone by Amiel Tieson method (adductor angle, popliteal angle, dorsiflexion angle and scarf sign). Achievement of milestones like social smile, recognition of mother, neonatal reflexs (Moro's and grasp), head circumference and persistence of seizure were evaluated. For those babies who could not come for follow up, telephonic interview of parents and local practitioners was conducted. They were asked about age, specific developmental milestones, weight gain, feeding, persistence of seizures and over all perception of parents about neurological status and development. Neurodevelopment outcome was considered abnormal if tone of baby was outside of Amiel Tieson score range and if no social smile or recognition of mother was noted by 3 months.

*Statistical analysis:* To detect 30% reduction in seizure control with phenobarbitone as compared to phenytoin with power of 80% and  $\alpha$  error of 0.05, at least 50 babies were required in each group. We decided to include 10-12 babies extra to adjust for protocol deviation, if any. Statistical analysis was done using intention to treat analysis. Results were analyzed using SPSS 13 software. Continuous data with normal distribution were analyzed by student *t* test and non-normally distributed data by Mann-Whitney Test. Categorical data was analyzed by chi-square test or Fischer exact test, where applicable.

## RESULTS

A total of 115 babies with clinically apparent seizures were screened during the study period. Out of them, 6 were excluded (3 refused to participate, 2 had major congenital malformations and 1 had seizure responding to documented hypocalcemia). Of the remaining 109 babies, 55 were randomized to phenytoin group (plan A) and 54 were randomized to phenobarbitone group (plan B). Baseline characteristics and seizures characteristics were comparable in both groups (**Table I**). In case of multiple types of seizures in a baby, he was classified on

the basis of first seizure type only.

Cessation of clinical seizure was observed in 8 of the 55 (14.5%) neonates who received phenytoin and 39 of 54 (72.2%) neonates receiving phenobarbitone first ( $P<0.001$ ). Babies in whom seizure control was not achieved with first drug, after cross-over, seizure control was achieved in 44/55 (80%) of the neonates assigned to receive phenytoin first and 52/54 (96.3%) of those assigned to receive phenobarbitone first ( $P=0.014$ ). After maximum dose of phenobarbitone, seizures were controlled in 49/55 (89%) in phenytoin group and 52/54 (96%) in phenobarbitone group ( $P<0.05$ ).

Median (range) time taken to control all seizures was 30 min (10 min–48 h) in hypoxic ischemic encephalopathy (HIE) stage II, 60 min (10 min–6 d) in HIE stage III, 52 min (15min–24 h) in meningitis, and 11 hours (30 min–3 h) in intracranial hemorrhage. There was no significant difference in seizure control in the two groups ( $P>0.05$ ).

Out of 109 babies enrolled in the study, 29 expired during NICU stay and 80 were discharged. Of these 80, 13 were lost to follow up, and 67 babies were followed at 3 months. Mortality and normal outcome was comparable in both groups. Normal neurological outcome at 3 months was seen in 80% in HIE II, 75% in meningitis and 11% in HIE III.

After clinical control of seizures, EEG was done in 72 babies out of which 66 (91.6%) had normal EEG record

and 6(8.4%) had abnormal EEG record. There was no significant difference in incidence of abnormal EEG records in the two groups. The common abnormalities noted were electrical spikes, and background abnormalities like “burst suppression” pattern or low electrical voltage.

Respiratory depression was found in 3 babies after phenobarbitone and 2 babies after midazolam. Bradycardia was seen in 2 babies with use of phenytoin. During hospital stay, 29 (26%) babies expired (16 in phenytoin group, and 13 in phenobarbitone group,  $P>0.05$ ). 23 of these 29 deaths were in babies with HIE stage III. Of the remaining, 4 were in HIE stage II, 1 each had meningitis and 1 had kernicterus. None of these mortalities were within 4 hours of giving drugs so likely to be unrelated to drugs used, but due to underlying condition. Serum levels of any of the drugs could not be done.

## DISCUSSION

Our study demonstrated that phenobarbitone is more efficacious than phenytoin in control of clinical seizures in term or near term neonates irrespective of the etiology. Superiority of phenobarbitone was observed both when given as a single drug at 20 mg/kg and even after crossover between two groups. Clinical control of seizure was probably accompanied by electrical control of seizures in majority. No significant side effect could be directly related to any of the drugs used.

Our study differed from Boylan, *et al.* [3], who demonstrated that phenobarbitone achieved electrical control of seizures in only 29% as a first line anticonvulsant in whom the background EEG was significantly abnormal. However, our study did not record background EEG signals, so their results may be difficult to compare to this study. Our study differed from Painter, *et al.* [4], who demonstrated that phenobarbitone and phenytoin are equally but incompletely effective as anticonvulsant in neonates. Control of electrical seizures was noted in about 45% babies with either drug and about 60% when combined [4]. However, they did not describe the efficacy of clinical control of seizures, so it is difficult to compare their results to ours. They also did not find any significant side effect related to any of the drugs used. Similar to our results, Gilman, *et al.* [8] reported 75% control of clinical seizure with phenobarbitone and 85% when combined with phenytoin. There are logistic advantages of use of phenobarbitone over phenytoin (*i*) it enters CSF (presumably brain) rapidly and with high efficacy, (*ii*) the serum level is predictable after the dose, (*iii*) it can be administered intramuscularly as well as intravenously for acute therapy and (*iv*) maintenance therapy is easily accomplished with oral therapy [5].

**TABLE I** BASELINE CHARACTERISTICS OF STUDY POPULATION

Parameters	Phenytoin group (n=55)	Phenobarbitone group (n=54)
Gestational age* (wk)	38.6 (1.45)	38.09 (1.87)
Weight* (kg)	2.71 (0.4)	2.55 (0.5)
Male sex	39 (70.9)	40 (74.1)
No of extramural deliveries	30 (70.9)	36 (67.0)
HIE stage 2 (n=42)	21 (38.2)	21 (38.9)
HIE stage 3 (n=44)	26 (47.3)	18 (33.3)
Cause of seizures		
Meningitis (n=18)	7 (12.7)	11 (20.4)
Intracranial bleed (n=2)	1 (1.8)	1 (1.9)
Kernicterus (n=4)	1 (1.8)	3 (5.6)
Type of seizure		
Subtle	27 (49)	24 (44)
Tonic	24 (43)	20 (37)
Clonic	6 (10.9)	8 (14)

in No. (%); \*mean (standard deviation).

**WHAT IS ALREADY KNOWN?**

- Phenobarbitone and phenytoin are equally but incompletely effective as anticonvulsant in neonates.

**WHAT THIS STUDY ADDS?**

- Phenobarbitone is significantly more efficacious than phenytoin in control of clinical seizures in term or near term neonates irrespective of etiology.

Mirzahi and Kellway have suggested that diagnosis of seizures may be inaccurate without EEG confirmation [9]. Murray and Boylan have demonstrated that only 1/3<sup>rd</sup> of neonatal EEG seizures display clinical signs and rest 2/3<sup>rd</sup> of these clinical manifestations are unrecognized by experienced neonatal staff. In recognition and management of neonatal seizures, clinical diagnosis is not enough [10]. The issue of end point of seizures is debatable. Most authorities recommend electrical control of seizure using 24-hour video EEG, but neither the machine, nor cerebral function monitoring (CFM), or the specialist interpreters are readily available. CFM monitoring, though easier to use and interpret is not sensitive enough to detect all seizures. Also, numerous experimental studies on adult and neonatal animal brain have shown that subtle seizure like activity may commonly originate from inferior colliculi of neonatal brainstem. Inferior colliculi of neonatal brain is particularly sensitive to injury by hypoxic ischemic encephalopathy which is the commonest cause of seizures in neonates (and in our study as well) [11-13]. So, such clinically apparent seizures are not likely to have an EEG correlate. Mizrahi and Kellaway have reported that subtle seizures in term and near term neonates have only inconsistent association with EEG seizure activity in as many as 85% of infants. They have also reported that approximately 85% of generalized tonic seizures in full term neonates are not associated with electrical activity and have poor response to anticonvulsants [10]. However, as stated earlier, in a overwhelming majority of neonatal units in both developed and developing world, bedside EEG is not available due to lack of expensive CFM equipments. Thus studies based on abolition of clinical seizures, may have more external validity and generalisability in NICUs, especially in third world countries.

In our study, 26% babies expired during NICU stay. Over two third of these babies were born at home and did not receive any resuscitation at birth. High mortality was probably due to babies coming in advanced stage of illness and seeking late care in a level II unit, without facility for ventilation. However, previous studies have also reported similar high mortality with HIE stage III

[14]. Our 3 month outcomes are also somewhat comparable to other studies. Robertson and Finer reported that neurological outcome was 100% normal in mild HIE, 71% normal in moderate HIE, while none were normal in severe HIE [15]. According to previous studies, in meningitis by both group B streptococcus and gram negative bacilli, 50% survivors had no sequelae, 40% had mild to moderate sequelae while only 10% had severe sequelae [16-18]. Lack of blinding of clinical outcomes, inability to monitor serum drug level and cerebral functions and only short term follow up were the limitation of our study.

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