RESEARCH PAPER

Effect of Withholding Phenobarbitone Maintenance in Neonatal Seizures: *A Randomized Controlled Trial*

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Objective: To compare the effect of withholding maintenance phenobarbitone on breakthrough seizures.

Design: A double blind randomized controlled trial.

Setting: Level II neonatal intensive care unit (NICU) of a teaching hospital in Northern India.

Participants: 152 term and near term neonates (34 weeks of gestation age) with admission weight ≥2 kg with clinically apparent seizures who received intravenous (IV) loading dose of 20 mg/kg of phenobarbitone.

Interventions: After 12 hours of seizure free period of the initial loading dose of phenobarbitone, one group received IV maintenance therapy and other 'no maintenance' (saline as placebo).

Main outcome measure: Breakthrough seizures from randomization till discharge.

Results: Baseline variables were comparable in the two groups. Breakthrough seizures occurred in 30 (40%) subjects in placebo group and 24 (31.2%) in phenobarbitone group with RR (95% CI) of 1.28 (0.83-1.97) (*P*=0.19). Seizure re-currence, re-hospitalisation, mortality and abnormal neurological assessment until 3 months were comparable in the two groups (*P*>0.05). Babies in either group with breakthrough seizures were more likely to be neurologically abnormal at 1 month than babies who did not have breakthrough seizures, but this difference decreased by 3 months.

Conclusion: In term and near-term neonates, those who respond to loading dose of phenobarbitone after a single seizure episode, withholding of phenobarbitone maintenance may not significantly increase the risk of breakthrough seizures.

Key words: *Neonatal convulsions, Management, Seizure recurrence.*

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Phenobarbitone prophylaxis has been used for weeks to months even after control of neonatal seizures, to minimize the risk of recurrence [1,2]. However, there is accumulating evidence that its long-term use may be associated with neuronal apoptosis leading to impairment of behavior, intelligence, cognition, learning and memory [3,4]. It has also been demonstrated that early phenobarbitone discontinuation after the neonate is clinically stable does not lead to increase in breakthrough seizures, even though the signs of neurological damage are still there [5,6]. Moreover, there is data to suggest that phenobarbitone administration after seizure control does not improve neurological outcome [7]. Though WHO has recently recommended stoppage of phenobarbitone if seizure free for >72 hours of loading dose [8], timing of phenobarbitone discontinuation after seizure control is a matter of debate and needs to be researched more. We planned this trial to determine if withholding use of phenobarbitone maintenance after initial loading dose, would result in increase in breakthrough seizures or affect early neonatal mortality and morbidity.

METHODS

The present study was a double blind, randomized control trial conducted at a level II neonatal intensive care unit (NICU) of a teaching hospital in northern India from September 2012 to September 2013. The study was approved by institutional ethics committee and was registered with Clinical Trial Registry of India.

Study population included were term or near-term neonates of ≥34 weeks of gestation up to 4 weeks postnatal age and weighing ≥2 kg. All types of clinical seizures were included in the study. The diagnosis of seizure was based on clinical observation only. Neonates with recurrence of seizures within 12 hrs of the loading dose of phenobarbitone, major congenital malformations, suspected storage disease (ruled out by metabolic screen), intrauterine infection (ruled out by serological screen)

and suspected chromosomal abnormalities (based on facial dysmorphism and other phenotypic abnormalities) were excluded from the study.

Participants were randomly assigned (1:1) by computer generated table to either Plan A or Plan B in blocks of eight. The paper slips with Plan A or B written on them were kept in a serially numbered opaque envelopes and sealed. Parents of babies, investigator, trial staff and statistician were masked to treatment allocation.

Standard definitions and type of seizures were followed [3]. Each subject was enrolled after obtaining written informed consent of the parent(s). After ensuring adequacy of airway, breathing and circulation, intravenous cannula was secured and blood sugar and serum calcium levels were done. If seizures persisted even after correction of hypoglycemia and hypocalcemia, baby was loaded with intravenous phenobarbitone at 20 mg/kg in 1:10 dilution with normal saline (NS) over a 15-20 min period at a rate of 1mg/kg/min. A responder was defined as a subject who remained seizure-free for a period of 12 hours after loading dose. All responders were randomized into two groups, 12 hours after the loading dose into Plan A or Plan B. Identical injectable solutions were made and labelled 'Solution A' or 'Solution B' in 20 mL syringes and covered by opaque tape from outside by a person not involved in any other process of the study and kept everyday morning in the refrigerator for 24 hours. Phenobarbitone (200 mg/mL) was diluted 1:20 in NS (1mL phenobarbitone + 19 mL NS) to make its concentration 200 mg/20 mL or 10mg/mL. Placebo was 20 mL of normal saline kept in an identical syringe. Maintenance dose was 2.5 mg/kg (of phenobarbitone) which was equivalent to 0.25 mL/kg/dose of prepared solution (as well as placebo). When an eligible case was admitted, the doctor on duty opened the envelope and gave the solution A or B accordingly, in dose of 0.25 mL/kg every 12 hourly for 5 days. Babies in both groups were monitored for occurrence of any breakthrough clinical seizures as a primary end point. The study intervention stopped after five days of seizure-free period. If a breakthrough seizure occurred, the baby was reloaded with 10 mg/kg of phenobarbitone and put on open-label maintenance of phenobarbitone till discharge. If the baby was neurologically abnormal at discharge, maintenance was continued after discharge and baby was reassessed at 1 month with repeat neurological examination by standard assessment format by trained attending neonatologist. Blood samples for analysis of serum phenobarbitone levels were obtained at 12 hours after the completion of loading dose (before randomization and giving first maintenance dose). Conventional EEG recording of 30 minute duration were made during wakefulness and spontaneous sleep before discharge.

Seizure recurrence, mortality, need for inotropic support, time to reach full oral enteral nutrition, duration of hospital stay, neurodevelopment status, seizure recurrence and re-hospitalization up to 3 months of age were secondary end points.

Neurodevelopment assessment was done at discharge, 1 month and 3 months of age by residents trained in Amiel-Tison Neurological Assessment [9]. For those babies who could not come for follow up at 1 and 3 months, telephonic discussion with parents or local treating practitioner was done. They were asked about weight gain, feeding, persistence of seizures, and over-all perception of parents about neurological status. The patients in whom phenobarbitone was continued, treatment was stopped as per the standard unit protocol [10].

Sample size calculation was done based on seizure control rates in study by Wasim, *et al*. [11]. Sample size of 76 babies in each group, with a two-group large-sample normal approximation test of proportions with a one-sided 0.05 significance level had 80% power to reject the null hypothesis that with and without maintenance dose are not equivalent (the difference in proportions: proportion of recurrence in maintenance - proportion in no maintenance, is 20% (absolute) or farther from zero in the same direction) in favour of the alternative hypothesis that the proportions in the two groups are equivalent, assuming that the expected difference in proportions is 0% and the proportion in the standard group is 56%. All study outcomes were evaluated on intention-to-treat basis.

Statistical analysis: Analysis of continuous data with normal distribution was done by unpaired t test and non-normally distributed data by Mann-Whitney test. Categorical data was compared using chi square or Fisher exact test, as applicable. Kaplan Meier survival analysis was done for occurrence of breakthrough seizure. *P* value of less than 0.05 was considered significant. Strata 12.1 software was used for statistical analysis.

RESULTS

Out of the total 184 babies with seizures admitted in our NICU during the study period, 152 babies fulfilled study criteria (***Fig.* 1**). The baseline variables were comparable in the two groups (***Table* I**).

Twelve hours after randomization of first loading dose of phenobarbitone, breakthrough seizures till discharge (primary outcome) occurred in 30 (40%)

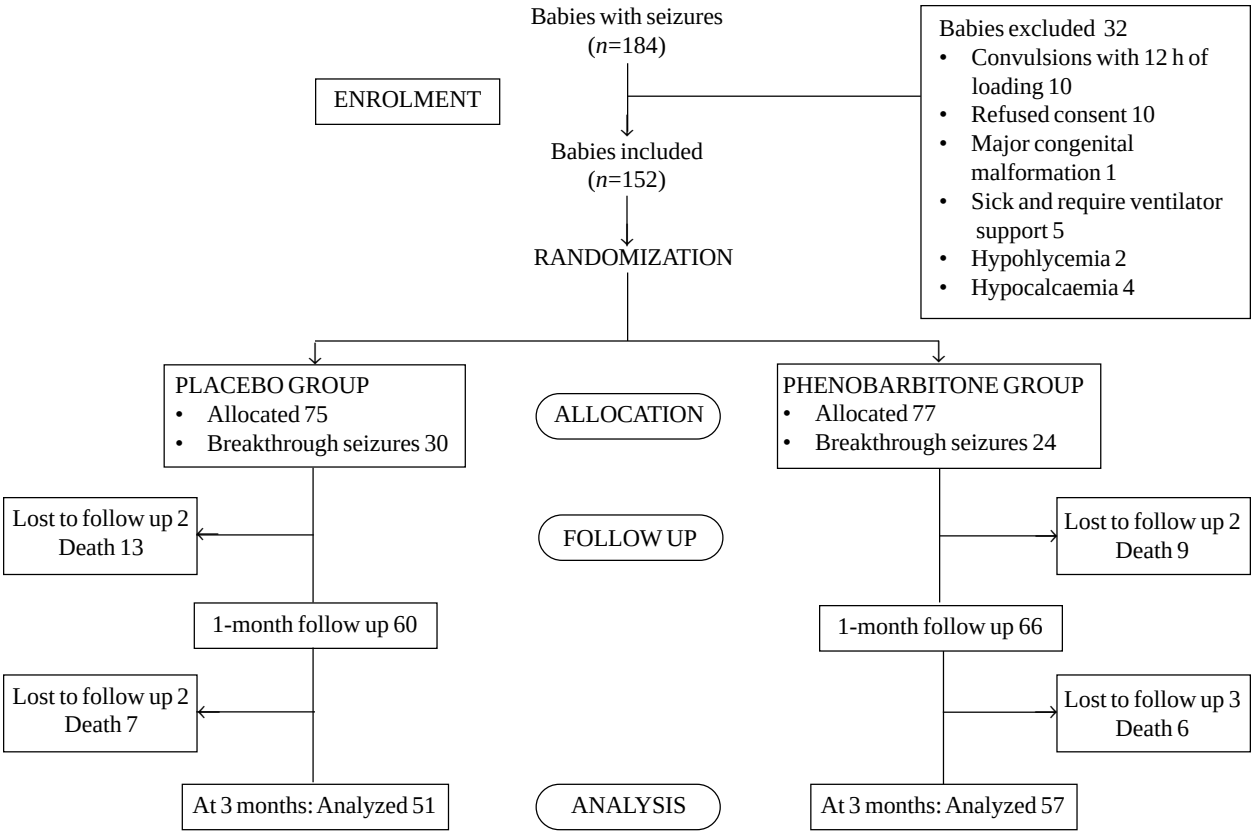

FIG. 1 *Flow diagram of participants.*

TABLE I BASELINE DATA OF NEONATES IN THE TWO GROUPS

	Placebo group (n=75)	*Phenobarbitone group (n=77)*
#Weight (g)	2677 (448.7)	2742 (342.7)
#Gestation (w)	37 (1.3)	38 (1.4)
*Male	41 (54.7)	50 (64.9)
*Intramural delivery	28 (37.3)	27 (35.0)
$Age at admission (h)	4 (0-28)	3 (0-16)
$Onset of convulsion (h)	12 (5-42.5)	12 (4-24)
*HIE (at admission)		
Stage I	1 (1.3)	4 (5.2)
Stage II	49 (65.3)	52 (68.8)
Stage III	14 (18.7)	9 (11.7)
#Serum PB level(µg/mL) at 12 h,	24.8 (23.4)	20.2 (22.0)
**Etiology*		
Birth asphyxia	65 (86.7)	69 (89.6)
Meningitis/sepsis	6 (8)	7 (9.1)
Metabolic	2 (2.7)	1 (1.3)
Intracranial hemorrhage	2 (2.7)	0

*PB: Phenobarbitone; HIE: Hypoxic ischemic encephalopathy; P>0.05 for all comparisons; * No.(%); #Mean(SD); $Median (IQR).*

subjects in placebo group and 24 (31.16%) in phenobarbitone group after first loading dose of phenobarbitone (*P*=0.19) with RR of 1.28 (95%CI) (0.8, 1.97) (***Table* II**).The age of onset of breakthrough seizures was comparable in two groups with maximum likelihood of breakthrough seizure within 72 hours of first episode (***Fig.* 2**). Other secondary outcomes were also comparable in the two groups (***Table* II**).

Subgroup analysis was done to compare the babies who developed breakthrough seizures in either of the groups (*n*=54) and those who did not develop any breakthrough seizures (*n*=98). Time to full feed and duration of hospital stay were significantly more in babies who developed breakthrough seizures. Babies with breakthrough seizure were also more likely to have abnormal neurological examination at discharge and 1 month, but this difference decreased by 3 months of age (*P*=0.06) (***Web Table* I**).

DISCUSSION

This double-blind randomized control trial of 152 babies in a Level II NICU found that the clinical breakthrough seizures till discharge are not likely to increase on

TABLE II SEIZURE RECURRENCE AND MORBIDITY IN THE TWO GROUPS

Outcome	*Placebo group (n=75)*	*Phenobarbitone group (n=77)*	*P value*
Breakthrough seizure during NICU stay*	30 (40.0)	24 (31.2)	0.19**
			1.28 (0.8-1.97)
Need of inotropic support*	31 (41.33)	31 (40.25)	0.89
Abnormal EEG after seizure control*	8/55 (14.54)	7/63 (11.110)	0.38
Time to full enteral nutrition (d) #	5.6 (3.24)	6.09 (3.79)	0.52
Duration of hospital stay (d) #	7.41 (4.32)	7.23 (4.20)	0.79
Mortality in NICU*Mortality at 3 months	13/75 (17.33)7/58 (12.06)	9/77 (11.66)6/53 (9.52)	0.360.19
Re-hospitalization till 3 months*	10/60 (16.67)	8/66 (12.12)	0.51
Seizure recurrence till 3 months*	2/60 (3.33)	7/66 (10.6)	0.10
Abnormal neurological outcome *			
Discharge (*n*=152)`	23/75 (30.66)	16/77 (20.77)	0.14
1 month (*n*=126)	12/60 (20.0)	9/66 (13.63)	0.37
3 Months (*n*=108)	2/51 (3.92)	2/57 (3.50)	0.79

Values indicate mean ±SD#, n (%); ** RR (95% Confidence interval), (P> 0.05) for all.*

withholding phenobarbitone maintenance after the loading dose. It was observed that mortality and abnormal neurodevelopmental outcomes till three months were slightly higher in those in whom phenobarbitone had been withheld, though it was not statistically significant.

Hellstrom, *et al*. [5] reported that despite short median duration of antiepileptic treatment of about 4.5 days, only 8.3% infants developed seizure recurrence in the first year of life. Theodore, *et al*. [12] have reported that little relation exists between the rate of phenobarbitone withdrawal and seizure control. Guillet, *et al*. [4] retrospectively studied the impact of outpatient phenobarbital prophylaxis on the frequency of seizure recurrence and long-term neurodevelopmental outcome at 1 to 11 years. He observed no significant difference in seizure recurrence, irrespective of maintenance therapy after discharge. It has been shown that asphyxia may lead to exaggerated expression of the sodium-potassium-chloride co-transporter (NKCC1) which renders the neonatal brain hyperexcitable [13,14].The variation in seizure control could also be attributed to varying levels of free phenobarbitone entering the brain in neonates with different sickness profiles [15].

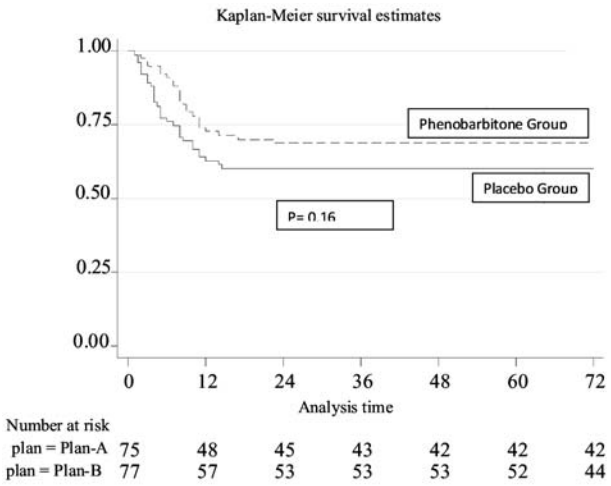

FIG. 2 *Kaplan-Meier curve for seizure control in the 2 groups.*

With concerns of phenobarbitone-related apoptotic neurodegeneration and related long term cognitive side effects [16], there was a felt need for shortening the maintenance therapy. Although recurrent seizures can potentially enhance the brain damage, there is insufficient evidence to suggest that prolonged treatment with phenobarbitone can actually prevent them. So, early recognition of seizures and targeted therapy of recurrences in high-risk babies may be the most appropriate option. Outcomes of babies may be improved by safely avoiding prolonged phenobarbitone therapy in babies who have already suffered an insult to their developing brain [4].

A limitation of our study was lack of cerebral function or continuous EEG monitoring. Presence of electrical seizures in absence of clinical correlates have been reported to be harmful [3]. Though we did not measure the serial serum phenobarbitone levels, sub-therapeutic

WHAT IS ALREADY KNOWN?

- The duration of phenobarbitone prophylaxis after control of acute neonatal seizures is debatable.

WHAT THIS STUDY ADDS?

- After clinical control of neonatal seizures with first loading dose of phenobarbitone, withholding phenobarbitone maintenance may not lead to seizure recurrence in term and near-term infants.

levels are less likely to contribute to breakthrough seizures, as breakthrough incidence was similar in the two groups.

Though cessation of all electrical seizures should be the therapeutic end point of phenobarbitone or other anti-epileptic drugs, majority of centres still lack good EEG monitoring. Moreover, there are concerns over inter-observer variation in continuous EEG or cerebral functioning monitoring [15]. So control of clinical seizures may be next best achievable goal, especially in developing countries. Further trials with larger sample size to detect even smaller differences in breakthrough seizures and neurological outcome are desirable. Such studies should also monitor for recurrence of electrical seizures and serial serum phenobarbitone levels to determine if declining levels could be contributing to seizure recurrence.

Contributers: PS, PG: collected and compiled the data for the study, and drafted the manuscript; AU: conceptualized and designed the study, finalized the manuscript. He will act as guarantor of paper; AS: helped in allocation concealment, blinding and pharmacy related issues in the study; SS: did phenobarbitone level analysis and provided intellectual inputs from protocol stage and helped in drafting the paper; SV: did the sample size calculation, statistical analysis and intermittent data check. Critical review was performed by all.

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WEB TABLE I SUBGROUP - ANALYSIS OF INFANTS WITH AND WITHOUT BREAKTHROUGH SEIZURES IN EITHER GROUP

No breakthrough seizures (n=98)	*Breakthrough seizures (n=54)*		*P value*
*HIE (at admission)**			
Stage II	63/92 (68.47)	38/50 (76.00)	0.12
Stage III	13/92 (14.13)	10/50 (20.00)	
Serum phenobarbitone level (mcg/mL)[#] at 12 h, mean (SD)	22.15 (21.87)	22.91 (22.65)	0.81
Infants with phenobarbitone level* <10 mcg/mL	28 (28.5)	16 (29.3)	0.89
Time to full enteral feeds[#] (d)	5.25 (3.44)	7.07 (3.43)	0.003
Duration of hospital stay[#] (d)	6.46 (3.67)	8.87 (4.77)	<0.001
*Abnormal Neurological examination**			
At discharge	20/98 (20.4)	19/54 (35.18)	0.03
At 1 month	9/82 (10.98)	12/44 (27.27)	0.02
At 3 month	1/73 (1.37)	3/35 (8.57)	0.06
*Seizure recurrence**			
1 month	5/82 (6.1)	4/44 (9.1)	0.57
3 month	5/73 (6.8)	4/35 (11.4)	0.50
Re-hospitalization rate*	9/82 (10.91)	8/44 (18.18)	0.29

HIE: Hypoxic ischemic encephalopathy. Value indicate mean (SD)[#], or n (%).*