Effect of withholding phenobarbitone maintenance therapy in neurodevelopmental outcome at 1 year of age in neonatal seizures

Pankaj kr. Ravi[1], Vikas Agarwal[2,*], Priyanka Gupta[3], Amit Upadhyay[4]

[1]Resident, [2,4]Associate Professor, [3]Senior Resident, Dept. of Pediatrics, LLRM Medical College, Meerut, Uttar Pradesh

***Corresponding Author:**
Email: drvikaspaed75@gmail.com

Abstract

Objective: To investigate effect of withholding phenobarbitone maintenance therapy in neurodevelopmental outcome at 1 year of age in neonatal seizures

Materials and Methods: Design: This study was conducted to evaluate neurodevelopmental assessment at 1 year of age of babies enrolled in a previous interventional randomized controlled trial done at our NICU. Participants: 152 late preterm and term infants were allocated to phenobarbitone maintenance group (n=77) or placebo group (n=75). We enrolled late preterm and term infants with seizures after receiving loading dose of phenobarbitone. Both phenobarbitone maintenance and placebo group participants were followed at 1 year of age and neurodevelopmental screening was done by Denver II. Outcome measure(s): Outcome was abnormal examination through Denver II at follow up at 12-18 months and to measure seizure recurrence & rehospitalisation in both groups.

Results: 152 babies were enrolled in this study. Outcome data was available for 92 (85.2 %) of the 108 alive infants at 1 year of age. The baseline characteristics of the babies in 2 groups were comparable. Abnormal examination as per Denver II occurred in 19/43 (44.19%) subjects in placebo group and 21/49 (42.86%) in phenobarbitone group. Seizure recurrence and rehospitalisation till 1 year of age were comparable in both groups.

Conclusion: This study concluded that withholding phenobarbitone maintenance immediately after loading dose of phenobarbitone in neonatal seizures does not result in worsening of neurodevelopmental outcome, or mortality and recurrence of seizures till 1 year of age.

Keywords: Denver II, Neurodevelopment outcome, Phenobarbitone, Seizures.

Introduction

Neonatal seizures are a common problem in neonatal unit. There is evidence from experimental data showing that neonatal seizures can adversely affect the developing brain.[(1)] Thus neonates with seizures are at risk for neonatal mortality and the survivors at risk for neurological impairment, developmental delay, and later epilepsy.[(2–6)] In earlier studies, the mortality was as high as 40% but decreased in subsequent reports to 20%.[(2,3,7–9)] However, the prevalence of long-term neurodevelopmental sequelae in survivors has remained unchanged at about 30%.[(2,7,10)] Although prolonged therapy of phenobarbitone has been associated with cognitive decline in older children and adults, their impact on neurodevelopmental outcomes of infants with neonatal seizures is largely unknown (11). Based on evidence of long term side effects of phenobarbitone, it's suggested to reduce the duration of anticonvulsants after control of neonatal seizures to as short as possible.

This increasing concern regarding detection of neurodevelopmental status following neonatal seizures and prolonged AED use at an earlier age has lead us to minimise duration of AED and to provide long term follow up to detect neurodevelopmental outcomes using screening tests. This will help in providing early intervention in such high risk neonates. We used Denver II as the developmental screening test, as it is a validated screening test with which many paediatricians around the world are familiar and it has been standardized for children in many countries .[(12-15)]

So we planned this study to evaluate the impact of neonatal seizures & withholding phenobarbitone maintenance on neurodevelopmental outcomes at 1 year of age. We tested the hypothesis that in late preterm and term infants withholding phenobarbitone maintenance is not inferior to phenobarbitone maintenance in assessing neurodevelopmental outcome at 1 year of age.

Materials and Methods

This study was conducted to evaluate the follow up outcomes of a previous interventional randomized controlled trial done at Division of Neonatology, Department of Pediatrics, L.L.R.M. Medical College Meerut by Saxena et al,[(16)] which compared the effect of withholding maintenance phenobarbitone on breakthrough seizures, mortality and morbidities in infants till NICU discharge.

All 152 infants randomised & enrolled in the previous study were followed for neurodevelopmental assessment at 12-18 months of age using Denver II. Data were collected by single investigator and quality assurance was done. The baseline characteristics at the time of randomisation were comparable in both groups. Patients included were babies who were ≥35 week gestation**,** weighing ≥2 kg and ≤28 days of postnatal age, admitted in NICU with clinically apparent seizures, and had no recurrence of seizures for 12 hours

of first loading dose of phenobarbitone of 20 mg/kg. A clinical criterion was used for the diagnosis of neonatal seizures.

Randomization was done by computer generated table to either Plan A or B in blocks of eight. This trial was designed as a double blind trial. To ensure blinding identical injectable solutions were made by person not involved in other process of this study in each syringe containing drug (phenobarbitone) and placebo (normal saline) daily outside and kept in the refrigerator. Phenobarbitone was given in standard maintenance dose.

When an eligible case was admitted, the doctor on duty opened the envelope and gave the solution A or B in dose of 0.25 ml/kg/doses every 12 hourly for next 5 days. The concealment of solution A & B was broken by the person not involved in the trial as placebo and phenobarbitone respectively only after the completion of trial and analysis.

All babies randomized in both groups were monitored for occurrence of any breakthrough clinical seizures. Breakthrough seizures were defined as occurrence of seizure from randomization till discharge from NICU. If no breakthrough seizure occurred, maintenance phenobarbitone /placebo were stopped after 5 days of seizure free period. If a breakthrough seizure occurred, the baby was reloaded with phenobarbitone and maintenance was continued with intention to treat. All babies at discharge had a neurological examination by the neonatologist. If the baby was neurologically abnormal, maintenance was continued after discharge, otherwise it was stopped and baby was reassessed at 1 month for neurological examination by the same neonatologist.[23] Conventional EEG recording of 30 min duration was made during wakefulness and spontaneous sleep before discharge.

Ethical clearance was obtained from the institutional ethics committee. The parents/families of infants enrolled in the original trial were contacted telephonically or by home visit and called for follow up examination. Separate trial registration was not done since the present study is a follow up study of previous trial (CTRI / 2012/ 11/ 003122).

Primary outcome of the study was abnormal examination through Denver II with follow up at 12-18 months. Denver II items were valued by the investigator directly with the child and in some cases are reported by the care giver whether the child performs certain task or not. The Denver II score was considered abnormal when the child failed in at least two items in four sections of the Denver II.[17] Secondary outcomes were mortality & seizure recurrence, abnormal test proportion in Denver developmental milestones and anthropometric analysis till 1 year of age. Anthropometric data were calculated using WHO multicentre growth reference study (MGRS) charts with corrected age 'z score' for the values were calculated for this data without corrected age by using 'WHO anthropometric calculator' v3.2. Subgroup analysis of babies with & without breakthrough seizures was done separately.

Sample Size

Based on previous studies held at neonatology unit in SVBP hospital, when the sample size in each group is 76, a two-group large-sample normal approximation test of proportions with a one-sided 0.05 significance level will have 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.

Statistical Analysis

Data was collected from a pre-designed proforma and was recorded on MS-excel for analysis. 't' test was used for continuous variables. Categorical data was compared using chi square or Fischer exact test as applicable. P value of less than 0.05 was considered significant. All analysis was done using commercial available software program STATA 11, Stata Corp LP, Texas, USA.

Results

Of the 152 babies enrolled in this study 44 (29 %) babies died by 1 year of age. Primary outcome data (Denver II) was available for 92 (85.2 %) out of 108 infants up to 1 year of age (Figure 1). The baseline characteristics of the babies lost in the study were not different to the babies followed up till 1 year. 92 children (60.5% of the original sample) were seen for a follow-up assessment at mean age of 14.1 ± 3 months. The baseline characteristics were similar in both groups (Table 1).

Table 1: Comparison of baseline characteristics of babies enrolled in study

	Placebo Group (n=75)	Phenobarbitone Group (n=77)	p value
Weight (grams)#	2676.9 (448.7)	2741.71 (342.7)	0.31
Gestation (weeks)#	37.28 (1.3)	37.70 (1.4)	0.06
Sex (Male)*	41 (54.7)	50 (64.9)	0.19
Intramural delivery*	28 (37.3%)	27 (35.0%)	0.95
Age on admission (hours)##	4 (28)	3 (19)	0.44
Onset of convulsion (hours)##	12 (35)	11 (30)	0.22
Duration of seizure (hours)#	0.32 (0.12)	0.36 (0.11)	0.06
HIE stage (at admission)# I	1 (1.33) 49 (65.33)	4 (5.19) 52 (68.83)	0.38

II III	14 (18.67)	9 (11.69)	
Mean serum phenobarbitone level (mcg/ml)# at 12hours (before starting maintenance)	24.78 (23.45)	20.21 (21.98)	0.61
Lab variables ABG (pH)# ABG (pH<7)* ABG (pH 7-7.2)* Abnormal Prothombin time	 7.06 (0.14) 15(28.3%) 30(56.6%) 25 (34.72%)	 7.09 (0.17) 9(16%) 37(66%) 22 (28.94%)	 0.15 0.07
Etiology Birth asphyxia Meningitis/Sepsis Metabolic Intracranial haemorrhage	 65 (86.7) 6 (8) 2 (2.7) 2 (2.7)	 69 (89.6) 7 (9.09) 1 (1.29) 0	 0.53
Breakthrough seizure during NICU stay	30 (40.00)	24 (31.16)	0.19
Abnormal EEG after seizure control*	8/55 (14.54%)	7/63 (11.110%)	0.38
Phenobarbitone treatment for >1 month of age	12/60 (20 %)	9/66 (13.63%)	0.37

HIE: Hypoxic ischemic encephalopathy. Value indicate mean ±SD#, number (%)*, median (IQR)##

Abnormal examination on Denver II at mean age of 14 months was observed in 19 (44.19%) subjects in placebo group and 21 (42.86%) in phenobarbitone group (P value 0.8). Regarding the assessment of development done through Denver II, 43.5 % (40/92) of the children were at risk for the overall development, and the most affected areas were the language (35.8 %) and fine motor development (31.5 %) (Fig. 2).

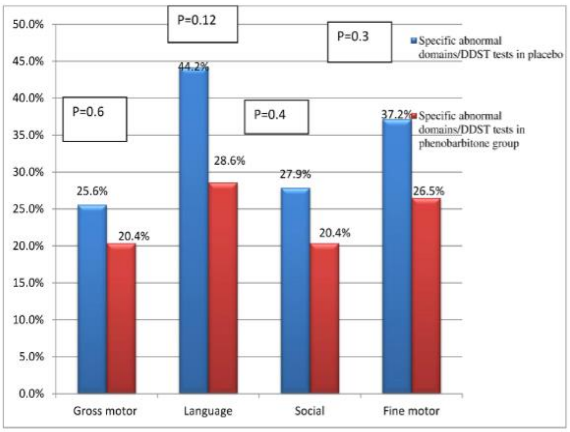

Fig. 2: Proportion of specific abnormal domanis/ total Denver II examinations in the two groups

Secondary outcomes: Mortality, rehospitalisation, seizure recurrence and anthropometry till 1 year of age were comparable in the two groups. There were 25 (33.3 %) deaths in placebo group and 19 (24.7 %) deaths in phenobarbitone group at 1 year of age (P value 0.5), (RR=1.35, 95% CI=0.81-2.23), (risk difference=8.6 %, 95 % CI= -5.8 to 23.15). Composite outcome of death & abnormal development in the 2 groups were in 55 % of the sample (Table 2).

On analysis of babies with breakthrough seizures, there was no significant difference in abnormal Denver II examination in the babies with breakthrough seizures and without breakthrough seizures (P value=0.66) (Table 3). On subgroup analysis, best outcome was observed in group receiving phenobarbitone maintenance which had no breakthrough seizures (17% mortality) as compared to group with breakthrough seizures (37.5%), (P value-0.048).

Table 2: Primary & secondary outcomes in the two groups

Primary Outcome	Placebo group (n=43)	Phenobarbitone group (n=49)	P value	Overall in two groups
Abnormal examination on Denver II	19/43 (44.19%)	21/49 (42.86%)	0.81	40 (43.5 %)
SECONDARY OUTCOMES				
Mortality till 1 year of age (deaths/total enrolled)	25/75 (33.3%)	19/77 (24.7%)	0.2	44 (28.9%)
Mortality at 3 month	20/75 (26.6%)	15/77 (19.5%)	0.2	35 (23%)
Mortality till 1 month of age(deaths/enrolled)	13/75 (17.3%)	9/77 (11.7%)	0.07	21 (13.8%)
Mortality in NICU/before discharge	13/75 (17.3%)	8/77 (10.4%)	0.07	21 (13.8%)
Seizure recurrence from discharge to 3 months	2/60 (3.33%)	7/66 (10.6%)	0.1	9 (7.1%)
Seizure recurrence from 3 months till 1 year of age	6 (13.95%)	5 (10.42%)	0.6	11 (12 %)
Rehospitalisation till 1 year of age	11 (25.58%)	10 (20.41%)	0.5	21 (22.8%)
Composite outcome of death & abnormal examination on Denver II	44/75 (58.66%)	40/77 (51.94 %)	0.4	84/152 (0.55 %)
Anthropometric z scores at mean corrected age 14 months				

WFA at follow up(Z score)#	-1.17 (1.16)	-1.16 (1.07)	0.9	
HFA at follow up(Z score)#	-1.48 (1.3)	-1.61 (1.27)	0.6	
HCFA at follow up(Z score)#	-1.5 (1.71)	-1.47 (1.58)	0.9	
WFH (Z score)#	-0.55 (1.09)	-0.50 (0.80)	0.8	
WFA (Z score) (<-3SD)*	2 (4.65%)	2 (4.08%)	0.9	4.35 %
HFA (Z score) (<-3SD)*	3 (6.98%)	7 (14.29%)	0.2	10.9 %
HCFA (Z score) (<-3SD)*	9 (20.93%)	8 (16.33%)	0.5	18.5 %
WFH (Z score)(<-3SD)*	1 (2.33%)	0	0.3	1.09 %

Table 3: Outcome comparison of babies who developed breakthrough seizures and who did not

Outcome	No breakthrough seizures (n=98)	Breakthrough seizures (n=54)	P value	RR
Mortality till 1 year of age	25 (25.51%)	19 (35.2%)	0.21	1.36 95% CI=0.832-2.24
Mortality in placebo group at 1 year of age	16/45 (35.5%)	9/30 (30 %)	0.7	
Mortality in phenobarbitone group at 1 year of age	9/53 (17 %)	9/24 (37.5 %)	0.048	
Abnormal examination by DDST	26/62 (41.9 %)	14/30 (46.6%)	0.6	1.112 95% CI=0.68-1.8
Abnormal examination in placebo group by DDST	11/26 (42.3%)	8/17 (47%)	0.76	
Abnormal examination in phenobarbitone group by DDST	15/36 (41.66%)	6/13 (46.15%)	0.78	

Discussion

The present study demonstrated that in late preterm and term infants withholding of phenobarbitone maintenance after its first (loading) dose, does not result in increase in poor neurological sequelae at 1 year of age. Abnormal neurodevelopmental test was observed in 19 (44.19%) babies in placebo group which was comparable to 21 babies (42.86%) in phenobarbitone maintenance group. We also found that the head size, rehospitalisation rates and seizure recurrence till 1 year of age were comparable in the two groups.

Despite being a common problem, no clear scientific guidelines are available for duration of phenobarbitone therapy for neonatal seizure.[2,18-21] Previous studies have reported that there is no significant difference in neonatal seizures on duration of phenobarbitone maintenance therapy and outcome in terms of neurodevelopment, seizure recurrence.[19-22] Due to encouraging results of trials on early cessation of phenobarbitone coupled with its well documented adverse effects, WHO had recently recommended reduction in duration of its maintenance therapy to three days after seizure control.[23]

Earlier studies had reported poor long term outcomes with both neonatal seizures[24] and HIE.[25] However, there have not been too many trials comparing effects of early cessation of phenobarbitone maintenance therapy on long term neurodevelopmental outcome. In a retrospective study, Maitre et al[26] observed neurodevelopmental outcome at 24 months of age by Bayley Scales of Infant Development II on 280 infants who developed clinical neonatal seizures and received either phenobarbitone (n=106), levetiracetam (n=33) or both (n=141). They demonstrated that longer exposure to phenobarbitone was associated with poor neurodevelopmental outcome than using levetiracetam. However they did not find any dose-effect relationship. There was also no evidence that any exposure or cumulative exposure to either AED was associated with increase in mortality. Their study reported 24 % mortality at 24 months of age which was largely comparable to 29 % in our study. Earlier studies have also reported similar mortality, ranging from 24-33 % in neonatal seizures.[22,25,26] This high mortality in our study could be due to high proportion of babies with HIE stage 3 (15.2 %) and the fact that almost two third of babies were born at home or peripheral centres and later referred to us. Comparing the two randomised cohorts we followed in our study, the mortality was largely comparable.

Previous studies have demonstrated close relation between seizures and the development of neurological deficits. Glass et al[27] observed that clinical neonatal seizures in birth asphyxia are associated with worse neurodevelopmental outcomes. Tekgul et al[18] observed neurodevelopmental outcome of seizures in term newborn infants of which 28% of survivors had long

term poor outcome at 12-18 months using Bayley scales II.

Neurodevelopmental screening in our study was determined by Denver IIdone at mean age of 14 months. 43.5 % of the children tested in our study were at risk for the overall developmental abnormality. Of all the domains, the language and fine motor development were affected the most. Earlier studies have reported that phenobarbitone exposure is associated with occurrence of major motor and cognitive impairments in early childhood.[26] At 24 months, increased exposure to phenobarbitone was associated with decreasing cognitive and motor scores.[28] Our results showed major delay in language and fine motor milestones at 1 year of follow up. But longer follow up is required in our cohort to detect actual incidence of these impairments. It has been shown that following HIE, severe sensory or motor loss can be diagnosed early during 1st year, but low developmental quotient, fine and gross motor impairments can be ascertained only during 2nd to 4th year. Abnormalities in cognitive function and personal social take as much as 4-7 years as to be diagnosed while learning disabilities may be known only by 7-9 years of age.[28]

Though Denver II is only the screening tool and not a diagnostic modality in itself, other studies also used Denver IIfor evaluating neurodevelopmental outcome in the high risk cohorts. Nair et al compared Denver IIat 12 months of age in 604 NICU graduates against the gold standard Developmental Assessment Scale for Indian Infants (DASII) and concluded that Denver IIhad high specificity, negative predictive value and accuracy at 1 year of age of assessment.[29]

In group of 28 babies with HIE, Hallioglu et al have reported that Denver IIwas a reasonable predictor of later neurological outcome.[30] Nunes et al[22] evaluated the neurological outcome using Denver IIin 101 neonates with seizures at mean age of 33 months. They demonstrated developmental delay in almost 35 % of patients, which is comparable to 43 % observed in our study.

The main limitation of our study was that Denver IIis not the ideal tool to evaluate neurodevelopment at 12-18 months of age. Though it's a good screening tool, it has limited sensitivity and positive predictive value to detect subsequent abnormal neurological outcome. DASII or Bayley Scales would have been more appropriate diagnostic tools. However, we used Denver IIas it widely used, easy to administer and requires no special training.It has been demonstrated in previous studies that electrographic seizures have major impact on subsequent neurodevelopment. Abnormal post-neonatal EEG and neuroimaging have been shown to be good predictors for developmental delay, but were not done in our study, is another limitation. Further trials with larger sample size to detect even smaller difference in neurological outcome are desirable.

Key Message

Our study concluded that withholding phenobarbitone maintenance immediately after loading dose of phenobarbitone in neonatal seizures does not result in increase in adverse neurodevelopmental outcome, or mortality and recurrence of seizures by 1 year of age.

What is Already Known?

Exposure to Phenobarbitone may lead to worse neurodevelopmental outcome.

What this Study Adds?

Withholding phenobarbitone maintenance does not lead to increase in developmental delay or recurrence of seizures.

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