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Role of Phenobarbitone Maintenance Therapy in Asphyxiated Neonate with Encephalopathy to Control Seizure- A Randomized Clinical Trial

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Abstract

Background: *Seizures after perinatal asphyxia may worsen brain injury. Phenobarbital (PHB) is commonly prescribed anticonvulsant worldwide to control seizure in asphyxiated neonates. The evidence of the best use of maintenance drugs is limited.*

Objective: *To assess the effectiveness of phenobarbitone maintenance therapy in asphyxiated neonates with seizure.*

Material & Methods: *A total of 79 asphyxiated neonates (HIE-II/ III), ≥35 weeks were enrolled from January 2019 -January 2020 in this randomized clinical trial where cases were categorized into three groups. Group A received phenobarbitone 4mg/ kg/day twice daily for 6 weeks and Group B received 2mg/kg/day once daily for 2 weeks while Group C didn't receive any anti-seizure medication after acute management. Clinical and electrophysiological study was done at discharge, one and half month of age. Data were analyzed by SPSS version 20.*

Result: *Mean age in days was 0.96 ± 1.77 in Group-A, 0.66 ± 1.20 in Group-B and 0.55 ± 1.30 in Group-C. Both Group A and C had seizure in 33.34% and 12.5% in group B at 1½ month. During discharge most of the cases had normal EEG, EEG abnormalities were found in 25% cases in group B, 16.67% in group C and 8.33% in group A. At 1 ½ month, EEG abnormality was found more among group C (33.34%) than group A (25%) and B (25%) which was statistically insignificant.*

Conclusion: *This study concluded that early discontinuation of phenobarbitone after acute management may not increase the risk of clinical and electrographic seizure in future.*

Key words: *PB (Phenobarbitone), Anti-seizure drugs, HIE, Neonatal seizure (clinical and electrographic)*

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Introduction

Perinatal asphyxia (PNA) causes damage to almost every organ of the body, particularly CNS. According to WHO, 23% of neonatal deaths in low-income countries are due to birth asphyxia and 3% of all infants (3.6 millions) suffer from moderate to severe birth asphyxia, of which approximately 840,000 live numbers develop serious squelae.[1,2] After PNA, the occurrence of seizures remains a significant neurologic event.

To date, phenobarbitone (PB) remains the most commonly prescribed first-line anti-seizure drugs (ASD) for treatment of neonatal seizures. PB modulates the postsynaptic effects of certain neurotransmitters. The modulation is primarily affecting the inhibitory GABA A receptor which enhance inhibition of synaptic transmission and interrupting the spread of epileptic activity.[3] Major mechanisms of PB are modifications of ionic (sodium and calcium) conductance in neuronal membranes.[4] WHO strongly recommended only the use of PB as a first-line ASD in management guidelines for neonatal seizure but this recommendation was based on very-low-quality evidence.[5] The use of PB is largely based on tradition, local protocols or personal preference. The debate concerning the best drugs, their dose and duration still continues.[6]

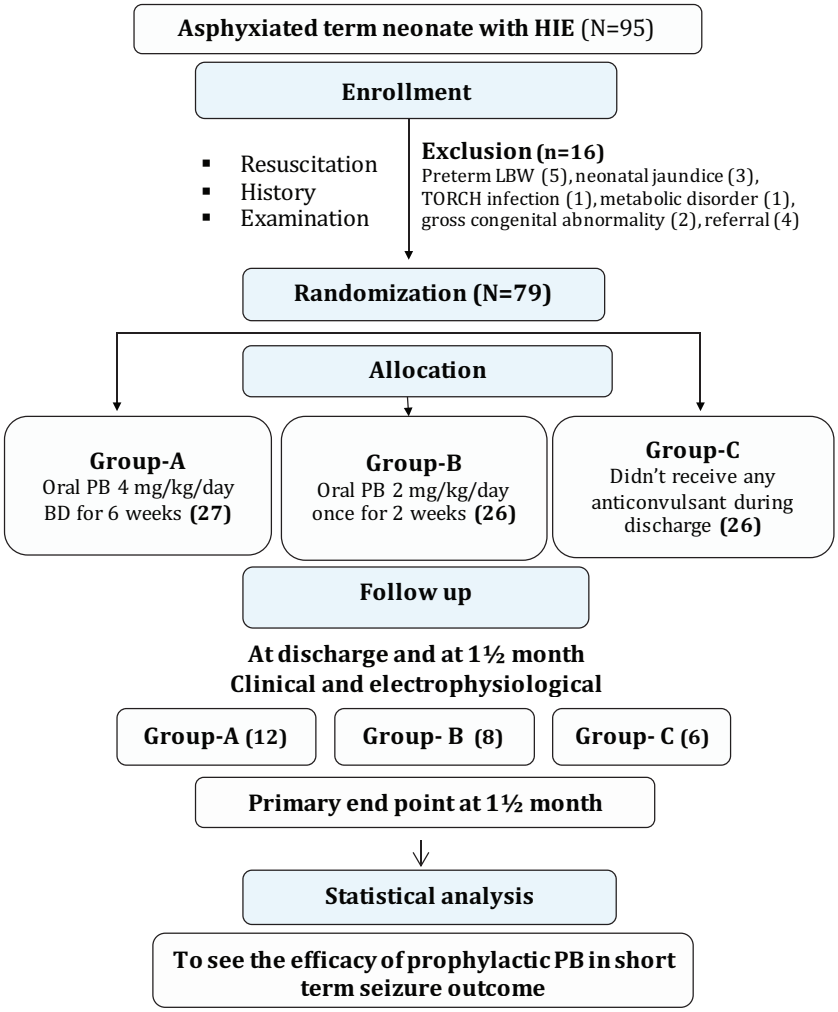
The most frequently encountered adverse characteristics of prolonged PB use are slowed motor and psychomotor speed, poorer attention and mild memory impairment. The developmental changes in neuronal chloride gradient leads to depolarization of immature neuron after GABA A receptor activation. Thus GABAegic medication (PB) in neonate may cause a paradoxical excitatory response.[7] Neonatal seizures are sometimes difficult to recognize clinically. Electrical seizures (as confirmed by EEG) have been shown to persist in 53% neonates treated with phenobarbitone/ phenytoin.[8] Therefore, for evaluating the efficacy of PB in controlling the seizure activity, clinical assessment alone should not be used. So the study was done to see the role of PB maintenance therapy in asphyxiated neonate with encephalopathy to control seizure both clinically and electrographically.

Materials and methods

This randomized clinical trial was done in Special care baby unit in Bashundhara Ad-din Medical College hospital from January 2019-January 2020. A total of 95 asphyxiated neonates with HIE-II/ III, gestational age ≥35 completed weeks who were admitted in this hospital were included in this study. Among them 16 cases were excluded due to LBW (5), neonatal jaundice (3), TORCH infection (1), metabolic disorder (1), gross congenital abnormality (2), Referral (4). After exclusion 79 cases were enrolled in this study and randomization was done by lottery method and categorized into three groups. Ethical approval was taken from institutional ethical committee. Before enrollment informed consent were taken from parents or caregiver. Group-A received PHB 4mg/kg/day twice daily for 6 weeks and Group-B received PHB 2mg/kg/day once daily for 2 weeks while Group-C didn't receive any anti-seizure medication after acute management. After admission, seizure was managed according to institutional protocol in every study cases. Immediate resuscitation was done. Thorough history and physical examination, investigation was done. Any complications during hospital stay were managed accordingly. Follow up was given regarding physical, neurological evaluation and electroencephalography at discharge and at 1½ month. Due to referral, complication, death and unaffordability of investigation 15 cases from group A, 18 cases from group B and 20 cases from Group C were dropped out for final analysis. Twelve cases from Group-A, 8 and 6 cases from group-B and group-C were analyzed at 1½ month, which was primary end point of the study. During this follow up period, occurrence of seizure was recorded and managed with anti- seizure drugs. Infantile spasm cases were treated with Inj ACTH, other seizures were managed with levetiracitum/ phenobarbitone based on seizure frequency and drug response.

Analysis was performed with SPSS software, versions 20.0. Continuous data that were normally distributed was summarized in mean, standard deviation, median, minimum and maximum. Skewed data was presented in the maximum, upper quartile, median, lower quartile, minimum and number of observations. Categorical or discrete data was summarized in frequency counts and percentages. For end points analysis, chi square test was used for categorical variables and an analysis of variance (one-way ANOVA Test) for continuous outcomes. CONSORT flow chart was used for summarization the number of patients screened, excluded prior to randomization by major reason and overall, the number of patients randomized and the number entering and completing each phase of the study. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

CONSORT flow chart



Result

Out of the total 95 asphyxiated babies with seizures admitted in our SCBU during the study period, 79 babies fulfilled study criteria. The baseline variables were comparable among the groups. Mean age was 0.96 ± 1.77 days in Group A, 0.66 ± 1.20 days in Group B and 0.55 ± 1.30 days in Group C and male was predominant among the study cases. Most of them were out born, delivered by NVD in hospital. Majority of them had obstructed and prolonged labor and needed immediate resuscitation. No significant difference was found between three groups considering gestational age, mean birth weight, OFC. All the study cases had seizure after birth asphyxia. Diminished reflexes were found more in Group-C (50%) followed by group A (40.74%) and group B (38.46%) without any statistically significant **(Table-I).** There was no significant difference found in duration of hospital stay and immediate outcome among the groups who received PB maintenance therapy for longer period (Group-A and Group-B) and who didn't (Group-C) receive PB maintenance therapy. Average hospital stay was longer in Group-A (8.39 ± 5.59 days) then Group-B and Group-C, but this was not statistically significant. Majority of the cases discharged after recovery. At 1½ month follow up no statistically significant difference in clinical seizure outcome was found among the groups. Both Group-A and Group-C had 33.34% seizure and Group-B had 12.5% seizure **(Table-II).** All study cases had no clinical seizure during discharge and most of them had normal electroencephalographic findings. Abnormal EEG findings were found more in Group-B (25%) and less in Group-A (8.33%). At 1½ month, more EEG abnormality was found among Group-C (33.34%) than Group-A (25%) and Group-B (25%). These findings were not statistically significant **(Table-III).**

Table I

Clinico-demographic profile among the study cases (N=79)

Variable	Group-A(27)	Group-B(26)	Group-C(26)	P value
Age (days) mean ± SD	0.96 ± 1.77	0.66 ± 1.2	0.55 ± 1.3	0.586
Gender (M:F)	1.8:1	1.6:1	1.4:1	0.899
Place of delivery (n)				
Home	12 (44.44%)	11 (42.30%)	6 (23.07%)	0.431
Hospital	15 (55.55%)	15 (57.69%)	20 (76.92%)	
Maternal age (Years)	25.46 ± 4.69	22.70 ± 5.4	23.46 ± 3.9	0.105
Obstructed/prolonged labor (n)	15 (55.55%)	11 (42.30%)	18 (69.23%)	0.105
Mode of delivery (n)				
NVD	22 (81.48%)	20 (76.92%)	21(80.76%)	0.876
LUCS	5 (18.51%)	6 (23.07%)	5 (19.23%)	
Meconium stained liquor	5 (18.51%)	3 (11.53%)	4 (15.38%)	0.807
Needed immediate resuscitation	22 (81.48%)	20 (76.92%)	23 (88.46%)	0.782
Gestational age(Weeks)	37.80 ± 0.49	37.58 ± 0.82	37.88 ± 1.3	0.528
Birth weight(Kg)	2.87 ± 0.45	2.76 ± 0.40	2.66 ± 0.47	0.232
OFC (cm)	34.11 ± 1.99	33.93 ± 1.7	33.4 ± 1.87	0.391
Convulsion	27 (100%)	26 (100%)	26 (100%)	0.108
Diminished reflexes	11 (40.74%)	10 (38.46%)	13 (50%)	0.801

Table-II

Short term outcome among the study cases (N=79)

	Group A (27)	Group B(26)	Group C(26)	
Hospital stay	8.39 ± 5.59	7.90 ± 4.39	7.83 ± 4.06	0.095
Immediate outcome				
Discharged	20 (74.07%)	20 (76.92%)	22 (84.61%)	
DOR	2 (7.40%)	1 (3.84%)	2 (7.69%)	0.477
Left against advice	1 (3.70%)	2 (7.69%)	2 (7.69%)	
Referral	4 (14.81%)	2 (7.69%)	0	
Died	0	1 (3.84%)	0	
At 1½ month	Group A	Group B	Group C	
	(12)	(8)	(6)	
Seizure outcome				
Seizure (7)	**4(33.33%)**	**1 (12.5%)**	**2 (33.34%)**	
Focal	3 (25%)	0	1 (16.67%)	0.422
Generalized	0	0	1 (16.67%)	
Infantile spasm	1 (8.33%)	1(12.5%)	0	
No seizure (19)	**8 (66.67%)**	**7 (87.5%)**	**4 (66.67%)**	

Table-III

Short term neurophysiological outcome among the study cases (N=26)

EEG findings	At discharge			P	At 1½ month			P
	Group A (12)	Group B (8)	Group C (6)	value	Group A(12)	Group B(8)	Group C(6)	value
Normal	11 (91.67%)	6 (75%)	5 (83.33%)	0.433	9 (75%)	6 (75%)	4 (46%)	0.733
Focal discharge	1 (8.33%)	0	1(16.67%)		2 (16.67%)	1(12.5%)	1(16.67%)	
Multifocal discharge	0	1 (12.5%)	0		1(8.33%)	1(12.5%)	0	
Generalized discharge	0	0	0		0	0	1(16.67%)	
Epileptic encephalopathy	0	1(12.5%)	0		0	0	0	

Discussion

In perinatal asphyxia, seizures are usually symptomatic of an underlying acute injury and independently of HIE severity associated with worse outcome. Treatment with anti-seizure drugs should be initiated as soon as possible.[7] Numerous surveys on current practice have shown that phenobarbitone is used as the first line drug world-wide.[9] This study found all study cases had seizure after asphyxiated birth and most of them recovered and became seizure free during discharge. At 1½months follow up 33.34% developed seizure (1 focal and 1 generalized) who didn't receive maintenance PB, 33.33% from group A, who received PB for long period also developed seizure. No statistical difference was found among these groups. Saxena P. et al.[10] in their study found that 31.2% case of PB group had breakthrough seizure and similar finding was present in placebo group. These results have similarity with present study. Saxena P. et al. also showed both groups in their study had same findings in abnormal EEG and seizure recurrence at 3 months.[10] There average duration of hospital stay was 7.23 and 7.40 days which were also similar to present study.

Hellstrom et al.[11] 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.[11] has reported that little relation exists between the rate of PHB withdrawal and seizure control. Guillet, et al.[13] retrospectively studied the impact of outpatient PHB 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.

Seizure burden is high within 1st 24-48 hours in acute symptomatic cases followed by a longer period of lower seizure burden. Because the recurrence risk in the neonatal period is low, many neonates can be safely discontinued from anti-seizure drugs after resolution of acute symptomatic seizure. There is no need to wean medications that have been used for <1 week.[7] Phenobarbitone has been shown to be incompletely effective in treatment of neonatal seizures resulting from varied etiologies, controlling seizures in only 43% of babies monitored electrographically by Painter MJ et al.[14] Gilman JT et al. in their study have demonstrated control of clinical seizures in up to 70% of subjects.[15]

Yozawitz E et al. showed PB in acute management did not adversely affect heart rate, respiratory rate, blood pressure, or blood gas values.[9] However, long term PB may lead to neuronal apoptosis which subsequently may lead to adverse neuro-developmental outcome.[9]

Conclusion:

Early discontinuation of phenobarbitone (PHB) after acute management may not increase the risk of clinical and electrographic seizure in future.

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