Original Article

Short Term Neurodevelopmental Outcome of Asphyxiated Term Neonates with Maintenance Phenobarbitone Therapy; Preliminary Findings of Ongoing Study in A Tertiary Care Hospital of Bangladesh

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Abstract

Phenobarbitone (PB) is the most commonly prescribed anticonvulsant worldwide to control neonatal seizure in asphyxiated neonates. In spite of limited clinical evidence regarding the best use of drug, their dose and duration: it appears that long term maintenance use of phenobarbitone might slow psychomotor development. Aim of this study was to assess the neuro developmental morbidity in asphyxiated neonates with long term anticonvulsant.

This randomized clinical trial enrolled 79 asphyxiated neonates with HIE-II/ III, gestational age ≥ 35 completed weeks from January 2020-January 2021 where cases were categorized into three groups by lottery method. Group A and B received PHB 4mg/kg/day twice daily for 6 weeks and PHB 2mg/kg/day once daily for 2 weeks respectively while Group C didn't receive any anti-seizure medication. Neurodevelopmental assessment was done at 6 months of age in every case. Data were analyzed by Chi-square & logistic regression test to find out the outcome.

Among 79 cases mean gestational age was 37.74±0.98 weeks, M: F was 3:2 and most of them were inborn (51.4%). At 6 months 49 cases were analyzed, 19 were in group A and 15 cases from group B and 15 cases from group C. Cognitive impairment was found 5.844 times more in group A (52.63%) followed by group B (6.67%) and group C (13.33%) (p= 0.001). Group A had 5.844 times more cognitive impairment than other two groups (P= 0.039). No significant functional impairment in motor, speech, hearing and vision were found among the study groups. This study concluded that prolonged use of maintenance Phenobarbitone may impair cognitive function.

Key words: Asphyxiated neonate, Neurodevelopmental outcome, Phenobarbitone

Introduction

Perinatal asphyxia (PNA) remains the major causes of neonatal mortality and morbidity in developing countries. According to WHO 23% of neonatal deaths are due to birth asphyxia and of which approximately 840,000 live numbers develop serious squeal.[1,2]

Phenobarbitone (PB) is the most commonly prescribed first-line anti-seizure drug (ASD) for treatment of neonatal seizures. PB acts on 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] Based on very-low-quality evidence, WHO has recommended phenobarbitone as a first-line ASD in the management guidelines for neonatal seizure.[5] 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

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after GABA A receptor activation. Thus GABAergic medication (PB) in neonate may cause a paradoxical excitatory response.[7] So the study was done to see the neuro developmental morbidity in asphyxiated neonates with long term use of PB.

Materials and methods

This randomized clinical trial was done in Special care baby unit in Bashundhara Ad-din Medical College hospital from January, 2020 -January, 2021. 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 low birth weight (LBW) (5), neonatal jaundice (2), TORCH infection (1), metabolic disorder (1), gross congenital abnormality (2), Referral (3). After exclusion 79 cases were enrolled in this study and randomization was done by lottery method and categorized into three groups. Group A and B received PB 4mg/kg/day twice daily for 6 weeks and PB 2mg/kg/day once daily for 2 weeks respectively while Group C didn't receive any anti-seizure medication after acute management.

Before enrollment, informed consent was taken from parents. 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, neurodevelopmental assessment at 6 month. Neurodevelopmental assessment was done according to developmental milestone. Inability to perform age appropriate function beyond the expected age was considered impaired development. Due to loss of follow up (24) and death (6), at 6 months 49 cases were analyzed and 19 were in group A and 15 cases from group B and 15 cases from group C.

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. The association of outcomes with treatment was estimated by computing the relative risk (RR) and 95% confidence intervals (CI) and by logistic regression. All p-values are two-sided and values lower than 0·05 were considered statistically significant CONSORT flow chart was used for summarization the number of patients screened, excluded prior to randomization by major reason and overall, thenumber 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.

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 17.36 ± 34.08 hours (0.72.33 ± 1.42 days) and males were predominant among the study cases. Most of them had normal vaginal delivery (NVD) (81.48% in Group A, 80.76% in Group C and 76.92% in Group B) in hospital and had obstructed and prolonged labor and needed immediate resuscitation. Gestational age ranged from 37.58 ± 0.82 to 37.88 ± 1.3 weeks among the groups, mean birth weight was 2.76 ± 0.44 kg, and mean OFC was 33.81 ± 1.85 cm. All study cases had seizure after birth asphyxia (PNA with HIE II). Diminished reflexes was found more in group C (50%) followed by group A (40.74%) and group B (38.46%), there was statistical significance [Table I].

At 6 months 49 cases were analyzed, 19 were in group A and 15 cases from group B and 15 cases from group C. Mean weight (7.10 ± 0.95 kg) and OFC (41.27 ± 2.41 cm) among group B were more than Group A (weight: 6.10 ± 1.07 kg, OFC: 40.22 ± 2.84 cm) and Group C (Weight: 6.48 ± 0.60 kg, OFC: 40.13 ± 1.50 cm) at 6 month but no statistical difference were found among the groups (Figure 1). Cognitive impairment was found more in group A (52.63%) followed by group B (6.67%) and group C (13.33%) (p= 0.001). No significant functional impairment in motor, speech, hearing and vision were found among the study groups [Table II]. When cognitive function was adjusted with other covariant (Age, sex, Place of delivery, Meconium-stained liquor, Gestation age, Birth weight, Number of anticonvulsants used for seizure control) there was 5.844 time more cognitive impairment in group A then group B and C (P = 0.039) [Table III].

CONSORT flow chart

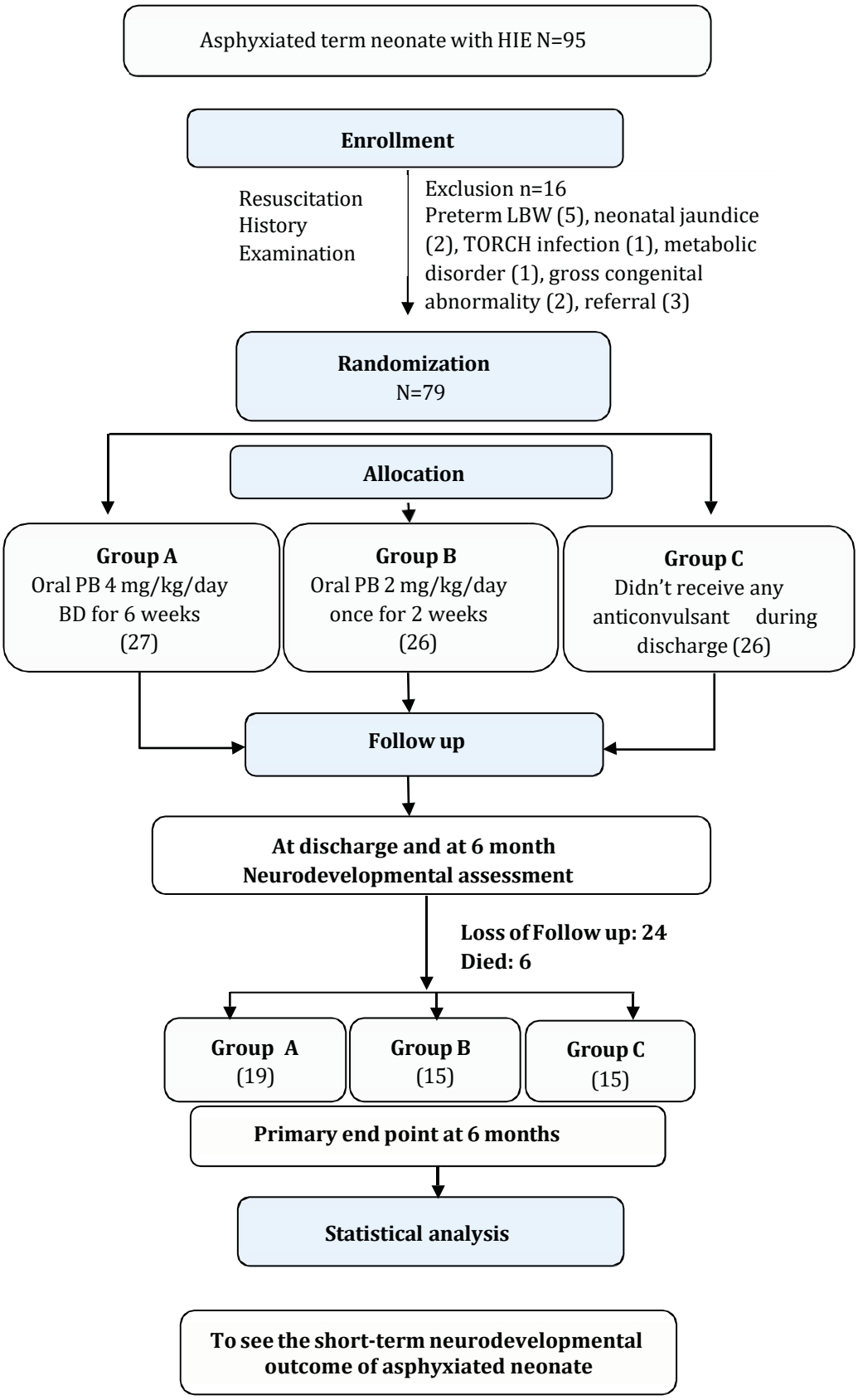

Table-I

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
Sex (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

One way ANOVA test

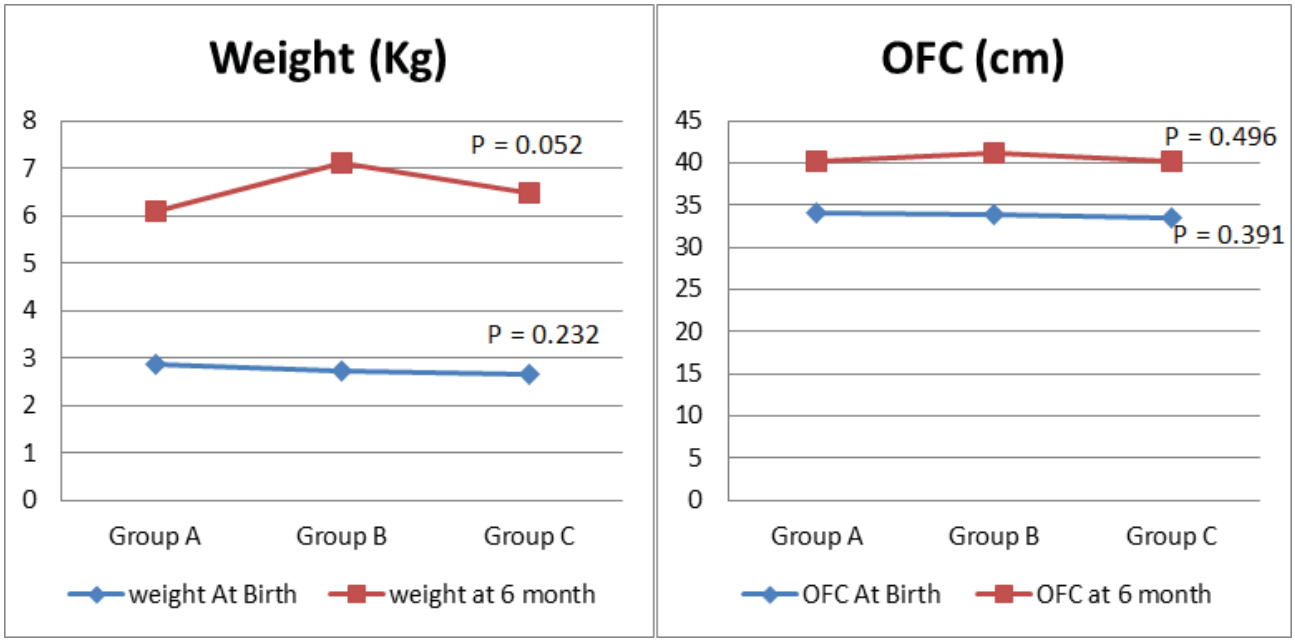

Figure 1: *Physical outcome among the study cases*

Table-II

Neurodevelopmental outcome among the study cases at 6-month n=49

Variable	Group A (19)	Group B (15)	Group C (15)	P value*
Cognitive impairment	10 (52.63%)	1 (6.67%)	2 (13.33%)	0.001
Motor delay	3 (15.78%)	3 (20%)	2 (13.33%)	0.648
Impaired speech	2 (10.52%)	2 (13.33%)	2 (13.33%)	0.955
Visual impairment	2 (10.52%)	1 (6.67%)	2 (13.33%)	0.909
Hearing impairment	2 (10.52%)	1 (6.67%)	1 (6.67%)	0.826

*Chi Square test

Table-III

Prediction of neurodevelopmental outcome in asphyxiated neonates n=49

Variable	Unadjusted OR 95% CI	P Value*	Adjusted OR 95% CI	P value**
Cognitive impairment	3.437(1.25-9.43)	0.001	5.844 (1.09-31.3)	0.039
Motor delay	0.969 (0.187-4.75)	0.64	0.464 (0.55-3.857)	0.301
Impaired speech	0.821 (0.133-5)	0.60	0.323 (0.134-4.6)	0.186
Visual impairment	1.143 (0.17-7.6)	0.62	0.389 (1.144- 3.47)	0.202
Hearing impairment	1.71 (0.217-13.5)	0.495	0.606 90.68-3.840)	0.431
Seizure	2.40 (0.473-12.1)	0.252	0.81(1.15-6.04)	0.231

*Chi square test **Logistic regression

Covariates were analyzed: Age, sex, Place of delivery, Meconium-stained liquor, Gestation age, Birth weight, Number of anticonvulsants used for seizure control

Discussion

To reduce excessive neuronal excitability associated with seizure formation, phenobarbitone reduces membrane excitability, increases postsynaptic inhibition, or changes neural network synchronization. Diminished neural excitability causes slowed motor and psychomotor speed, as well as reduced attention and slight memory impairment.[8,9] Phenobarbitone is effective anticonvulsants, but long-term use can result in clinically significant adverse effects. It can cause hyperactivity, behavioral difficulties, drowsiness, and possibly dementia as a side effect. The reported seizure cessation rates by PB vary between 33% - 40% after giving a single loading dose of 15-20 mg/kg.[10] Gilman, et al. showed rapid sequential loading with PB (up to 40 mg/kg) could improve the clinical response rate in neonates with seizures till a cumulative response rate of 77%.[11] The present study also showed that initial seizure control rate with PB was same as previous study. Maitre et al. in their study showed that increased exposure to PB was associated with significant decreasing cognitive and motor scores. They also concluded that increased exposure to PB is associated with worse neuro-developmental outcomes.[12] This finding was consistent with present study. We found more cognitive impairment among the group who received PB twice for 6 weeks than who didn't receive PB for longer period. On a variety of developmental parameters and over a wide range of follow-up durations, studies in pediatric

populations demonstrated significant deficits owing to PB exposure after birth.[13]

We assessed all developmental domains. Few studies on pediatric neurology, particularly the effect of long term PB on cognitive function have been conducted globally- as it clearly evidences. On a 20 years literature search we failed to yield any evidence in this spectrum neither in Bangladesh and globally. Hence, it remains crucial to look deep-inside into it to determine its hidden/ unexplored issues- which globally has not been conducted so far.

PB causes neurotoxicity and poor neurodevelopmental outcomes, as has been well documented in animal models. In the developing rat brain, PB therapy at levels comparable to those used to treat seizures in humans has been proven to trigger neuronal death. [14,15] PB has also been shown to interfere with maturation of synaptic connections. [16]

Conclusion:

Significant cognitive functional impairment was found among the asphyxiated neonates who received long term maintenance Phenobarbitone. However large scale, long term follow up study may justify the statement more accurately.

Limitation of this study: It is a single center study, small sample size. We didn't use any psychometric tool for precise assessment of cognitive function.

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