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Predictors of Duration of Phenobarbitone Therapy in Seizures of Neonates with Hypoxic-Ischemic Encephalopathy

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ABSTRACT

Objective: *Perinatal asphyxia with hypoxic-ischemic encephalopathy associated with seizures is one of the leading cause of neonatal mortality and morbidity in Bangladesh. Phenobarbitone remains the drug of choice in treatment of neonatal seizures. This study was conducted to determine the predictors of duration of Phenobarbitone therapy in seizures of neonates with Hypoxic-Ischemic Encephalopathy (HIE).*

Methodology: *The study was conducted in Neonatal Intensive Care Unit (NICU) of East West Medical College Hospital from 1st february 2016 to 31st january 2017 on fifty neonates with HIE and seizures. The dose and duration of phenobarbitone therapy for initial control of seizure was noted. Total duration of phenobarbitone therapy after control of seizure to prevent further recurrences was also noted. Follow up was given up to 3 months of age to see any recurrence of seizures.*

Results: *Out of the 50 neonates,25 cases (50%) responded well within 24 hours. Mean duration of phenobarbitone therapy after initial control of seizure was 4.70 ± 2.93days and Mean total duration of therapy was 6.89 ± 3.58 days in cases who responded well within 24 hours.. 3 (6%) cases had recurrence of seizures. The recurrence cases required more than 72 hours for initial control of seizure (p 0.006) and had poor primitive reflexes and activity after initial control of seizure (p 0.0002). Mean duration of phenobarbitone therapy after initial control of seizures was 6.33 ± 6.11 days and Mean total duration of phenobarbitone therapy was also longer 9.67 ± 7.37 days.*

Conclusion: *Neonates who have good initial response and have better reflexes required short duration of phenobarbitone therapy. It should be discontinued soon after control of seizure. Neonates with HIE III, those requiring more than 72 hours for initial response and poor reflexes after initial control of seizure may require longer duration of phenobarbitone therapy (more than 7 days) to prevent recurrence of seizures. Thus, judicious use of phenobarbitone will minimize the unnecessary non-specific treatment.*

Keywords

Perinatal asphyxia, Hypoxic- Ischemic Encephalopathy, Seizure, Phenobarbitone.

Introduction

Neonatal seizures continue to present a diagnostic and therapeutic challenge to paediatricians worldwide. Neonatal seizures are often manifestation of significant neurologic disease and a major predictor of adverse neurological outcome in the newborn [1-3]. Majority of neonatal seizures occur in the first week of life [1,4]. Clinical seizures occur in 0.5 to 3 /1000 term live births [3-6]. The incidence is higher in preterm birth 10 to 15 /1000 births [1,3-

6]. Most neonatal seizure has a specific cause. The most common cause is Hypoxic-Ischemic encephalopathy (32%), followed by intracranial haemorrhage (17%), central nervous system infection (14%), infarction (7%), metabolic abnormalities (6%), inborn errors of metabolism (3%), and unknown (10%) [1,2,4]. Despite major advances in neonatal care during recent years, perinatal hypoxic-ischaemic cerebral injury remains a major cause of long term neurological sequelae in childhood[7]. HIE is characterized by clinical and laboratory evidence of acute or subacute brain injury due to asphyxia (i.e. hypoxia, acidosis). 15-20% of infants with HIE die in the neonatal period, and 25-30% of survivors are left with permanent damage to CNS tissues that manifest later as cerebral palsy or mental retardation [8]. The incidence of HIE is reported to be 1.8-6/ 1000 full-term infants [9].

Immediate management of seizures includes stabilization, identification of the cause and specific treatment [3,5]. Administration of anti-convulsant drugs is needed to control and prevent seizure recurrence. Phenobarbitone remains the drug of choice in the treatment of neonatal seizures. It enhances gamma-amino butyric acid (GABA) inhibition and may limit glutamate excitation. It is administered intravenously, with a loading dose of 20mg/kg, followed by maintenance dose of 5mg/kg/day [10,11].

Regarding Phenobarbitone therapy, several major issues remain unresolved, including optimal dose, the importance of eliminating electrographic seizures and the optimal duration. Routine anticonvulsant therapy following perinatal asphyxia should be restricted to those babies who are having prolonged or frequent clinical seizures [12-13]. General recommendation is to withdrawal of anticonvulsants once seizures are controlled and neurological examination is normal [5]. But controversies remain as to optimum duration of phenobarbitone therapy after initial control of seizure to prevent recurrences and thus avoid further damage to the brain. There is no indication that prolonged treatment of anticonvulsant therapy reduces the risk for the later development of epilepsy [14,15]. The only recommendation for continuing anticonvulsant therapy (phenobarbitone, 5 mg/ kg/ day) is in the setting of profound neonatal encephalopathy or severe brain injury and then only for 6-8 weeks [13]. Unnecessarily prolonged treatment should be avoided because of concern about possible adverse effects of anticonvulsants on the developing brain [16]. All the available data regarding Phenobarbitone therapy in neonatal seizure are from developed countries. A very few publications are available from this subcontinent. This prospective study is designed to determine the predictors of duration of Phenobarbitone therapy in controlling neonatal seizures without further recurrences.

Materials and Methods

The study was conducted in NICU of East West Medical College Hospital. This was a prospective observational study from 1st February 2016 to 31st January 2017.

Term newborn baby aged 0 to 28 days with history of perinatal asphyxia and with active convulsion or history of convulsion were included in this study. Neonates with gross congenital anomalies and Convulsion due to metabolic or other causes were excluded from the study. For each baby, a detailed history was recorded in a questionnaire, from the mother or the attendants. Information like age, sex, maternal history, perinatal history was recorded. Weight of the baby was recorded. Gestational age was determined from maternal records and also by the ultrasonography report of the pregnancy profile. History of apnoea, cyanosis, convulsion, respiratory distress was also recorded. Thorough physical and neurological examination including primitive reflexes, level of consciousness, muscle tone, posture prognosis etc. were recorded. Relevant investigations including complete blood count, serum calcium, serum electrolyte, random blood sugar, ultrasonography of brain were done in each baby . Electroencephalogram was not done because it is a costly procedure and it was not routinely practiced in the unit. Dose and duration of Phenobarbitone were noted. Discharged babies were followed up once in a month up to 3 months of age. During each follow up any recurrence of seizure was recorded and thorough physical and neurological examinations were done. A total of 65 cases were enrolled. Among the 65 cases, 3 died during the hospital stay and 12 were lost during the follow up. Finally, total 50 cases were included in the study. The collected data of the neonates having seizures were analyzed thoroughly. In addition to descriptive statistics such as frequency tabulation, mean and standard deviation, statistical analysis was limited to comparisons of proportions with the Fisher's exact test for categorical data and independent sample t test for continuous data. SPSS for Windows version-12 was used for data entry and analysis.

Results

In this study, 72% were male and 28% were female, male-female ratio 2.6:1. Mean birth weight was 2475.50 ± 587.35 grams. Out of 50 cases, 94% were of 0-5 days and only 6% of 6-10 days age group. 96% were graded as HIE II and only 4% as HIE III. Among the 50 neonates with HIE, in 32 (64%) patients seizure began within first 24 hours of birth. 22 neonates (44%) were presented with poor activities and poor primitive reflexes and 28(56%) with that of moderate type. 32 neonates (64%) were hypertonic and 18(36%) were hypotonic at presentation. 96% patients received loading dose of inj. Phenobarbitone 20mg/ kg. 0nly 4% received a second dose of 10mg/ kg to control seizure, 90% patients received maintenance dose of inj. Phenobarbitone 5mg/kg/day and 10% received 10mg/ kg/ day.

Out of 50 patients, 50% responded well and their convulsion was stopped within first 24 hours. 24% patients responded within 24-48 hours, 20% within 49-72 hours and 4% within 73-96 hours. Only 1 patient took more than 10 days to stop convulsion (Figure 1). The duration of Phenobarbitone therapy after initial control of seizure was for 2-3 days in 56% patients, 4-5 days in 24%, 6-7 days in 12% and more than 7 days in 8% patients (Figure 2). The total duration of phenobarbitone therapy was 3 to 20 days (mean 7 days). Among them 52% patients received treatment only for

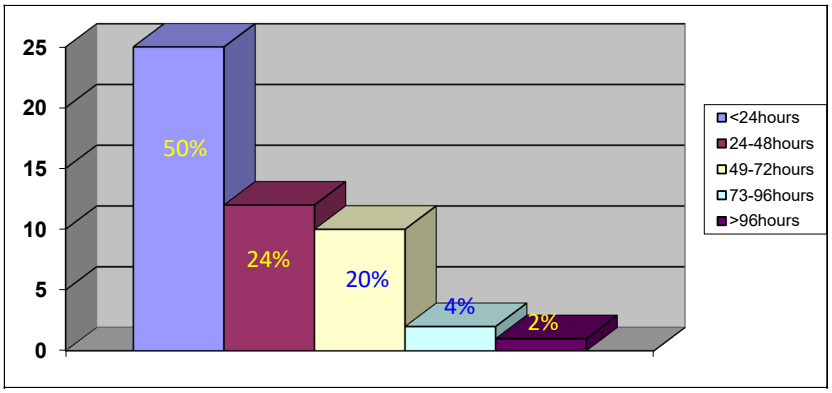

Figure 1: Initial response to control seizure after initiation of treatment (n=50).

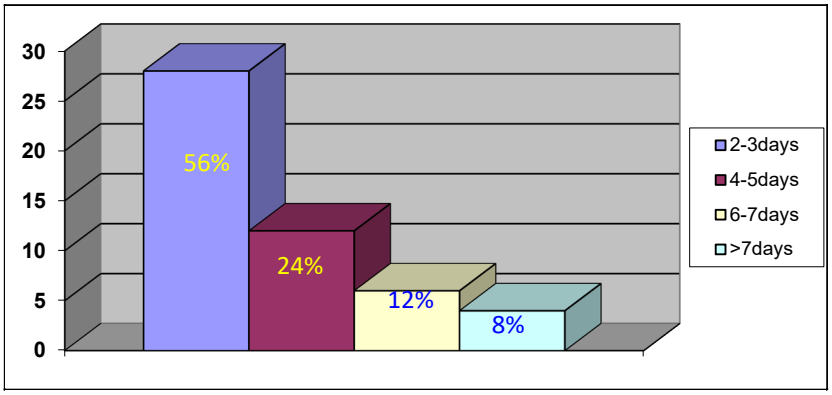

Figure 2: Duration of Phenobarbitone therapy after initial control of seizure (n=50).

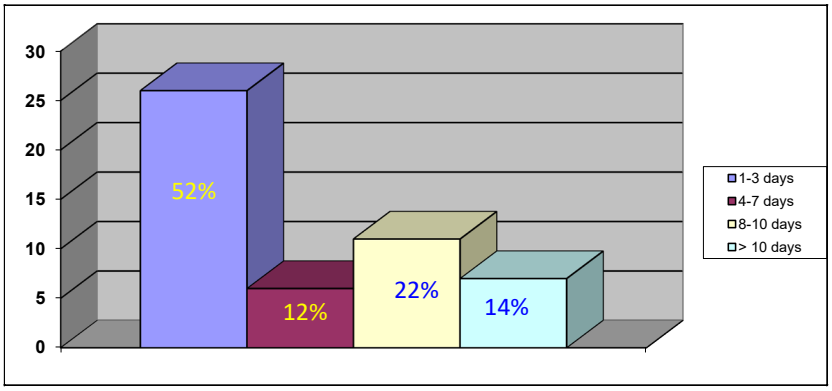

Figure 3: Total duration of Phenobarbitone therapy (n=50).

1-3 days, 12% for 4-7days, 22% for 8-10 days and 14% for more than 10 days (Figure3). Out of 50 neonates, 46(92%) had moderate and 4(8%) had poor activity and primitive reflexes at the time of withdrawal of phenobarbitone therapy.

3(6%) patients developed recurrence of seizures. Among the three recurrence cases, 2 patients took more than 72 hours to stop convulsion after initiation of phenobarbitone therapy. One patient took 48 hours but had recurrence. The duration of initial response to control seizure is significant in relation to recurrence of seizure (p 0.006) (Table 1). Out of 4 neonates who had poor reflexes at time of discontinuation of phenobarbitone therapy, 3 patients had recurrence. Poor primitive reflexes showed high significance in relation to recurrence of seizure (p 0.0002). The duration of phenobarbitone therapy after initial response to control seizure shows no significance with recurrence of seizure (p 0.38), but it is observed that the recurrence cases needed a longer mean duration (6.33 ± 6.11) of treatment after control of seizure in comparison to nonrecurrence case (Table 2).The mean total duration (9.67 ± 7.37) of phenobarbitone therapy in recurrence cases was longer than the non-recurrence cases (6.89 ± 3.58), but it was not statistically significant (p 0.22) (Table 3).

Table 1: Relationship between recurrence of seizures with the duration of initial response to control seizure.

	Duration of initial response to control seizure		Total n (%)	p value
	Less than 72 hours n (%)	More than 72 hours n (%)		
Recurrence	1(2.13)	2 (66.66)	3 (6)	0.006
No recurrence	46 (97.87)	1(33.33)	47 (94)	
Total	**47(100)**	**3 (100)**	**50 (100)**	

Table 2: Relationship between recurrence of seizures with duration of Phenobarbitone therapy after initial control of seizure.

	Duration of phenobarbitone therapy after initial control of seizure	
	Mean ± SD	**p value**
Recurrence	6.33 ± 6.11	0.38
No recurrence	4.70 ± 2.93	

Table 3: Relationship between recurrence of seizures with total duration of Phenobarbitone therapy.

	Total duration of phenobarbitone therapy	
	Mean ± SD	**p value**
Recurrence	9.67 ± 7.37	0.22
No recurrence	6.89 ± 3.58	

Discussion

Phenobarbitone remains the anti-convulsant of choice in the treatment of neonatal seizures. The long-term administration of phenobarbitone in neonates may be associated with adverse neurological outcome. The timing of stopping phenobarbitone maintenance after acute seizure control in neonates is a matter of debate [17]. This prospective study is aimed to find out the predictors of duration of Phenobarbitone therapy in seizures of neonates with HIE which will appropriately control and prevent recurrence of seizures.

In this study, among the 50 neonates with HIE, in 32 (64%) patients seizure began within first 24 hours of birth. Mean birth weight was 2475 ± 587.35 grams. They presented with active convulsion (during admission / at the time of inclusion) or history of convulsion. 44% of the neonates had poor primitive reflexes and 56% with that of moderate type at initial presentation. These findings are consistent with the study done by Mannan et al[18] and Sarkar's study [19].

As the first line anticonvulsant therapy, loading dose of Phenobarbitone, 20mg/ kg i.v. was given in 48 (96%) patients and 2 (4%) patients required 10 mg/ kg as a second dose to stop convulsion. Maintenance dose of Phenobarbitone, 5mg/ kg/ day i.v. was given in 90% patients and 10% patients required 10 mg/ kg/ day. Ramesh A[10] reported that the effective concentration of phenobarbitone was achieved by a loading dose of 20 mg/ kg and maintenance dose of 5 mg/ kg/ day. In another study by M Sima et al [20]showed that phenobarbitone wt normalized loading dose of 15 mg/kg led to simulated target peak concentration and wt normalized maintenance dose of 3mg/kg lead to steady state within therapeutic window.

Most of the neonates i.e. 25 (50%) cases responded well and their convulsion were stopped within 24 hours. The patients who took more than 72 hours for the initial response to control seizure need longer duration of phenobarbitone therapy and had more chance to develop recurrence (p 0.006).

For taking the decision to discontinue phenobarbitone therapy, neurologic examination was taken as an important variable. Maximum patients (92%) had moderate activity and primitive reflexes at the time of withdrawal of Phenobarbital therapy. Most of them regained back normal muscle tone (86%) and posture (94%). Among the 4 patients with poor reflexes at the time of withdrawal of phenobarbitone therapy, 3 (75%) cases had recurrence and it is statistically highly significant (p 0.0002).

In a study, done by Gal P [21], anticonvulsant was discontinued shortly after seizure control and follow up of those patients shown no recurrence of seizure. Another study by Ankush Jindal et al [17] showed that early withdrawal of phenobarbitone does not lead to significant increase in rate of seizure recurrence. Shellhaas et al. [22] reported that early discontinuation of phenobarbitone is not harmful in cases who responds early with the treatment. Hellstrom et al. [14] done a study with 31 patients, where duration of anticonvulsant was for median 4.5 days and recurrence of seizure occur in three (8.3%) patients. In our study, only three (6%) patients developed recurrence of seizure.

In our study, the mean total duration of phenobarbitone therapy in recurrence cases was longer (9.67 ± 7.37) than the non-recurrence cases (6.89 ±3.58), but it was not statistically significant (p 0.22). Ankush Jindal et al. [17] reported in one study, incidence of seizure recurrence was similar in early phenobarbitone withdrawal and phenobarbitone continued groups.

Patient with initial good responses continue their treatment for mean duration of (4.70 ± 2.93) days. Although the duration of phenobarbitone therapy after initial control of seizure shows no significance with recurrence of seizures (p 0.38), it is observed, that the recurrence cases received a longer mean duration (6.33 ± 6.11) of treatment after control of seizure, but it could not help to prevent recurrences.

Conclusion

Most seizures of neonates with HIE responded well with a short duration of phenobarbitone therapy. Patients who have good initial response with better reflexes, phenobarbitone therapy should be discontinued soon after control of seizure. Neonates with HIE III, those requiring more than 72 hours for initial response and poor reflexes after initial control may require longer duration of phenobarbitone therapy (more than 7 days) to prevent recurrence of seizures. Thus, judicious use of phenobarbitone will minimize the unnecessary non-specific treatment.

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