Comparative Trial of Phenobarbitone vs Phenytoin in Moderate and Severe Perinatal Asphyxia in Term Neonates

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Abstract
A prospective, hospital-based open-label randomised trial was conducted with primary aim to compare the clinical seizure control after administration of either drug, Phenobarbitone or Phenytoin in term neonates with moderate or severe perinatal asphyxia. Secondary aim was to compare the neurodevelopmental outcomes at 3 months of age. Study participants included 120 term neonates (n=120) with perinatal asphyxia with clinically apparent seizures. Seizures were controlled in 8 out of 60 (13.33%) neonates who received phenytoin as compared to 43 out of 60 neonates (71.67 %) neonates who received phenobarbitone (p < 0.001). Phenobarbitone is more efficacious than Phenytoin in achieving clinical seizure control when used as first line anticonvulsant in term neonates with moderate or severe perinatal asphyxia. The early neurodevelopmental outcome at 3 months of age was similar when either of the drugs was used.

Keywords: Neonatal seizures, phenobarbitone, phenytoin, perinatal asphyxia.

Introduction
Seizures constitute the most common neurological emergency in babies¹¹, occurring most commonly during the neonatal period than at any other time of life². The most common etiology of neonatal seizures is hypoxic-ischemic encephalopathy (HIE) due to perinatal asphyxia. Evidence suggests that neonatal seizures have an adverse effect on the neurodevelopmental progression and may also predispose to cognitive, behavioural or epileptic complications later in life³⁴. Phenobarbitone is the most commonly used first line drug for neonatal seizures worldwide because of its good safety profile, despite growing evidence that it is ineffective in many babies and may itself impair neurodevelopmental outcome⁵⁷. Phenytoin is the second most commonly used agent for treatment of neonatal seizures⁸. However, there is limited data from randomised controlled trials supporting the choice of any anticonvulsant and there remains a need for evidence-based guidelines for management of neonatal seizures⁹¹¹. This study was conducted to assess the control of seizures after administration of phenobarbitone and phenytoin in term neonates with perinatal asphyxia.
Materials and Methods
This prospective, hospital-based open-label randomised trial was conducted in the Neonatal Intensive Care Unit of a tertiary care teaching hospital in India over a period of one year. The study was conducted on 120 term neonates admitted with perinatal asphyxia and clinically apparent seizures, i.e. babies with moderate or severe perinatal asphyxia. The criteria for diagnosis of perinatal asphyxia as suggested by National Neonatology Forum of India was – baby having gasping and inadequate breathing or no breathing at 1 minute\(^1\). Perinatal asphyxia was assessed according to Levene Grading System. The clinical criteria for diagnosis of neonatal seizures was:

i. Clonic movement which could be unifocal, multifocal or generalized.

ii. Tonic posturing with or without abnormal gaze.

iii. Subtle seizures and spontaneous paroxysmal, repetitive motor or autonomic phenomenon like lip smacking, chewing, paddling, cyclic movements.

Inclusion Criteria: All inborn term neonates, admitted with moderate or severe perinatal asphyxia with clinically apparent seizure.

Exclusion Criteria:
1. Seizures due to hypoglycemia, hypocalcemia or any other metabolic disorder, meningitis, intracranial haemorrhage or other causes.
2. Neonates with major congenital malformation.
3. Neonates who had already received anticonvulsants.

Informed written consent was obtained from the parent/guardian of the child. 120 patients satisfying the above mentioned criteria were randomized into two groups. The randomization was performed by a person not directly related to the study with the help of table of random numbers, by using serially numbered opaque envelopes. In order to keep the number of patients equal in both the groups, permuted block randomization was performed. The eligible participant was assigned the treatment regarding the anticonvulsant to be given as mentioned in the envelope. The patients were thus assigned to two groups A and B of 60 neonates each. Each group had 45 neonates with moderate asphyxia and 15 neonates with severe asphyxia.

Protocol for Giving Anticonvulsants: Name, age, sex, weight, head circumference and length were recorded on a pre-structured proforma. Airway patency, breathing and circulation were ensured based on standard guidelines. A cannula was secured and blood sampling for blood sugar, serum calcium and other tests as indicated in that individual patient was done. Hypoglycemia was defined as blood sugar <40 mg/dL and hypocalcemia was defined as total serum calcium <7 mg/dL\(^1\). If seizures persisted even after correction of hypoglycemia and hypocalcemia, babies were randomized to either Phenytoin (Group A) or Phenobarbitone (Group B).

**Group A:** Baby was loaded with injection Phenytoin @ 20 mg/kg slow i.v. infusion over 30 minutes at rate <1 mg/kg/minute under cardiorespiratory monitoring. If seizure persisted/recurred, the baby was given injection Phenytoin @ 10 mg/kg slow i.v. infusion over 30 minutes under cardiorespiratory monitoring. If seizures persisted/recurred, baby was randomized to either i.v. Phenytoin or Phenobarbitone in the doses as mentioned below.

**Group B:** Baby was loaded with injection Phenobarbitone @ 20 mg/kg slow i.v. infusion over 30 minutes under cardiorespiratory monitoring. If seizure persisted/recurred, baby was reloaded with i.v. Phenobarbitone @ 10 mg/kg each to a maximum of 40 mg/kg. If seizure persisted/recurred, baby was crossed over to receive i.v. Phenytoin in abovementioned dose.

If seizure persisted/recurred after two drugs, then a third line drug like Midazolam i.v. @ 0.1 mg/kg/dose was used.

Administration of the drug was planned to be discontinued if respiratory depression (cessation of respiration for more than 20 seconds or less than 20 seconds associated with cyanosis or bradycardia) or bradycardia (heart rate <80/minute) developed after use of either of the drugs although no such case was
observed during the study. The babies were monitored throughout their hospital stay and their final outcome was recorded as clinical control of seizures (seizure was said to be controlled if there was seizure free period of 24 hours after giving anticonvulsant).

Once the baby was seizure free for 5 days, anticonvulsants were stopped in the same order as they were started except Phenobarbitone. When the baby started tolerating 50% of enteral feeds intravenous Phenobarbitone was changed to oral. Phenobarbitone was stopped last at discharge if neurological examination of the baby was normal. Phenobarbitone was continued even after discharge if neurological examination was not normal and baby was again evaluated at age of 1 month and 3 months. Secondary aim of the study was to compare the neurodevelopmental outcomes at 3 months of age in both groups. Neurological assessment was done using Amiel-Tison Protocol$^{[13]}$ and developmental screening was done using Trivandrum Developmental Screening Chart at 3 months of age.

**Table 1: Baseline Characteristics of Study Population**

| Parameters                        | Group A (n=60) | Group B (n=60) |
|-----------------------------------|---------------|---------------|
| Age at admission (minutes)        | 26.13         | 27.30         |
| Males                             | 29            | 27            |
| Females                           | 31            | 33            |
| Weight (kg)                       | 2.97          | 3.03          |
| Head Circumference (cm)           | 34.40         | 34.50         |
| Mode of Delivery                  |               |               |
| Vaginal                           | 44            | 37            |
| Caesarean Section                 | 16            | 23            |
| Maternal Age (years)              | 29.26         | 28.81         |
| Moderate Perinatal Asphyxia       | 45            | 45            |
| Severe Perinatal Asphyxia         | 15            | 15            |
| Type of Seizures                  |               |               |
| Tonic Posturing with Abnormal gaze| 19            | 18            |
| Tonic Posturing without abnormal gaze | 15        | 13            |
| Paddling movements of limbs       | 11            | 14            |
| Clonic movements                  | 8             | 10            |
| Lip smacking                      | 5             | 4             |
| Chewing movements                 | 2             | 1             |

**Statistical Analysis**

Computer software Microsoft Excel and SPSS version 10.0 for Windows was used to analyse the data. Qualitative data was reported as percentages. Chi square test was used to evaluate the Relationship between the two groups. Mean and standard deviation (SD) was calculated and reported for quantitative variables. Unpaired student’s t test was used to test the statistical difference in mean value. A p-value of <0.05 was considered to be statistically significant. All p-values reported were two-tailed.

**Results**

In the present study, 120 term neonates with moderate or severe perinatal asphyxia were taken. Patients were randomly divided into two groups A and B, of 60 neonates each. Baseline characteristics were comparable in both the groups (Table 1).

In moderate asphyxia cases, in Group A, after first loading dose of Phenytoin, seizure was controlled in 2 out of 45 (4.44%) neonates as compared to seizure control in 9 out of 45 (20%) neonates in Group B, after first loading dose of Phenobarbitone ($p < 0.05$).

After second loading dose of drug, seizure control was seen in 4 out of 43 (9.30%) cases in Group A, compared to 11 out of 36 (30.56%) neonates in group B ($p < 0.05$). Also, in Group B after third loading dose of Phenobarbitone, seizure control was seen in 13 out of 25 (52%) moderate asphyxia cases. Hence, after maximum loading doses of drugs in babies with moderate asphyxia, seizures were
controlled in 6 (13.33%) neonates in Group A and 33 (73.33%) in Group B (p< 0.001). (Table 2)
In severe asphyxia cases, seizure was controlled in none of the 15 neonates in group A after first loading dose of Phenytoin, as compared to seizure control in Table 2: Seizure Control After Maximum Loading doses in Moderate Asphyxia Cases.

| Result                        | Group A (n=45) | Group B (n=45) |
|-------------------------------|---------------|---------------|
| Seizures controlled          | 6 (13.33%)    | 33 (73.33%)   |
| Seizures not controlled      | 39 (86.67%)   | 12 (26.67%)   |

1 out of 15 (6.67%) neonates in group B after first loading dose of Phenobarbitone (p>0.05). After second loading dose of drug, seizure was controlled in 2 out of 15 (13.33%) neonates in group A and 4 out of 14 (28.57%) neonates in group B (p> 0.05). Also, in Group B after third loading dose of Phenobarbitone, seizure control was seen in 5 out of 10 (50%) severe asphyxia cases. Hence, after maximum loading doses of drugs, in severe asphyxia, seizures were controlled in 2 (13.33%) neonates in Group A and 10 (66.67%) in Group B (p = 0.002). (Table 3)

Table 3: Seizure Control after Maximum Loading doses in Severe Asphyxia Cases

| Result                        | Group A (n=15) | Group B (n=15) |
|-------------------------------|---------------|---------------|
| Seizures controlled          | 2 (13.33%)    | 10 (66.67 %)  |
| Seizures not controlled      | 13 (86.67%)   | 5 (33.33%)    |

In Group A (n=60), after complete loading of Phenytoin, seizure was controlled in 8 (13.33%) neonates while in 52 (86.67%) neonates seizure was not controlled. In Group B (n=60) after complete loading doses of Phenobarbitone, seizure control was seen in 43 (71.67%) neonates while in 17 (28.33%) neonates seizures were not controlled (p< 0.001).

Out of all the neonates with severe asphyxia who received and responded to either drug for seizure control, 1 out of 2 cases expired in the Group A, while 6 out of 10 cases expired in the Group B. There was no significant difference in the mortality in the two groups and the deaths were likely to be related to the underlying severity of the illness.
On follow up, at three months age, neurological examination and developmental outcome was observed abnormal in 1 (16.67%) neonate with moderate asphyxia in Group A (n=6) and in 3 (9.09%) neonates of Group B (n=33). The neurological examination and developmental outcome at 3 months was observed abnormal in 1 (50%) neonate with severe asphyxia in Group A (n=2) and in 4 (40%) neonates of Group B (n=10). Remaining neonates, i.e. 1 (50%) in Group A and 6 (60%) in Group B died during hospital stay.

Discussion
The study was conducted to evaluate seizure control after use of Phenytoin or Phenobarbitone in neonates with perinatal asphyxia. The present study compared the effect of anticonvulsants on seizures due to perinatal asphyxia only, which was graded as moderate or severe perinatal asphyxia according to Levene Grading system. However, studies by Painter et al[5] and Boylan et al[6] carried their drug trials on seizures due to any etiology like perinatal asphyxia, meningitis, intracranial haemorrhage, CNS malformation, kernicterus, etc. The present investigator did not find any study in which the effect of anticonvulsants was studied on seizures only due to perinatal asphyxia. In the present study only term neonates were taken as subjects while studies by Painter et al[5] and Boylan et al[6], included neonates irrespective of their gestational age.
The diagnosis of seizures and the end point of seizure control in this study was determined clinically. It was observed that the most common seizure type in both the groups in the present study was tonic posturing with abnormal gaze. This was different from earlier studies by Painter et al[5] and Boylan et al[6] in which seizures and their control were diagnosed electrographically or electroclinically using EEG recording.
In the present study, the clinical control of seizures in perinatal asphyxia was achieved in 43 out of 60 neonates (71.67%) after receiving Phenobarbitone as first line anticonvulsant while only 8 out of 60 patients (13.33%) responded to Phenytoin as first line anticonvulsant. This demonstrates that Phenobarbitone is more efficacious than Phenytoin.

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in clinical control of seizures due to perinatal asphyxia. The results demonstrated by the present study differed from those reported by Boylan et al[6], who demonstrated that Phenobarbitone failed to achieve seizure control in all of the 4 patients of HIE enrolled in their study. Boylan et al[6] studied a total of 14 babies with seizures irrespective of their etiology and concluded that Phenobarbitone was ineffective as a first line anticonvulsant treatment in babies with severe seizures in whom the background EEG was also severely abnormal. However, the present study did not record background EEG signals due to non-availability of equipment, so their results may be difficult to compare with this study.

The present study differed from study by Painter et al[5], who had demonstrated that Phenobarbitone and Phenytoin are equally but incompletely effective as anticonvulsants in neonates. Control of electrical seizures due to etiologies like perinatal asphyxia, CNS malformation, CNS infection, etc. was noted in about 45% babies with either drug and about 60% when combined. However, they did not describe the efficacy of these drugs in clinical control of seizures, so it is difficult to compare their results with the present study.

The seizures in the present study were diagnosed only clinically. However, Mizrahi and Kellaway[14] have suggested that diagnosis of seizures may be inaccurate without EEG confirmation. Murray et al[15] have demonstrated that only 1/3rd of neonatal EEG seizures display clinical signs while the rest two-thirds of these clinical manifestations are unrecognized by experienced neonatal staff. Hence, clinical diagnosis may not be enough in recognition and management of neonatal seizures. Also, it is recommended by some authorities that electrical control of seizure using 24-hour video-EEG should be used to determine the end point of seizures. However, the same remains unfeasible, as the machine, cerebral function monitoring (CFM), or the specialist interpreters may not be readily available. Also it has been reported by Mizrahi and Kellaway[14] that subtle seizures in term and near term neonates have only inconsistent association with EEG seizure activity in as many as 85% of infants. In majority of neonatal units in both developed and developing world including the hospital where the present study was conducted, due to lack of expensive CFM equipments, bedside EEG is not available. Hence the seizures were diagnosed and the end point of seizure control was determined, only clinically.

Conclusions
In the study it was concluded that Phenobarbitone is more efficacious that Phenytoin in achieving clinical seizure control when used as first line anticonvulsant in term neonates with moderate or severe perinatal asphyxia. However, the early neurodevelopmental outcome at 3 months of age was similar when either of the drugs was used. Hence larger randomised controlled studies are recommended to study the outcome in babies with moderate or severe perinatal asphyxia when either Phenytoin or Phenobarbitone is used for seizure control.

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