International Journal of Contemporary Pediatrics
Koul H et al. Int J Contemp Pediatr. 2022 Mar;9(3):253-257
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20220449

Original Research Article

Comparative trial of seizure recurrence in phenobarbitone maintenance for 72 hrs versus till discharge in moderate to severe perinatal asphyxia in term infants

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Received: 28 December 2021
Revised: 28 January 2022
Accepted: 03 February 2022

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ABSTRACT

Background: This study was done to look for seizure recurrence in moderate to severe perinatal asphyxia when phenobarbitone was stopped at seizure free interval of 72 hours versus those in whom phenobarbitone was continued upto discharge.
Methods: It was a open label randomized trial conducted in neonatal intensive care unit of department of Pediatrics, SMGS from November 2014 to October 2015. This study was conducted on term babies (>37 weeks) with birth asphyxia with moderate to severe encephalopathy according to Levene classification with seizures within 24 hours admitted in NICU.
Results: Recurrence of seizures was 6 (10%) in whom phenobarbitone was continued upto discharge and 8 (13.3%) in whom phenobarbitone was stopped after 72 hours of seizure free interval. These results were statistically comparable.
Conclusions: There is no beneficial effect of giving phenobarbitone for more than 72 hour in neonates having moderate to severe perinatal asphyxia who are neurologically normal.

Keywords: Asphyxia, Antiepileptic drugs, Development, EEG, Mortality, Seizures, Phenobarbitone

INTRODUCTION

Neonatal seizures are most commonly caused by hypoxic- ischemic encephalopathy, infection, metabolic abnormalities and birth trauma.[1] Perinatal asphyxia is an important cause of brain injury throughout the world in full term infants.[2] Birth asphyxia incidence ranges from 6 to 26 in 1000 live births.[3] Following perinatal asphyxia the incidence of seizure is as high as 50-68%.[4] Phenobarbitone is the traditional agent chosen to treat neonatal seizures.[5] As neonatal seizures are often self limited, it is reasoned that not all seizures require treatment and that anticonvulsant therapy should be quickly discontinued.[6] Inhibition of brain development may occur due to Long term anticonvulsant use.[7]

According to WHO guidelines antiepileptic drugs are stopped after seizure free interval of 72 hrs in neonates with normal neurological examination and / or normal EEG only on expert recommendations.[8] No study has been conducted which describes when anticonvulsants should be stopped in neurologically normal neonates having moderate to severe birth asphyxia so this study was done to look for seizure recurrence in moderate to severe perinatal asphyxia when phenobarbitone was stopped at seizure free interval of 72 hours versus those in whom phenobarbitone was continued upto discharge.

METHODS

It was a open label randomized trial conducted in neonatal intensive care unit of department of pediatrics, SMGS from November 2014 to October 2015.

This study was conducted on term babies (>37 weeks) with birth asphyxia with moderate to severe encephalopathy according to Levene classification with seizures (clinically apparent seizures) within 24 hours admitted in NICU. Neonates were enrolled according to Neonatology Forum of India which suggested that birth asphyxia to be diagnosed when "baby has gasping and inadequate breathing or no breathing at 1 minute". Categorization was done according to Levene classification.

One hundred and twenty patients were enrolled in the present study. Term new born (>37 weeks) with birth Asphyxia with moderate to severe encephalopathy, on phenobarbitone who had remained seizure free for 72 hours and were neurologically normal at 72 hours were enrolled in the study. Term babies having congenital malformations, suspected intraventricular haemorrhage, meningitis, suspected sepsis, hypocalcemia and hypoglycemia were excluded. Informed written consent was obtained from the parent/guardian of the child. One hundred and twenty patients satisfying the above mentioned criteria were the subjects for the study and were randomized into two groups. Allocation was done by a web based random number sequence generator. Separate person who was not involved in the study generated the random sequence. Restricted randomization was done using variable sized blocks within each stratum. Allocation was concealed by placing the allocation sequence in opaque, temper proof sealed, serially numbered envelopes. In order to keep the number of patients equal in both groups, permuted block randomization was done. The eligible candidates who had seizures following perinatal asphyxia were started on phenobarbitone. The patients who remained seizure free for 72 hours and were neurologically normal based on Amiel-Tison protocol were then randomized to either group A (phenobarbitone stopped within 72 hrs) or group B (phenobarbitone continued upto discharge). Each group had 50 neonates with moderate asphyxia and 10 neonates with severe asphyxia.

Details of name, age, sex, weight, head circumference, and length were recorded on a pre structured proforma. Patency of airway, breathing and circulation were ensured based on standard guidelines. A cannula was secured and blood samples for blood sugar, serum calcium and other tests as indicated in that patient were drawn. Patient who had seizures following perinatal asphyxia were started on phenobarbitone. The patients who remained seizure free for 72 hours and were neurologically normal based on Amiel-Tison protocol were then randomized to either group. If neurological examination is not normal then phenobarbitone was continued after discharge, and baby re evaluated at age of 1 month and 3 months. In control group if child was seizure free for 72 hours and was neurologically normal phenobarbitone was continued upto discharge. In case group if child was seizure free for 72 hours and was neurologically normal phenobarbitone was stopped. We looked for seizure recurrence in both groups.

Stastistical analysis

The results obtained were analysed using computer software Microsoft Excel and Statistical package for social sciences (SSPS) version 10.0 for windows. Qualitative data was reported as percentages. Relationship between the two groups was evaluated using Chi-square test. Mean and standard deviation was calculated and reported for quantitative variables. The statistical difference in mean value was tested using student's 't' test. A p value of <0.05 was considered statistically significant.

RESULTS

50 neonates having moderate perinatal asphyxia and 10 neonates having severe perinatal asphyxia were enrolled in both groups. In moderate to severe perinatal asphyxia after seizure free interval of 72 hours it studied the seizure recurrence when phenobarbitone was stopped after 72 hours of seizure free interval and in those whom phenobarbitone was continued upto discharge.

Table 1: Enrollment details.

	Group A	Group B	P value
Age at Admission	3.34±2.93	2.39±2.01	0.068
Male gender	36	44	0.121
Female gender	24	16	
Weight at birth	2.84±0.298	2.76±0.271	0.121
NVD	35	42	0.183
LSCS	25	18	
Age at onset of seizure	4.28±1.70	3.90±2.03	0.279
Apgar score at 1 minute	4.2	3.9	0.158
Apgar score at 5 minute	6	5.8	0.195

The mean age of admission was 3.34±2.93 in Group A (phenobarbitone stopped after seizure free period of 72 hrs) and the mean age in group B (phenobarbitone continued till discharge) was 2.39±2.01. It was comparable between the two Groups. There were more

males in group B 44 (73.3%) as compared to group A 36 (60%). There were more females in group A 24 (40%) as compared to group B 16 (26.7).

Table 2: Comparison based on recurrence of seizure in two groups (moderate asphyxia).

Recurrence of Seizure	Group A		Group B		P value
	No.	%	No.	%	
Yes	4	8	4	8	
No	46	92	46	92	1
Total	50	100	50	100	

Table 3: Comparison based on recurrence of seizure in two groups (severe asphyxia).

Recurrence of seizure	Group A		Group B		P value
	No	%	No	%	
Yes	2	20	4	40	
No	8	80	6	60	0.629
Total	10	100	10	100	

Table 4: Comparison based on recurrence of seizure in two groups.

Recurrence of seizure	Group A		Group B		P value
	No.	%	No.	%	
Yes	6	10	8	13.3	0.569
No	54	90	52	86.7	
Total	60	100	60	100	

The difference between the two groups was statistically comparable. The number of neonates of weight 2.5 to 3 kg which were taken in group A were 51 (85%) and group B were 54 (90%). Number of neonates of weight 3.1 to 3.5 kg which were taken in group were A 9 (15%) and group B were 6 (10%). Mean weight of group A (2.84 kg) and group B (2.76 kg) was statistically comparable. Mean Apgar score at 1 minute in Group A was (4.2) and Group B (3.9) which was statistically comparable. Mean Apgar score at 5 minute in Group A (6.0) and Group B (5.8) was statistically comparable in two groups (Table 1).

In moderate perinatal asphyxia seizure recurrence was observed in 4(8%) out of 50 patients who received phenobarbitone till discharge. In neonates whom phenobarbitone was stopped after 72 hours of seizure free interval seizure recurrence was noted in 4(8%) out of 50 neonates. These results were statistically comparable (Table 2).

In severe perinatal asphyxia seizure recurrence was observed in 2 (20%) out of 10 neonates who received phenobarbitone till discharge. In neonates whom phenobarbitone was stopped after 72 hours of seizure free interval seizure recurrence was observed in 4 (40%) out of 10 neonates. Recurrence of seizures was 6 (10%) in whom phenobarbitone was continued upto discharge and 8 (13.3%) in whom phenobarbitone was stopped after 72 hrs of seizure free interval. These results were statistically comparable (Table 3).

In this study it was concluded that the seizure recurrence in neonates whom phenobarbitone was continued upto discharge was similar to those neonates in whom phenobarbitone was stopped after 72 hours of seizure free interval (Table 4).

Hence, it was concluded that there is no beneficial effect of giving phenobarbitone for more than 72 hour in neurologically normal neonates having moderate to severe perinatal asphyxia as there is no effect on seizure recurrence and neurodevelopment outcome.

DISCUSSION

The number of subjects in the present study was 120, which is comparable to the cohort of 120 neonates by Gilman et al, 115 subjects by Pathak et al and 146 neonates in Kwon et al et al.[9-11] This study was done in both inborn and outborn neonates similar to study conducted by Ghrepelli et al and Hellstrom et al.[12,13] In the present study only term babies >37 weeks of age were included. It was similar to study conducted by Painter et al in which term and near term infants were included, Hall et al and Yin et al in which term infants were taken.[14-16] Whereas in the Gilman et al, Hellstrom et al and Velaphi et al both term and preterm infants were included.[9,13,17]

The present study is a prospective study conducted on term infants having moderate to severe perinatal asphyxia. The study conducted by Kwon et al and Carli et al were retrospective studies.[11,17]

In the present study only clinically apparent seizures were given anticonvulsants and seizure recurrence were also noticed in the form of any clinically apparent seizures which is similar to the study conducted by Pathak et al where clinically apparent seizures were included in the study similar to the present study. In a study by Painter et al and Castro et al only EEG confirmed seizures were included.[10,14,18]

In the present study only seizures due to perinatal asphyxia were included in the study all other causes were ruled out. In study conducted by Donn et al, Daljit et al and Velaphi et al only neonates who had seizures due to perinatal asphyxia were included in the study similar to the present study.[17,19,20] In study carried out by Scarpa et al, Ghrepelli et al and Hellstrom et al neonates were included who had seizures irrespective of the etiology of the seizures.[12,13,21] No study was conducted in which phenobarbitone was stopped at 72 hours of seizure free interval and in which development was assessed upto 3 months of age.

There were 6 (10%) patients who had seizure recurrence when phenobarbitone was continued upto discharge. There were 8 (13.3%) patients who had seizure recurrence in patients in whom phenobarbitone was stopped after 72 hours of seizure free interval. The result was statistically comparable so there was no difference in recurrence of seizure in neurologically normal neonates once seizures were controlled for past 72 hours. It was similar to the study conducted by Kwon et al in which study phenobarbital prophylaxis did not improve seizure recurrence.[11]

In the study conducted by Hellstrom et al it was concluded that despite the short duration of antiepileptic treatment (median 4.5 days), only 8.3% of patients had seizure recurrence during their first year of life which is comparable to the present study.[13] But in this study all type of seizures were included irrespective of etiology of seizures. In the present study only seizures due to perinatal asphyxia were included in the study but only clinically apparent seizures were included. In the present study background EEG signals were not recorded due to non availability of equipment, so the results are difficult to compare with this study.

The seizures in the present study were diagnosed only clinically. However, Mizrahi and Kellaway have suggested that diagnosis of seizures may be inaccurate without EEG confirmation.[22] Murray et al have demonstrated that only 1/3rd of neonatal EEG seizures display clinical signs and rest 2/3rd of these clinical manifestations are unrecognized by experienced neonatal staff.[23] Hence, in recognition and management of neonatal seizures, clinical diagnosis is not enough. Most authorities recommend electrical control of seizure using 24-hour video-EEG, but neither the machine nor cerebral function monitoring (CFM), or the specialist interpreters are readily available. Mizrahi and Kellaway have reported that subtle seizures in term and near term neonates have only inconsistent association with EEG seizure activity in as many as 85% of infants.[22]

A study conducted by Pharm et al a comparison of reports indicated no difference in seizure recurrence rates when anticonvulsants were stopped early in the neonatal period or when treatment was given longer, even in the high-risk group.[24] This is comparable to the present study in which no difference in neurological outcome obtained in the two groups whether phenobarbitone was continued up to discharge or when phenobarbitone was stopped after 72 hours of seizure free interval. In a study by Hellstrom et al fifty eight of 283 (4.5%) neonates in tertiary level neonatal intensive care had seizures.[13] Seizure recurrence was present in only three cases (8.3%) one infant receiving prophylaxis, one treated for 65 days, and in one infant treated for six days. Owing to the small number of infants with seizure recurrence, no clinical features could be specifically related to an increased risk of subsequent seizures. In present study in moderate perinatal asphyxia seizure recurrence was observed in 4(8%) out of 50 patients who received phenobarbitone till discharge and in severe perinatal asphyxia seizure recurrence was observed in 2 (20%) out of 10 neonates who received phenobarbitone till discharge.

Limitations

This study was done by open label trial, no blinding was done so risk of bias. In this study only clinically apparent seizures were included. In this study only 120 patients were enrolled out of which 60 were in moderate and 60 in severe perinatal asphyxia group which is a small sample size.

CONCLUSION

In this study it was concluded that the seizure recurrence in neonates whom phenobarbitone was continued upto discharge was similar to those neonates in whom phenobarbitone was stopped after 72 hours of seizure free interval. The mortality was comparable in neonates in whom phenobarbitone was continued upto discharge to those in whom phenobarbitone was stopped after seizure free interval of 72 hours. Hence, it was concluded that there is no beneficial effect of giving phenobarbitone for more than 72 hour in neurologically normal neonates having moderate to severe perinatal asphyxia as there is no effect on seizure recurrence and neurodevelopment outcome.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Clancy RR. Summary proceedings from the neurology group on Neonatal seizures. Europe PMC. 2006;117(3pt2):S23-7.
2. Evans DJ, Levene M, Tsakmakis M. Anticonvulsants for preventing mortality and morbidity in full term newborns with perinatal asphyxia. Cochrane Database of Systematic Reviews. 2007;3:CD001240.
3. Bhutta ZA. Paediatrics in the Tropics. Manson's Tropical Infectious Diseases. 2014;1197-1214.e2.
4. Sankar JM, Agarwal R, Deorari A, Paul VK. Management of neonatal seizures. Indian journal of paediatrics. 2010;77:1129-35.
5. Clancy RR. Summary proceedings from the neurology group on Neonatal seizures. Europe PMC. 2006;117(3pt2) S23-7.
6. Bartha AI, Shen J, Katz KH, Rebecca E. Mischel, Katherine R. Yap, JudithA.Ivacko, Ena M.Andrews, Donna M, Ferriero, Laura R, Ment, Faye S. Silverstein Neonatal seizures: multicenter variability in current practices. Pediatric Neurology. 2007;37 85-90.

7. Marsh ED, Brooks-Kayal AR, Porter BE. Seizures and antiepileptic drugs; does exposure alter normal brain development. Epilepsia. 2006;47(12):1999-2010.
8. WHO Guidelines 2011: Guidelines on neonatal seizures. 2011.
9. Gilman JT, Gal P, Duchowny MS, Weaver RL, Lawrence J. Ransom Rapid sequential Phenobarbital treatment of neonatal seizures AAP gateway. 1989;83:674-78.
10. Garima Pathak, Amit Upadhyay,Umesh Pathak,Deepak Chawla and Sneh P Goel. Phenobarbitone and phenytoin for treatment of neonatal seizures: open label randomized control trial, Indian Pediatrics, 2013;50(8):753-7.
11. Guillet R, Kwon J. Seizure recurrence and developmental disabilities after neonatal seizures: outcome are unrelated to use of phenobarbitone prophylaxis. Journal of child neurology. 2007;22:389-95.
12. Gherpelli JL, Pas JA, Leone CR, Ramoz JLA. Diament Seizure recurrence in infants with neonatal convulsions. rq neuro-psiquiat. 1992;50(1):31-6.
13. Hellstrom-Westas G, Blennow M, Lindroth I, Rosen NW. Low risk of seizure recurrence after early withdrawal of antiepileptic treatment in the neonatal period: Archives of Disease in Childhood. Fetal and Neonatal Edition. 2007;72(2):F97-101.
14. Painter MJ, Scher MS, Stein AD. Phenobarbitone compared with phenytoin for treatment of neonatal seizures. N eng J Med. 1999;341:485-9.
15. Hall RT, Hall FK, Donna K. Daily High-dose phenobarbital therapy in term newborn infants with severe perinatal asphyxia: A randomized, prospective study with three-year follow-up:Journal of Pediaatrics. 1998;132(2):345-8.
16. Lai YH, Ho CS, Chiu NC, Tseng CF, Huang YL. Prognostic Factors of Developmental Outcome in Neonatal Seizures in Term Infants. Paediatrics and Neonatology. 2013;54(3):166-72.
17. Velaphi S, Mokhachane M, Mphahlele R, Beckh-Arnol E. Effect of prophylactic phenobarbital on seizures, encephalopathy and mortality in neonates with perinatal asphyxia. South African Journal of Child Health. 2013;7:1.
18. Conde JR, Borges AAH, Martínez EDC, Campo G, Soler RP. Midazolam in neonatal seizures with no response to phenobarbital. Neurology. 2005;64(5):876-9.
19. Donn SM, Grasela TH, Gary W. Goldstein Safety of a higher loading dose of phenobarbital in the term newborn. Pediatrics. 1985;75:1061-64.
20. Singh D, Singh A. A randomized controlled trial of phenobarbital in neonates with hypoxic ischemic encephalopathy. The Journal of Maternal-Fetal & Neonatal Medicine. 2005;18:6:391-5.
21. Scarpa P, Chierici R, Tamisari L, Fortini C, Volpato S. Criteria for discontinuing neonatal seizure therapy: A long-term appraisal. Brain and Development. 198;5(6):541-8.
22. Mizrahi EM, Kellaway P. Characterization and classification of neonatal seizures. Neurology. 1987;37(12):1837-44.
23. Murray DM, Boylan GB, Ali I, Ryan CA, Murphy BP, Connolly S. Defining the gap between electrographic seizure burden, clinical expression and staff recognition of neonatal seizures. Arch Dis Child Fetal Neonatal Ed. 2008;93(3):F187-91.

Cite this article as: Koul H, Saini GS. Comparative trial of seizure recurrence in phenobarbitone maintenance for 72 hrs versus till discharge in moderate to severe perinatal asphyxia in term infants. Int J Contemp Pediatr 2022;9:253-7.