Study of breakthrough seizures in newborns with hypoxic-ischemic encephalopathy after stopping anticonvulsant therapy

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Received - 25 December 2019 Initial Review - 16 January 2020 Accepted - 10 February 2020

ABSTRACT

Background: Neonatal seizure is a distinct clinical response to neurological dysfunction. Hypoxic-ischemic encephalopathy (HIE) is a leading cause of neonatal seizures. Neonates with seizures are at risk of neurodevelopmental impairment, cognitive, behavioral disorders, epilepsy in later part of life, and even death during the neonatal period of life. **Objective:** The objective of the study was to study the occurrence of breakthrough seizures in a newborn with HIE after stopping anticonvulsant therapy. **Materials and Methods:** The study was a prospective cross-sectional study done in a Level III NICU of a tertiary hospital in Western India. A total of 35 full-term newborns with evidence of perinatal hypoxia with HIE II, III as per Sarnat and Sarnat staging and magnetic resonance imaging were enrolled. Patients with seizures were treated with intravenous phenobarbitone (PB). Patients were observed for breakthrough seizures after discontinuation of PB and were followed up at high-risk outpatient department until 6 months of age. **Results:** A total of 31 (88.6%) cases of 35 did not manifest breakthrough seizures. There were four (11.4%) cases which manifested breakthrough seizure after stopping anticonvulsant therapy and three had HIE III ($p=0.044$). Maternal anemia was observed to have a statistically significant association with breakthrough seizures ($p<0.0001$). There were nine cases with an abnormal neurological examination, three manifested breakthrough seizures, and there was no statistical correlation between neurological examination and occurrence of clinical and breakthrough seizures ($p=0.0165$). **Conclusion:** After initial seizure control by anticonvulsant therapy, breakthrough seizures are not increased after withholding the maintenance therapy.

Key words: *Breakthrough seizures, Hypoxic-ischemic encephalopathy, Perinatal hypoxia/asphyxia, Phenobarbitone*

A neonatal seizure is a response to neurological impairment/insult/dysfunction which jeopardizes the development, cognition, and behavior [1]. Around 80% of seizures occur in 24–48 h and they may occur until the end of 1st week of life [2]. Hypoxic-ischemic encephalopathy (HIE) due to perinatal asphyxia is the most common cause of neonatal seizures. Approximately 50–65% of HIE cases manifest neonatal seizures in the initial 12 h of life; however, a few seize by 24–48 h of life [3,4]. The anticonvulsant of choice in neonatal seizures is phenobarbitone (PB) [5]. Due to the lack of set guidelines, babies with HIE are put on long-term PB therapy which has adverse effects on the developing brain such as neuronal apoptosis leading to impairment of behavior, intelligence, cognition, learning, and memory [6-8].

Breakthrough seizures are implied to an event that occurs during treatment, despite initial control, warranting a change of therapy. It does not include the cases in which seizures reoccurred and control was gained by increasing the drug dose [9]. At present, neurological examination and electroencephalogram (EEG) are done to decide if PB has to be continued.

PB prophylaxis was earlier used for weeks to months even after control of neonatal seizures, to minimize the risk of recurrence [10,11]. It has also been demonstrated that early PB discontinuation after the neonate is clinically stable which does not lead to an increase in breakthrough seizures, even though the signs of neurological damage are still there [12,13]. Moreover, there is data to suggest that PB administration after seizure control does not improve neurological outcomes [14]. The implications of anticonvulsants, regardless of the dose and duration, are known to be detrimental for the developing brain. This study was taken up to study the profile of breakthrough seizures in HIE since there are no set guidelines pertaining to the use and the duration of antiepileptic therapy.

MATERIALS AND METHODS

It was a hospital-based prospective cross-sectional study done in a Level III NICU and high-risk outpatient department of a tertiary care hospital of Western India. Term newborns (37 0/7 weeks–41 6/7 weeks) with evidence of perinatal asphyxia (with HIE II, III), i.e., history (cord prolapse, antepartum hemorrhage, cord around neck, prolonged second stage of labor, abruptio placentae, fetal distress, and meconium aspiration), clinical

(Sarnat and Sarnat staging), or radiological evidence magnetic resonance imaging (MRI) were included in the study. Newborns on multiple anticonvulsants and those with prematurity, congenital anomalies, HIE I, neonatal encephalopathy other than HIE, and neonatal epileptic encephalopathy were excluded from the study.

Confirmation of HIE was done by history of a loop of umbilical cord around neck, cord prolapse, prolonged second stage of labor, meconium aspiration, antepartum hemorrhage, and fetal distress at birth. The presence of the following findings confirmed HIE [15]: (1) Acidemia with a pH of <7.0 in the blood sample taken from the umbilical cord (mixed or metabolic acidemia), (2) Apgar scores of <3 of 10 at 5 min, (3) signs of neurologic dysfunction (e.g., seizures, abnormal muscle tone, and encephalopathy), and (4) multiorgan dysfunction, i.e., kidneys, lungs, liver, heart, and intestine.

Clinical examination and confirmation of seizures were done by neonatologist and pediatric neurologist. Clinical examination was noted in structured clinical pro forma. Radiological evidence was seen on MRI. After confirmation, the cases were categorized into Stages 2 and 3 using Sarnat and Sarnat staging. A total of 38 cases with HIE II and III were treated with PB and were planned for follow-up. Ethical committee clearance was obtained before starting the study. Informed consent from the parents of the cases enrolled in the study was taken.

After shifting to NICU, the patients were provided oxygen (as needed) and ventilatory support as per Downe's score (if >6). All patients were kept nil by mouth and given IV fluid @ 2/3rd maintenance of 10% dextrose. Euglycemia and euthermia were maintained. The 1st and 2nd line of antiepileptics used at our NICU was PB and Levetiracetam, respectively. Abnormal movements were video recorded and confirmed with neonatologist and pediatric neurologist for the presence or absence of seizures. Patients were monitored for oxygen saturation, heart rate, blood pressure, urine output, neurological status – activity, tone, reflexes, general body movements, and abnormal movements. The protocol used for antiepileptic administration was any seizure of duration >3 min, associated with a change in cardiovascular status (bradycardia, desaturation, and hypotension) and with frequency >3/h treated with IV PB.

PB was administered at an initial dose of 20 mg/kg in 1:10 dilution with normal saline over 20 min at 1 mg/kg/min. A total dose of 40 mg/kg, consisting of a first and second loading dose of 20 mg/kg each was planned for all the cases. After 72 h of PB therapy, IV fluids were liberalized as per improvement in the tone and reflexes. Inotropic support was weaned off and feeds were commenced. Intravenous lines were removed. MRI scan for all cases was done at 5–7 days of life. The patient who had obtained complete oral feeds and hemodynamic stability was observed for another 5 days for any abnormal movements and only then discharge was planned.

The patients were discharged and subsequently followed up first at 48 h of discharge, second at 15 days, and subsequent four follow-up visits were done monthly followed by one at 6 months. Neonatal neurological examination was done on discharge and 6 months follow-up. The developmental assessment was done on follow-up using Trivandrum developmental screening chart. Tone assessment was done by physiotherapists using Amiel-Tison angles with the help of a goniometer. The patients were planned for a repeat MRI scan, brainstem evoked response audiometry, and EEG at 3 months. At the end of 6 months, three patients of the 38 were lost to follow-up.

The sample size calculation was based on the incidence and prevalence of HIE. The incidence of HIE is between 1.3 and 1.7/1000 live births [16]. The prevalence of HIE was found to be 2.42/1000 infants [17]. The prevalence was 0.24% with a 2% acceptable margin of error at 97% confidence level. The sample size calculated using Epi7 software was 27. All the data were compiled into MS Excel spreadsheets and analyzed using SPSS version 17.

RESULTS

A total of 59 newborns were screened for perinatal hypoxia, 15 had HIE I, and they were, hence, excluded from the study. Among the remaining 44 cases, six needed the next line of antiepileptic (Levetiracetam). The demographic status of the cases is illustrated in Table 1.

Association between maternal risk factors and breakthrough seizure is illustrated in Table 2. Maternal anemia was found to have a statistically significant association with breakthrough seizures. Mothers of all four cases of breakthrough seizure had anemia during pregnancy ($p<0.0001$). Prolongation of the 2nd stage of labor was also found to have an association with breakthrough seizures, but it was not statistically significant.

Association between complications at/after birth and breakthrough seizure is illustrated in Table 3. Of five cases with meconium aspiration syndrome, three manifested breakthrough seizures. This association was statistically significant ($p<0.013$).

Of 35 cases of HIE, 26 (74.3%) had HIE II and the other nine (25.7%) had HIE III. Of the total four cases who manifested breakthrough seizures, three had HIE III. These data were statistically significant ($p=0.044$).

We observed that at discharge, neurological examination of 21 patients was abnormal, of which three had breakthrough seizures. Of the remaining 17 patients with a normal neurological examination, only one had breakthrough seizures ($p=0.40$). There were three patients who were lost to follow-up in 6 months. At 6 months, the number of patients with normal neurological examination increased to 26 and only one patient manifested breakthrough seizure. The number of patients with abnormal neurological examination significantly reduced to nine, of which only three manifested breakthrough seizures. These data were statistically significant ($p=0.01$).

DISCUSSION

Our study highlights that, neither withholding anticonvulsant therapy nor the abnormal neurological examination at discharge and at 6 months in a patient with HIE, increases the risk of seizure. A Cochrane review concluded that anticonvulsants to

Table 1: Demographic profile of the study population (n=35)

Parameters	Number of cases	Percentage
Gender		
Male	20	57.1
Female	15	42.9
Gestational age (weeks)		
37–39	25	71.5
40–41	10	28.5
Mode of delivery		
Vaginal	19	54.3
Lower segment caesarean sections	16	45.7
Parity		
Primigravida	21	60
Multigravida	14	40

Table 2: Association between maternal risk factors and breakthrough seizure

Risk factors	Breakthrough seizure		Z value	p-value
	Yes (n=4)	No (n=31)		
IVF treated	1 (25)	7 (22.58)	0.11	0.92
2nd stage of labor >2 h	3 (75)	19 (61.29)	1.41	0.16
2nd stage of labor >1 h	1 (25)	12 (38.71)	1.41	0.16
Maternal diabetes	2 (50)	13 (41.93)	0.30	0.76
Maternal anemia	4 (100)	11 (35.48)	7.51	<0.0001
Maternal hypertension	2 (50)	13 (41.93)	0.55	0.58
Maternal hypothyroidism	1 (25)	7 (22.58)	0.11	0.92

Table 3: Association between complications at/after birth and breakthrough seizure

Event	Breakthrough seizure		Total
	Yes	No	
Loop of cord around of fetus	0	14	14
Breech presentation	0	2	2
Meconium aspiration syndrome	3	2	5
Deep transverse arrest	0	2	2
Meconium stained liquor	1	8	9
Abruptio placentae	0	3	3
Total	4	31	35

term infants immediately after the event of perinatal hypoxia cannot be recommended for routine clinical practice, other than in treating clinical seizures [18]. Another Cochrane showed that PB and phenytoin had a similar effect in treating seizures in 50% of infants [19]. At present, the antiepileptic of choice for neonatal seizures is PB. Studies have shown that seizures owe a threat to the developing neonatal brain, but the drugs available for seizure control have been found to cause neuronal apoptosis as well [20]. PB's long-term usage has been associated with impairment of cognitive function, motor milestone delays, and poor neurodevelopmental outcome [21].

Saxena *et al*. found that though recurrent seizures were a potential threat to the brain, there was insufficient evidence to support the notion that long-term usage of PB can prevent seizure recurrence. They concluded that after clinical control of neonatal seizures with loading doses of PB, withholding maintenance, PB therapy may not cause seizure recurrence in full-term infants [22]. In the present study, Of 38 cases with HIE II and III, only four (11.4%) cases manifested breakthrough seizures. In a similar study done by Saxena *et al*. which had 75 patients in the placebo group and 77 patients in the PB group, 30 (40%) of 75 and 24 (31.2%) of 77 (p=0.19) patients manifested breakthrough seizures [22].

In the present study, 60% of cases were born to primigravida mothers and rest 40% to multigravidas. In a previous study by Dalal and Bodar, it was observed that primipara had more chances of getting birth asphyxia [23]. In a study conducted by Babu *et al*., primiparity was found to be a statistically significant maternal risk factor for perinatal hypoxia with 54.9% occurrence in cases [24].

Our study documented that maternal anemia was found to have a statistically significant association with breakthrough seizures (p<0.0001). Anemia causes a decrease in the oxygen-carrying capacity of the hemoglobin which could have led to intrapartum hypoxia in the fetus. Bhunia and Saharia also found that 87.71% cases of perinatal hypoxia were born to mothers with anemia [25].

We also observed that prolonged second stage of labor in primigravida and multigravida (62.7% and 37.1%) had a high association with perinatal hypoxia. Prolongation of the stages of labor eventually leads to fetal distress which might have resulted in perinatal hypoxia. A large percentage of cases in our study underwent prolonged labor; this finding was also consistent with the previous study by Bhunia and Saharia who observed 15% of cases to have prolonged labor and ended up with HIE (p=0.0264) [25]. A similar study by Babu *et al*. identified prolongation of the second stage of labor as a significant maternal risk factor related to perinatal hypoxia (37.4% in cases vs. 4% in control, p<0.0001) [24].

Meconium aspiration syndrome was observed in five (14.3%) cases and of these, three cases manifested breakthrough seizures (p<0.013). In the study by Reddy *et al*., risk factors predisposing to perinatal hypoxia were found to be poor antenatal care (24%) and meconium-stained liquor (20%). The study proved that both ante and intrapartum factors are important in causing perinatal hypoxia [26]. Babu *et al*. also observed a statistically significant association with meconium being associated with 42% cases of HIE and p<0.0001 [24].

The study documented that many patients had an abnormal examination at discharge and 6 months follow-up but manifested no clinical or breakthrough seizures. The result obtained at 6 months were statistically significant and indicated that providing prophylactic PB for seizures to patients with abnormal neurological examination might not be required. Only one patient manifested breakthrough seizure despite a normal neurological examination at discharge and follow-up. The study highlighted that there could be no correlation between neurological examination and the occurrence of clinical and breakthrough seizures.

Therefore, cessation of clinical seizures with the loading dose of PB without maintenance dose may not cause breakthrough seizures among the full-term babies with HIE. Even if the maintenance dose is not prescribed, the chances of the patients getting breakthrough seizures are less likely. Saxena *et al*. concluded that breakthrough seizure until discharge is not likely to increase by withholding PB maintenance after the loading dose. It was also concluded that cessation of electrical seizures should be the end-point of antiepileptic therapy if available. The next best achievable mark to stop PB therapy in developing countries can be control of clinical seizures [22].

The prime limitation of the study was the lack of a control group. Another limitation was a lack of cerebral function or continuous EEG monitoring amplitude-integrated EEG (aEEG) so as to keep a check on electrical seizures if clinical seizures were absent. Serum PB levels could not be measured. Multicentric randomized controlled trial (RCT) studies with larger sample sizes are needed to pick up small differences in breakthrough seizures and neurological outcomes.

CONCLUSION

After initial seizure control by anticonvulsant therapy, withholding the maintenance therapy does not increase the chances of breakthrough seizures. Abnormal neurological examination is not a good clinical indicator to judge the continuation of anticonvulsant therapy. Multicentric RCT studies with larger sample sizes are needed to pick up small differences in breakthrough seizures and neurological outcomes.

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Funding: None; Conflict of Interest: None Stated.

How to cite this article: Malwade S, Nayak M, Chalipat S, Agarkhedkar S. Study of breakthrough seizures in Newborns with hypoxic-ischemic encephalopathy after stopping anticonvulsant therapy. Indian J Child Health. 2020; 7(2):66-69.

Doi: 10.32677/IJCH.2020.v07.i02.007