IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Seizures in term babies and neurodevelopmental outcome: a follow-up study

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Abstract

Introduction: Neonatal period is the most vulnerable time for the occurrence of seizures. There are various etiological factors of neonatal seizures and increasing evidence suggests that neonatal seizures are associated with adverse neurodevelopment outcomes.

Objectives: The objectives were determination of causes of neonatal seizures with outcome during management and long-term post-natal outcome.

Material & Methods: This was a prospective cross-sectional Hospital based study conducted in Rangpur Mother and Children Hospital from 1st July to 2017 to 30th June 2022. Term newborn babies admitted in Neonatal Intensive Care Unit with convulsion were the samples. A prepared and pretested "Protocol" containing Part-A and Part-B was used - Part-A in Neonatal Intensive Care Unit and Part-B in the attached Disability Research Center for periodic follow up. Standard guidelines were followed in clinical diagnosis, laboratory investigations and management of convulsion. The survivors were followed-up periodically. Simple statistical calculations were performed.

Results: A total of 234 term neonates with convulsion were admitted from 1st July 2017 to 30th June 2018. Among them, 15 expired during treatment, 10 babies taken out on Risk Bond by parents and 212 children were discharged and referred to Disability Research Center for follow-up assessment. Follow-up was continued up to 30th June 2022 and 37 children were lost from regular follow-up. Finally, data from 175 children were analyzed. Among these 110 (62.9%) children were male and 65 (27.1%) were female. HIE stage-II was present in 133 (76.0%) samples and 20 (11.3%) had metabolic disturbances. Clonic convulsion was present in 114 (65.0%) samples and subtle convulsion in 45 (26.0%) samples. HIE was the potent predictor for developing neurodevelopmental sequelae.

Conclusions: Neonatal seizures have different etiology. Among them HIE stage-II is the predominant cause of admission as well as adverse neurodevelopmental outcomes.

Key words: Term baby, convulsion, NICU admission, neurodevelopmental outcome.

Introduction: Neonatal period is the most vulnerable time for the occurrence of seizures. Health care professionals face a clinical challenge during management and to minimize the occurrence of long-term morbidities[1]. The incidence of neonatal seizure varies from 1.5 to 3.0 per 1000 live births in developed countries but in developing countries the rate is higher because the mode of delivery, ante-natal and intra-natal care are different[2]. There are various etiological factors and mechanism of neonatal seizures but 80-85% is predominantly accounted by Hypoxic Ischemic Encephalopathy (HIE). Others are intracranial hemorrhage (IVH), severe birth injuries, metabolic disturbances and infections etc[3,4].

Irrespective of underlying cause and mechanism, increasing evidence suggest that neonatal seizures are associated with adverse neurodevelopment outcomes such as cerebral palsy (CP), developmental delay, psychomotor deficits, epilepsy and other disabilities[5,6]. There are many studies in abroad regarding outcomes of neonatal seizures[7,8], but there are few studies in our country[9,10] related to long-term outcomes of neonatal seizures. So, this study was conducted with the objective of determination of causes of neonatal seizures with outcome during management and long-term outcome up to 4 years of age.

Methodology: This was a prospective cross-sectional hospital-based study conducted in Rangpur Mother and Children Hospital (RMCH) from 1st January 2018 to 31st Dec 2022. The sampling method was purposive in nature. All the term newborn babies having birth weight 2.5kg or more and admitted up to 31st Dec 2018 in Neonatal Intensive Care Unit (NICU) with convulsion or convulsion developed after admission was included as samples. A prepared and pretested "Protocol" was used to record the information for the diagnosis, management and periodic follow up of the baby[11,12]. The protocol contained two parts - part A and part B. Part-A was used in NICU and part-B in attached Disability Research Center (DRC) for post-natal follow up. Part A contained birth history, physical and neurological assessment of the babies, imaging studies and laboratory investigations. Part-B contained the domains of Denver Developmental Screening Test II[13]. HIE was diagnosed according to modified Sarnat criteriae[14]. Abnormal movements described by Volpe[15] were regarded as convulsion. Neonatal Sepsis was diagnosed following Rodwells criteriae[16].

Counselling sessions for parents was arranged daily as a routine practice and written consent was taken to do the necessary investigations of their babies. Written ethical clearance was taken from the hospital authority. Laboratory studies included CBC, blood culture, blood glucose, serum calcium plus magnesium levels, serum electrolytes and CSF studies. In case of ambiguity in diagnosis serum ammonia, urine and serum organic and amino acid analysis by TMS and serum parathormone level were performed. Electroencephalogram (EEG) recording was taken by a portable EEG machine (Maximus RMS-32). Computed Tomography (CT) scan was done in cases having suspicion of IVH. Convulsion was controlled by phenobarbitone as a primary drug and then phosphenytoin, lorazepam and leviteracetam either singly or in combination in refractory cases along with treatment of primary cause[17]. The survivors were transferred to DRC attached in this hospital for follow-up periodically. Each child was assessed by trained development therapist every four months through Denver Developmental Screening Test-II. Hearing tests

was done from a nearby Audiological center and vision assessment was performed from a nearby Eye hospital following recommendations described in a review study[18]. Data were documented into the protocol and then entered into the computer for descriptive analysis.

Results: A total of 730 term neonates were admitted in NICU from 1st January to 31st Dec 2018. Among them 234 (32%) had convulsion and received treatment. Among these 234 babies, 12 (5%) expired during treatment in NICU and 10 (4.3%) babies were taken out by parents on Risk BOND due to no immediate improvement. Remaining 212 (29.0%) children were discharged from NICU and referred to DRC of the same hospital for periodic follow-up. Follow-up was continued up to 31st Dec 2022. During follow-up, 37 children were lost from regular follow-up due to various reasons and data from 175 children were analyzed. Among these 110 (62.9%) children were male and 65 (27.1%) children were female (Table-1).

Among all the samples 151 (86.3%) had initiation of convulsion within 3 days of birth with 18 (10.3%) babies within 3-7 days (Table 2). Again 133 (76.0%) had HIE stage II and 20 (11.3%) had metabolic disturbances. Infection was third cause of convulsion and among these babies 9 (5.6%) had sepsis and 4(2.8%) had viral encephalitis. Four (2.8%) babies had IVH. There was no detectable cause in 5 (2.9%) babies by completed investigations (Table-3). Out of all samples, 114 (65.0%) developed clonic convulsion followed by subtle convulsion in 45 (26.0%) babies (Table-4). HIE stage-II was the potent predictor for developing CP (66.2%) and other neurodevelopmental sequelae in postnatal life (Table-5).

Table 1: General characteristics of the samples

Parameters	No
Total term babies Admitted	730
Babies with convulsion	234
Expired during treatment	12
Risk BOND discharge	10
Discharged for follow-up	212
Average hospital stays (in day)	09
Lost from follow-up	37
Data analysis	175
Male babies	110
Female babies	65

Table 2: Time of onset of convulsion

Time	No	%
Birth to 3 days	151	86.3
Three to 7 days	18	10.3
Seven to 28 days	06	3.4

Table 3: Causes of convulsion

Causes	No	%
HIE stage II	133	76.0
Metabolic disturbance		
Hypoglyceamia	11	6.2
Hypocalcaemia	9	5.1
Infection		
Septicaemia	9	5.1
Viral Encephalitis	4	2.4
Intraventricular haemorrhage (IVH)	4	2.4
Undetermined	5	2.8
Total	**175**	**100.0**

Table 4: Types of convulsions

Type	No	%
Clonic	114	65.1
Subtle	45	25.9
Tonic	12	7.0
Myoclonic	4	2.0
Total	175	100.0

Table 5: Neurodevelopment outcomes

Predictor (No)	CP	Global Delay	Epilepsy	Blindness	Deafness
HIE stage II (133)	88	13	29	1	2
Hypoglyceamia (11)	2	9	-	-	-
Hypocalcaemia (9)	6	2	1	-	-
Septicaemia (9)	6	3	-	-	-
Viral encephalitis (4)	-	2	1	1	1
IVH (4)	-	2	1	-	-
Undetermined (5)	2	2	1	-	-

Discussion: Neonatal seizures are the most common and distinctive clinical manifestations of neurological dysfunction in the newborn infant. Despite increasingly sophisticated neonatal intensive care Pediatricians managing seizures face challenges to control convulsion in neonates. Death rate in acute stage is also high. In this study 5% newborn term babies died during acute stage of convulsion. The death rate in term babies have been stated as 7-30% in neonatal convulsion in several studies in abroad[19,20,21]. The death rate has been shown as 24% in Bangladesh in another study[22]. The lower rate of death in this study may be due to the fact that over the last several years neonatal care in our country has been improved due to many programmes implemented by Govt. as well as in private sector. The health care seeking behavoiur of parents has also been changed and treatment facilities has been increased in health care giving centers[23].

There are various causes of seizures in neonates but a few causes are frequently encountered. HIE stage-II is the most common cause of seizure in neonates[24]. Antenatal care (ANC) has long been considered a critical component of the continuum of care of women during pregnancy and survival and thriving of women and newborn. Bangladesh has made impressive gains in reducing maternal and neonatal mortality over the past several decades. But ANC of pregnant mothers' lags behind standard guidelines[25,26]. WHO has recommended at least 4+ ANC from conception to child birth but till now only 37% pregnant women attend at least four ANC contacts and 47% of births occur in health care facilities[27,28]. Moreover, the content of ANC is not adequate and in- depth picture of pregnant women is not complete[29,30]. These lead to unfavorable fetal outcome with HIE in most cases. A hospital-based study conducted in Bangladesh has also shown HIE as the most common (48%) cause of neonatal seizure[31]. Mizrahi had similar observation and found HIE as the highest (46%) cause of convulsion in his study[32]. A few previous studies have shown these unfavorable prenatal and perinatal determinants leading to HIE as the principal cause of convulsion[33,34,35].

In this study 86.3% neonates had convulsion within the first 3 days after birth. Another hospital-based study has shown that convulsion in the neonates occur most commonly (77%) within the first 3 days of life. This result support our finding[22]. Another study has shown that 84% neonates had convulsion in first 3 days in their samples[7].

The gold standard method of diagnosis of convulsion is continuous EEG recording. This was not available in our setting. Instead, usual portable EEG machine was used to detect electrographic seizure in our samples. In both of these procedures, there is chance of getting false negative reports because the surface electrodes may not detect the deep-seated foci of convulsion in neonatal brain. Moreover, the effect of sedatives used to control convulsion may also affect EEG recording[36,37]. So, seizures were diagnosed by observation in our samples considering any unusual repetitive and stereotyped movement as recommended by another author[38]. Most of the neonates (65.1%) in our samples had clonic convulsion. Clonic convulsion primarily occurs in term babies and the finding in the present study is almost like previous study where 54% term neonates had clonic type of convulsion[7]. The second common type of convulsion was subtle convulsion. Subtle convulsion usually occurs in preterm babies[39,40]. The lower rate of subtle convulsion is due to samples characteristics as our samples were term babies. Tonic convulsion was only

12% in this study. This low prevalence may be due to the fact that the samples in this study were term babies whereas tonic convulsion mainly occurs in preterm babies[41].

Among the 175 samples suffering from convulsion in neonatal period 133 (76%) babies were admitted with HIE stage-II. Among these 133 samples 88 (66.2%) developed CP in the postnatal period. The other disabilities following HIE were epilepsy in 29 (21.8%) children, global delay in 13 (9.9%) children, blindness in 1 (0.75%) child and deafness in 2 (1.5%) children. There is a spatial relationship between HIE and CP. CP was originally described as a sequel of HIE. CP is the most frequent motor disability following HIE. One previous study has stated that 41% samples suffering from neonatal seizure developed CP in post neonatal period[7]. Another study has described that among term babies suffering from seizure in neonatal period, 31% manifested as CP[41]. Two other studies have also shown that CP is the frequent postnatal sequel of HIE[42,43].

The second frequent morbidity was epilepsy. The aforementioned study has also described that among term babies suffering from seizure in neonatal period 32% manifested as epilepsy[41]. A recent literature review demonstrated that around 18% of newborn suffering from neonatal seizures developed post-neonatal epilepsy[44]. Another two previous studies have demonstrated 33% and 48% prevalence of epilepsy respectively in term babies having neonatal seizures[45,46]. The next morbidity was global developmental delay. Several studies have shown that neonatal seizures are associated with development of various neurological and cognitive impairments in postnatal life[47-50]. These studies have stated that HIE is the principal predictor of abnormal neurodevelopmental impairments. There is hypoxic injury of the brain in HIE. Seizures in hypoxic brain increases extra risk for global developmental delay. One of these previous studies has shown that among term babies suffering from seizure in neonatal period 43% manifested global developmental delay[41]. Tegul and co-workers have described that 68% term babies in their study had global developmental delay suffering from convulsion in neonatal period[7]. Nunes and co-workers have described that 35% term babies in their study developed global developmental delay suffering from convulsion in neonatal period[19].

There was low prevalence of visual and hearing defects in our samples. The low prevalence in this study may be due to the fact that the visual defect especially ROP and sensory neural hearing loss usually occurs in preterm babies. A survey conducted in Bangladesh has shown that as many as 31% preterm babies developed ROP[51]. There is only one study where 8% term neonates had visual defect after convulsion[7]. Similarly, a screening database on preterm babies in Poland has shown that sensory hearing loss was present in 0.1% to 11.0% cases and hearing loss was proportional to the degree of prematurity[52].

Conclusion: Many newborn babies develop seizure in neonatal period. Neonatal seizures have different aetiologies; among them HIE is the predominant cause of admission in NICU. These babies are at risk of developing various adverse neurodevelopmental outcomes. There were a few limitations of this study. Therapeutic hypothermia was not applied, which would have possibility to change rate of neurological outcomes. MRI could delineate the brain

structures in a better way that would be helpful to detect more definite causes. Continuous video EEG was not used to detect electrographic seizures.

Acknowledgement: The author expresses his gratefulness to all physicians and nursing staffs of NICU of RMCH and Developmental Therapist of DRC for their continuous support and devotion to continue this study and making this manuscript for publication.

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