

Neonatal Risk Factor for Seizures in Term Neonate: A Hospital - Based Case Control Study

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Abstract: *Objective:* Assessing the neonatal risk factors for seizure in first 72 hours of life in term neonate.

Design: Case control study.

Setting: Department of Paediatrics, Neonatology unit tertiary care centre Govt. Medical College, Nagpur.

Method: A 210 cases *i.e.* term neonate with seizure within first 72 hours of life and 210 controls *i.e.* term neonate without seizure in first 72 hours of life were randomly selected as study subject over a period of two year. Seizures were defined as per standard definition. Data were collected regarding age of onset of seizure, birth weight, Apgar score at 1 minute and 5 minute, type of delivery. Appropriate investigation was done and neonates were followed up till discharge or death

Results: In 73% neonate's subtle seizure was most common and occurs within 48-72 hours of life. Neonates with low birth weight had 0.22 times more risk of seizure than normal weight. Birth asphyxia was most significant risk factor for seizure and had 4.66 times more risk of seizure ($P < 0.001$). Presence of low Apgar score at 1 minute and 5 minute are found to be significant in univariate analysis but in multiple logistic regression analysis it is found that 5 minute Apgar score is more significant than 1 minute. Low Apgar score at 5 minute had 1.29 times more risk of seizure. In study population 7.1% neonates died in case group compared to 1.4% in control group which was statistically highly significant (OR 3.98, 95% CI 1.23-16.7, $P < 0.0095$) and most common cause of death was severe birth asphyxia and sepsis.

Conclusion: Early identification and timely intervention of neonatal risk factor may reduces the seizure in term neonate.

Keywords: Apgar score, Birth asphyxia, Low birth weight, Neonatal seizure, Term neonate.

INTRODUCTION

Even with improved perinatal care, seizures are the most common neurological neonatal emergency. The exact incidence of neonatal seizure is unknown as many of the clinical manifestations are subtle which often escape detection and all seizure activities shown in electroencephalography cannot be detected clinically. The estimated incidence of neonatal seizures is 1-3.5 per 1000 live births and highest within first 72 hours of life [1-3]. The most prevalent known cause of neonatal seizure is hypoxic ischemic encephalopathy which has been reported approximately 1-2 per 1000 live births [4]. Other etiologies includes septicemia with or without CNS infections, transient metabolic disorders, intracranial hemorrhages, cerebral malformations, inborn errors of metabolism, kernicterus, pyridoxine dependency, maternal narcotic withdrawal, drug toxicities [5]. Early and accurate detection of seizure and its etiology is important for guiding specific therapy and to determine prognosis. Despite its clinical significance and incidence, there are number of problems in diagnosis and management [6].

Several neonatal risk factors like birth weight, gender, birth asphyxia, apgar score, place of birth and

mode of delivery are important regarding predictors of seizure in term neonate. The aim of present study is to assess the neonatal risk factors associated with seizures in first 72 hours of life in term neonate.

MATERIAL AND METHODS

A hospital based case control study was carried out in the Government Medical College, tertiary care & referral hospital that provide care to underprivileged, socioeconomically deprived population of central India from September 2011 to August 2013. Sample size was estimated assuming proportion of neonatal seizure in neonate born to mothers with cesarean section 29% and 14% in case and control group respectively with power of 90% and alpha error of 5%. The study population comprised of 210 cases (Term neonate with seizures within first 72 hours of life) and 210 controls (Term neonate without seizure in first 72 hours of life) were included after getting ethical clearance from institutional ethical committee and informed consent from parent.

Seizure were defined as involuntary muscle contractions, abnormal tonic extension or jerky movements of any part of limb, face or mouth that was not stimulus sensitive or repetitive abnormal chewing, ocular or pedaling movements so that seizure mimics like jitteriness/tremors and benign sleep myoclonus can be excluded. Jitteriness/tremors was defined as

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involuntary movements of equal amplitude and faster equiphasic rhythm and benign sleep myoclonus as involuntary movement abolished by arousal, stimulus sensitive never occur in wakefulness and with normal neurological examination [7, 8]. We classify seizure into subtle, clonic, tonic and myoclonic as per Volpe classification [9]. The controls were randomly selected from a pool, which included those born at same hospital.

Birth asphyxia was defined as neurological dysfunction with Apgar score less than or equal to 6 at 5min or later or evidence of fetal or perinatal hypoxia or distress or suggestive laboratory investigation (arterial PH <7 from cord blood or immediately after birth+endorgan dysfunction [10].

A pretested, semi structural questionnaire was used which comprising of detail clinical history of maternal and perinatal risk factors and clinical examination. Data were collected regarding age of onset of seizure, type of delivery, birth weight, Apgar score at 1 minute and 5 minute, need for and type of resuscitation. Relevant investigations were carried out and neonates were followed up till discharge or death.

STATISTICAL ANALYSIS

Statistical software STATA version 10.0 was used for statistical analysis. Continuous variable were compared between cases and controls by performing unpaired 't' test. Categorical variable were compared by performing chi square test. Significant risk factor for neonatal seizure was identified by univariate analysis on the basis of odd's ratio and 95% confidence interval. A multiple logistic regression analysis was performed to evaluate the independent effect of risk factor on neonatal seizure. P<0.05 was considered as statistical significant.

RESULTS

In present study, age and gender distribution does not show statistical significant difference while mean birth weight, Apgar score at 1minute and 5minute were significantly differ in case and control group. The demographic data of seizure cases and controls are presented in Table 1

In case group 57.6% neonates develops seizure within 48-72 hours compared to 26.7% in 24-48 hours

Table 1: Characteristic of Cases & Control (n, %)

Characteristic	Cases n=210	Control n=210	P value
Neonatal			
Age in hours (Mean ± SD)	23.90 ± 15.28	23.57 ± 15.18	0.8244
<24	130(61.9)	126(60.0)	
24-48	63(30.0)	66(31.42)	
48-72	17(8.1)	18(8.58)	
Gender (n,%) male	118(56.2)	107(50.9)	0.258
Birth weight (gms) (Mean ± SD)	2220 ± 460	2450 ± 430	<0.0001
<1500	2(0.9)	0(0)	
1500-1999	56(26.7)	31(14.8)	
2000-2499	121(57.6)	145(69.0)	
2500-3499	25(11.9)	28(13.3)	
>3500	6(2.9)	6(2.9)	
Apgar score at 1min (Mean ± SD)	7.17 ± 1.77	8.10 ± 1.49	<0.0001
3-6	47(20.5)	20(9.5)	
7-9	163(79.5)	190(90.5)	
Apgar score at 5min (Mean ± SD)	7.80 ± 1.73	8.17 ± 1.33	0.0140
3-6	40(19.0)	26(12.4)	
7-9	170(81)	184(87.6)	
Mode of delivery			
Cesarean	115(54.8)	71(33.8)	<0.00001
Normal	95(45.2)	139(66.2)	
Parity			
Primiparous	141(67.1)	139(66.2)	0.939
Para 2	17(8.1)	19(9.0)	
Para>/3	52(24.8)	52(24.8)	

and 15.7% in first 24 hours suggested risk of seizure is increases as age advances ($P=0.00000$). Subtle type of seizure was observed in 73% cases followed by clonic (16%), tonic (10%) and myoclonic (1%).

Neonates with low birth weight had 0.22 times more risk for seizures than normal weight neonates while neonates with low Apgar score at 5 min had 1.29 times more risk of seizure than neonates normal apgar score ($P<0.003$). Birth asphyxia is found to be highly significant in this study. Neonates with birth asphyxia had 4.66 times more risk of seizure with P value <0.001 . Neonates born to mother with cesarean delivery had 2.18 times more risk for seizure than normal vaginally delivered. (Table 2)

Table 2: Predictors of Neonatal Seizure in Term Neonate (From Multiple Logistic Regression)

Predictor	OR	95% C I	P value
Birth weight	0.22	0.12-0.38	<0.0001
Apgar score at 5min	1.29	1.09-1.54	0.003
Birth Asphyxia	4.66	2.44-8.90	<0.001
Cesarean Delivery	2.18	1.40-3.38	0.001

In study population 7.1% neonates died in case group compared to 1.4% in control group which was statistically highly significant (OR 3.98, 95% CI 1.23-16.7, $P<0.0095$). In case group, total 15 neonates expired, out of which 6 due to severe birth asphyxia, 4 neonates expired due to neonatal sepsis, 3 because of neonatal meningitis and 2 had developed intraventricular hemorrhage. In controls, 2 neonates expired due to severe birth asphyxia and one because of sepsis. Neonates with seizure had 3.98 times more risk of mortality than control.

DISCUSSION

Neonatal seizure can exert a range of adverse effect on brain development. The disruption of process such as cell division, myelination and stabilization of synapse during seizure activity in the neonate interferes with normal brain maturation. Altered neuronal connectivity might account for increased susceptibility of the developing brain to suffer subsequent seizure induce injury during adolescence or early adulthood. The elucidation of modifiable maternal risk factor for neonatal seizure might facilitate early diagnosis, treatment and possible prevention of neonatal seizure and their long term adverse sequelae [11].

Present study reveals that birth weight is a significant risk factor for seizures. Most of the seizures that developed in neonates with birth weight of 2000 to 2499 gms and <2000 gms had 95% CI between 0.12-0.38 with P value <0.0001 . Neonates with low birth weight had 0.22 times more risk of seizures than normal weight neonates. Similar observation of two times more risk of seizure were recorded by Rima saliba *et al.* [12], Sahana G [13], Mary Jo Lanska *et al.* [4], Ara R and Uddin MN *et al.* [14], F. Kuti BP *et al.* [15], Rajput UC and Deshmukh LS [16].

The mechanism of birth asphyxia in term neonate is usually partial or prolonged hypoxia and it is clinically evaluated by perinatal history, apgar score, multi-system impairment and neurological examination. Neonates with birth asphyxia were found to have 4.66 times more risk for seizure as compared with control. This findings are similar with study done by Manoel RR Holando *et al.* [17] suggested that hypoxic ischemic encephalopathy was one of the major risk factor for seizure in term neonates in first 48 hours of life. Our finding is an agreement with the data reported by Shah FU *et al.* [18] who correlate time of neonatal seizures onset and underlying neurological lesions. Malik AR *et al.* [19] also concluded the neonatal seizures were predominantly caused by hypoxic ischemic encephalopathy and independent of gestational age.

Presence of low Apgar score at 1 minute and 5 minute are found to be significant in univariate analysis but in multiple logistic regression analysis it is found that 5 minute apgar score is more significant than 1 minute. A 5 minute Apgar score was a significant risk factor for neonatal seizure that can be attributed to significant asphyxia in neonate who didn't respond to resuscitation at delivery room. Neonates with low apgar score at 5 minute had 1.29 times more risk of seizure. Volpe suggested that the parameter of asphyxia based on apgar score has greater predictive value for the neurological outcome rather than for seizures. Study done by Manoel RR Holando *et al* revealed that low apgar score at 1 minute was a significant risk factor compared to 5 minute Apgar score in preterm neonates.

In our study, risk of neonatal seizure was found to be 2.37 times more with cesarean delivered neonate than normal vaginally delivered. Similar high risks of neonatal seizures with cesarean delivered neonates were reported by Deborah *et al.* [20], Rima M Salibha *et al*, and Manoel RR Holanda *et al.* Our study did not identify common indication for cesarean section such

as failure to progress in labor, previous cesarean section or fetal malpresentation and fetal distress because such factor could have been surrogate for perinatal hypoxia in the newborn. Therefore it could not be stated that cesarean section per se places the neonate at risk for seizure. Additional studies stratifying cesarean section deliveries by indication might be needed to better understand the mechanism underlying the risk of neonatal seizure associated with cesarean section and to more carefully discern whether this risk is truly independent of fetal distress

In our study, majority (57.6%) neonates developed seizure between 48-72 hours and subtle seizure was most common followed by clonic, tonic and myoclonic. However study done by Rima Saliba *et al.* reported 46% of seizures in term small for gestational age neonate within 48 hours of life and McIntire *et al.* [21] & Minchom *et al.* (7) reported two fold increases the incidence of seizure in first 24 hours of life in term small for gestational age neonates.

Mortality in present study is statistically more significant in case group compared to control. The common cause of mortality was severe birth asphyxia and sepsis. Similar types of mortality pattern were reported by Anand *et al.* [22]. It is indicated that early recognition of perinatal hypoxia and sepsis by effective antenatal care and timely resuscitation improve the mortality and long term adverse neurological outcome in term neonate.

CONCLUSION

Our study concludes neonates with low birth weight had more risk of seizure than normal weight. Birth asphyxia was most significant risk factor for seizure and had 4.66 times more risk of seizure. Presence of low Apgar score at 1 minute and 5 minute are found to be significant in univariate analysis but in multiple logistic regression analysis it is found that 5 minute Apgar score is more significant than 1 minute. Low Apgar score at 5 minute had 1.29 times more risk of seizure. Study also concludes mortality was significantly high in neonates with seizure and severe birth asphyxia and sepsis were commonest cause of mortality. So early identification of perinatal hypoxia and timely neonatal resuscitation improve the mortality and long term adverse neurological outcome in neonatal seizure.

STRENGTH OF STUDY

Case control study and adequate sample.

LIMITATION OF STUDY

Unavailability of resources for diagnosis of seizure like video assisted EEG for diagnosis of seizure.

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