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Original Research Article

A prospective study to determine etiology, clinical profile and neurodevelopmental outcome of neonatal seizures admitted in newborn unit of Chengalpattu Medical College and Hospital, Tamil Nadu, India

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ABSTRACT

Background: Newborn with neonatal seizures is at risk of neurodevelopmental delay. The aim of this study was to determine the factors affecting the adverse outcome of neonatal seizures and to study the significant factors associated with poor neurodevelopmental outcome in neonatal seizures.
Methods: This was a prospective study done at neonatal intensive care unit (NICU) in Chengalpattu Medical College during the period from June 2017 to September 2018. A total of 110 neonates with seizures admitted in NICU from first hour of life to 28 days of age were included in the study. Detailed history was collected in preformed proforma, and followed up to one year and neurological assessment done at 4th month, 8th month and 1 year. The Hammersmith infant neurological examination (HINE) was done at 4 and 8 month and the Bayley–III assessment was done at 1 year of age to determine the neurodevelopment outcome.
Results: Out of 110 newborns with seizures, 86 cases were followed up to 1 year of age. Neurological assessment done by HINE determined abnormal neurodevelopment in 33.6% neonates. Bayley-III scale assessment found cognitive delay in 10.9%, language delay in 20%, motor delay in 5.55%, socio-emotional delay in 30%, and adoptive delay in 31.8% cases. Delayed developmental outcome is significantly associated with onset of seizures, frequency of seizure, poor 5 minute Apgar score, abnormal EEG, and hypoxic ischemic encephalopathy (HIE).
Conclusions: The delayed developmental outcome high among the neonates with subtle and myoclonic seizures. Mortality and neurological impairment was after neonatal seizure is associated with Onset and frequency of seizures, low Apgar score at 5 min, findings of USG cranium, CT brain, EEG, and HIE.

Keywords: Bayley-III scale, Hammersmith infant neurological examination scale, Neonatal seizures, Neurodevelopmental outcome

INTRODUCTION

Neonatal seizures occur more frequently in the neonatal period than at any other time of life. Estimates of the incidence of neonatal seizures vary according case definition, method of ascertainment and definition of neonatal seizures, range from 1.5 to 3.0 per 1000 live births.[1,2] The occurrence of neonatal seizures may be the first clinical indication of neurological disorder. Developmental immaturity influences many aspects of diagnosis, management, and prognosis of seizures in newborn.[3] The most common causes of seizures as per the recently published studies from the country are hypoxic ischemic encephalopathy, metabolic disturbances

(hypoglycaemia and hypocalcemia) and meningitis.[4,5] Other factors reported with adverse outcome are type and onset of seizures, status epilepticus, gestational age, Apgar score, birth weight, need for resuscitation, neurological examination at onset of seizure, electroencephalogram (EEG) and radiological findings (USG and CT).[6] Etiology could, however, vary between different centres depending upon the patient population (term versus preterm), level of monitoring (only clinical versus electrical and clinical seizures), etc.

The purpose of the present study was to determine the etiology, clinical profile of neonatal seizures in the study population and to assess their association with the adverse outcome and to evaluate the significant factors associated with poor neurodevelopmental outcome in neonatal seizures by using Hammersmith infant neurological examination (HINE) and Bayley scales.

METHODS

This was a prospective study conducted in neonatal intensive care unit (NICU) in Chengalpattu Medical College during the period from June 2017 to September 2018.

Inclusion criteria

- After getting approval from institutional ethics committee and informed consent form the parents a total of 110 neonates with seizures admitted in NICU from first hour of life to 28 days of age were included in the study.

Exclusion criteria

- Neonates of parents who refused to give consent were excluded from the study.

A predesigned proforma was used in the study to evaluate detailed demographic data, etiology, clinical history, antenatal and maternal risk factors. Data were collected regarding time of onset of seizure, type, duration and frequency of seizure, neurological examination at the onset of the seizure. Maternal and perinatal history including gestational age, type of delivery, birth weight, Apgar score at 1 and 5 min and need for and type of resuscitation at the time of birth were recorded. Detailed clinical examination was done and whenever required investigations like total blood count, CRP, RFT, electrolytes, LFT, serum Calcium, blood sugar level, blood culture, CSF study, screening for inborn error of metabolism, ultrasound cranium, and CT scan of brain was done. EEG was done to all the cases during the discharge time or during the follow up time.

At the time of discharge neurological examination was done by using Hammersmith infant neurological examination (HINE) for term babies and for preterm babies HINE was done at 40 weeks of postmenstrual age.[7] Then at every follow up of 4th month, 8th month and 1 year were done. HINE has three sections of examination i.e. 1. Neurological items; postures, cranial nerve function, reflexes, tone, movements. 2. Development of motor function; head control, sitting, crawling, rolling, grasping, walking. 3. State of behaviour; consciousness, social orientation, emotional state. HINE is clinical tool, it has 26 neurological items. Each item scores separately from 0 to 3, maximum score is 78. The individual score can be added to achieve a global score. It can range from a minimum of 0 to maximum of 78. The optimal score at 3rd month of age is 67, at 6th month is 70 and at 12th month is 73. Any value below this optimal global score is taken as abnormal HINE.

Neurological development skills were assessed by Bayley scale IIIrd edition during the follow up period of one year.[8] Bayley scale assesses infant and toddler development across 5 domains; cognitive, language, motor, social-emotional, and adoptive behaviour. The qualitative description of composite scoring includes very superior (130 and above), superior (120-129), high average (110-119), low average (90-109), borderline (70-79), and extremely low (69 and below).

Statistical analysis

Data was entered in excel spread sheet and analyzed by SPSS software version 20. The continuous data were expressed by means of mean±standard deviation and ordinal variables by median and range. Frequencies and proportions were also calculated. Appropriate test like t test, chi square test were used to determine significant association between various study variables and the outcome. Significant association was considered with p value <0.05. Variables that showed significance in univariate analysis ($p<0.05$) were further subjected to multivariate logistic regression analysis to determine the significant independent association of the variables and the outcome of the study.

RESULTS

This study included 110 neonates with seizures, out of 110 cases 11 cases lost follow up during study period and 13 cases died due to complications. Finally, 86 cases followed up to one year.

In 110 cases, 65.5% (n=72) neonates with seizures were male and 34.5% (n=38) were female. Out of which 90 cases were term and 20 were preterm.

Among which 81 cases were inborn, which contributes about 73.6%, 28 were out born that was about 25.5% hospital delivery and 1 (0.9%) case was home delivery with body weight of 0.9kg. Majority of the babies (54.5%) cases had normal weight, whereas 12.7% had a low birth weight (1-1.5kg).

Table 1: Demographic characteristics of study population.

Variables	Number (n=110)	Percentage
Sex		
Male	72	65.5
Female	38	34.5
Gestational age		
Term	90	81.8
Preterm	20	18.2
Delivery place		
In born	81	73.6
Out born	28	25.5
Home delivery	1	0.9
Birth weight (in kg)		
1-1.49	14	12.7
1.5-2.49	35	31.8
2.5-3.49	57	51.8
3.5-4	3	2.7
>4	1	0.9

Clinical characteristics of the neonates were presented in Table 2. In present study subtle 44.5% (n=49) and myoclonic seizures 44.5% (n=49) were most common seizures followed by tonic and clonic seizures (10% and 0.9%) respectively. About 49 cases had seizures within 24 hours of their life. Whereas 29.1% (n=32) had seizures between 24 to 72 hours of life and remaining cases had seizures after 72 hour of life. Single episode of seizures was observed in about 65 cases (59.1%), and 40.9% (n=45) had multiple episodes of seizures. Foetal distress was observed in 39 cases. Out of 110, 62 cases required resuscitation. 1 minute Apgar score below 3 was noticed in 62 cases (56.4%) and at 5 minute Apgar score about 26.4% (n=29) neonates had score less than 6.

USG of cranium was done in all cases. Out of 110 cases, 51 cases had abnormal pathological findings like cerebral edema or increased bilateral hyperechogenicity or both findings. About 6 cases had hydrocephalus, one had intracranial hemorrhage.

Neuroimaging i.e. CT brain was done in 49 cases. Among them 14 cases had abnormal findings within them 6 cases had hydrocephalus with dilated ventricles. EEG had been done to which ever cases required during postnatal period. EEG done for 68 cases, among them 12% (n=14) cases had abnormal EEG.

In this study most common etiological factor that contributes neonatal seizures was HIE (48.2%), followed by different forms of metabolic abnormalities. Within metabolic abnormalities, 16 cases had hypoglycemia, 10 had hypocalcemia, one had hypokalemia 0.9%, hyperkalemia and hypernatremia in each 3 cases respectively (Figure 1). Other etiologies like unknown cause contributes to 17.3% (n=19), meningitis 7.3% (n=8), and intracranial hemorrhage 1.8% (n=2) (Table 3).

Table 2: Distribution of different variables of study population.

Variables	Number (n=110)	Percentage
Type of seizures		
Subtle	49	44.5
Tonic	11	10.0
Clonic	1	0.9
Myoclonic	49	44.5
Onset of seizures (in hours)		
<24	49	44.5
24-72	32	29.1
>72	29	26.4
Frequency of seizures		
Single	65	59.1
Multiple	45	40.9
Fetal distress		
Yes	39	35.5
No	71	64.5
Apgar score at 1 min		
<3	62	56.4
≥6	48	43.6
Apgar score at 5 min		
<6	29	26.4
≥6	81	73.6
Resuscitation required		
Yes	62	56.4
No	48	43.6
EEG		
Normal	54	49.1
Abnormal	14	12.7
Not done	42	38.2
USG cranium		
Normal	52	47.3
Other pathological findings	51	46.4
Intracranial hemorrhage	1	.9
Hydrocephalus with dilated ventricles	6	5.5
CT brain		
Not done	61	55.5
Normal	35	31.8
Abnormal	8	7.3
Hydrocephalus with dilated ventricles	6	5.5

At the time of discharge, 62 cases were normal, 32 cases had hypertonia with brisk reflex and 3 cases had hypotonia. Mortality was noted in 13 cases. Table 5 summarizes the association of variables with outcome of the study. Significant association was seen ($p<0.001$) between the parameters frequency of seizures, Apgar score at 5 min, need for resuscitation, EEG, USG findings and associated etiology with the outcome. About 59.1% cases had single episodes of seizures. Among them 21.5% had tone abnormalities with no mortality.

Table 3: Distribution of cases according to etiology.

Etiology	Number (n=110)	Percentage
HIE	53	48.2
Metabolic abnormalities	18	16.4
Intracranial hemorrhage	2	1.8
Meningitis	8	7.3
Sepsis with metabolic abnormalities	7	6.4
Unknown causes	19	17.3
HIE with metabolic abnormalities	3	2.7

Whereas 40.9% cases had multiple episodes of seizures, among them 46.6% had tone abnormalities with 28.9% mortality.

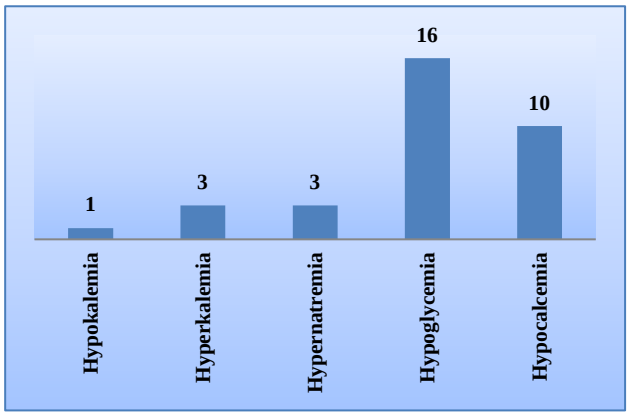

Figure 1: Distribution of metabolic abnormalities among study population.

Risk factors like fetal distress was noticed in 39 cases, among them 41% had tone abnormalities and with mortality rate of 20.5%.

Out of 110 cases, 26.4% (n=29) cases had APGAR score of less ≤6 at 5 minute. Among them 58.6% had tone abnormalities and mortality was observed in 34.5% cases.

Table 4: Condition of the neonates at the time of discharge.

Condition at the time of discharge	Number (n=110)	Percentage
Normal	62	56.4
Hypertonia with brisk reflex	32	29.1
Hypotonia	3	2.7
Death	13	11.8

Out of 51 cases, tone abnormalities was noted in 23 cases related with various pathologies under abnormal USG findings of cranium and 10 cases died while on treatment in NICU.

CT brain was done in about 49 cases, in that 12.8% cases had abnormal study. Among them, 12 cases had tone abnormalities.

Abnormal EEG was found in 14 cases, among these 11 cases had tone abnormalities and 1 case died.

Among etiologies, HIE had most common neurological abnormalities (n=53) cases.

Among them 27 cases had tone abnormalities compared to other etiologies and 17% had mortality.

Neurological assessment had been done by HINE. All the cases were followed up at 4th month, 8th month and at 1 year.

During these follow up periods abnormality in the assessment was noticed in 40.9%, 36.4% and 33.6% cases respectively.

At one year of age to Bayley-III assessment was done to all 86 cases.

With Bayley-III assessment composite score <70 i.e. extremely low was taken as developmental delay in all domain.

Authors found cognitive developmental delay in 10.9% cases, language delay in 20%, motor delay in 5.5%, socio-emotional delay in 30% (n=33) had, and adoptive behavior delay in 31.8% cases.

Etiological association with neurological outcome was given in Table 8.

The common etiological factor associated with developmental delay was HIE followed by unknown etiologies and metabolic abnormalities.

Relation of risk factors with neurological developmental delay was summarized in Table 9.

Onset and frequency of seizures, Apgar score at 5 min, findings of USG cranium, CT brain, EEG, and HIE was found to have significant association ($p<0.05$) with neurological developmental delay at 1 years of age in study population.

Table 5: Association of different variables with outcome of the study.

Variables		Normal N (%)	Hypertonia with brisk reflex N (%)	Hypotonia N (%)	Death N (%)	Total N (%)	P value N (%)
Birth weight	1-1.49	7 (50)	5 (35.7)	1 (7.1)	1 (7.1)	14 (100)	0.43
	1.5-2.49	19 (54.3)	10 (28.6)	1 (2.9)	5 (14.3)	35 (100)	
	2.5-3.49	34 (59.6)	17 (29.8)	1 (1.8)	5 (8.8)	57 (100)	
	3.5-4	1 (33.3)	0 (0)	0 (0)	2 (66.7)	3 (100)	
	>4	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)	
Seizures	Subtle	23 (46.9)	17 (34.7)	1 (2.0)	8 (16.3)	49 (100)	0.176
	Tonic	4 (36.4)	5 (45.5)	0 (0)	2 (18.2)	11 (100)	
	Clonic	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	
	Myoclonic	35 (71.4)	9 (18.4)	2 (4.1)	3 (6.1)	49 (100)	
Onset of seizures	<24	21 (42.9)	20 (40.8)	0 (0)	8 (16.3)	49 (100)	0.013
	24-72	22 (68.8)	4 (12.5)	1 (3.5)	5 (61.5)	32 (100)	
	>72	19 (65.5)	8 (27.6)	2 (6.9)	0 (0)	29 (100)	
Frequency of seizures	Single	51 (78.5)	13 (20)	1 (1.5)	0 (0)	65 (100)	0.001
	Multiple	11 (24.4)	19 (42.2)	2 (4.4)	13 (28.9)	45 (100)	
Gestational age	Term	10 (50)	5 (25)	1 (5)	4 (20)	20	0.539
	Preterm	52 (57.8)	27 (30)	2 (2.2)	9 (10)	90	
Fetal distress	Yes	15 (38.5)	16 (41)	0 (0)	8 (20.5)	39 (100)	0.008
	No	47 (66.2)	16 (22.5)	3 (4.2)	5 (7)	71 (100)	
Apgar score at 5 min	≤6	2 (6.9)	17 (58.6)	0 (0)	10 (34.5)	29 (100)	0.001
	>6	60 (74.1)	15 (18.5)	3 (3.7)	3 (3.7)	81	
Resuscitation required	Yes	24 (38.7)	27 (43.5)	1 (1.6)	10 (16.1)	62	0.001
	No	38 (79.2)	5 (10.4)	2 (4.2)	3 (6.3)	48	
EEG	Normal	26 (61.9)	7 (16.7)	0 (0)	9 (21.4)	42	0.001
	Abnormal	34 (63)	16 (29.6)	1 (1.9)	3 (5.6)	54	
	Not done	2 (14.3)	9 (64.3)	2 (14.3)	1 (7.1)	14	
USG cranium	Normal	44 (84.6)	5 (9.6)	2 (3.8)	1 (1.9)	52	0.001
	Other pathological findings	18 (35.3)	22 (43.1)	1 (2.0)	10 (19.6)	51	
	Intracranial hemorrhage	0 (0)	1 (100)	0 (0)	0 (0)	1	
	Hydrocephalus with dilated ventricles	0 (0)	4 (66.7)	0 (0)	2 (33.3)	6	
CT brain	Not done	36 (59)	14 (23)	0 (0)	11 (18)	61 (100)	0.001
	Normal	25 (71.4)	6 (17.1)	3 (8.6)	1 (2.9)	35 (100)	
	Abnormal	1 (12.5)	7 (87.5)	0 (0)	0 (0)	8 (100)	
	Hydrocephalus with dilated ventricles	0 (0)	5 (83.3)	0 (0)	1 (16.7)	6 (100)	
Etiology	HIE	17 (32.1)	27 (50.9)	0 (0)	9 (17)	53	0.001
	Metabolic abnormalities	17 (94.4)	0 (0)	1 (5.6)	0 (0)	18	
	Intracranial hemorrhage	0 (0)	2 (100)	0 (0)	0 (0)	18	
	Meningitis	3 (37.5)	3 (37.5)	0 (0)	2 (25)	8	
	Sepsis with metabolic abnormalities	5 (71.4)	0 (0)	1 (14.3)	1 (14.3)	7	
	Unknown cause	19 (100)	0 (0)	0 (0)	0 (0)	19 (100)	
	HIE with metabolic abnormalities	1 (33.3)	0 (0)	1 (33.3)	1 (33.3)	33	

Table 6: HINE at different time periods of follow up in study population (n=110).

Assessment variables	Assessment at different periods		
	4th month N (%)	8th month N (%)	At one year N (%)
Not done	13 (11.8)	13 (11.8)	13 (11.8)
Normal	47 (42.7)	46 (41.8)	49 (44.5)
Abnormal	45 (40.9)	40 (36.4)	37 (33.6)
Lost follow up	5 (4.5)	11 (10)	11 (10)

Table 7: Neurological assessment by Bayley (composite score equivalents) in study population (n=110).

Assessment variables	Cognitive assessment N (%)	Language assessment N (%)	Motor assessment N (%)	Social-emotional assessment N (%)	Adaptive behavior assessment N (%)
Lost follow up	11 (10)	11 (10)	11 (10)	11 (10)	11 (10)
Average	20 (18.2)	21 (19.1)	30 (27.3)	12 (10.9)	10 (9.1)
Low average	24 (21.8)	16 (14.5)	18 (16.4)	21 (19.1)	18 (16.4)
Borderline	30 (27.3)	27 (24.5)	32 (29.1)	20 (18.2)	23 (20.9)
Extremely low	12 (10.9)	22 (20)	6 (5.5)	33 (30)	35 (31.8)
Not done	13 (11.8)	13 (11.8)	13 (11.8)	13 (11.8)	13 (11.8)

Table 8: Association of etiology with neurological outcome of the study.

Etiology	Developmental delay (n=21)	Developmental delay with tone abnormality (n=16)	Death (n=13)	Normal (n=49)	Lost follow up (n=11)	Total (n=110)
HIE	12 (22.6)	10 (18.9)	9 (17)	18 (34)	4 (7.5)	53 (100)
Metabolic abnormalities	3 (16.7)	0 (0)	0 (0)	13 (72.2)	2 (11.1)	18 (100)
Intracranial hemorrhage	0 (0)	2 (100)	0 (0)	0 (0)	0 (0)	2 (100)
Meningitis	0 (0)	1 (12.5)	2 (25)	4 (50)	1 (12.5)	8 (100)
Sepsis with metabolic abnormalities	2 (28.6)	0 (0)	1 (14.3)	4 (57.1)	0 (0)	7 (100)
Unknown cause	4 (21.1)	3 (15.8)	0 (0)	10 (52.6)	2 (10.5)	19 (100)
HIE with metabolic abnormalities	0 (0)	0 (0)	1 (33.3)	0 (0)	2 (66.7)	3 (100)

Table 9: Association of risk factors with developmental delay at 1 year of age.

Variables		Yes N (%)	No N (%)	RR	CI 95%	P
Onset of seizures	Yes	27 (55.1)	22 (44.9)	2.17	1.00-4.69	0.04
	No	22 (36.1)	37 (63.1)			
Frequency of seizures	Yes	24 (36.90)	41 (63.1)	0.46	0.21-0.01	0.04
	No	25 (55.6)	20 (44.4)			
Foetal distress	Yes	21 (52.5)	19 (47.5)	1.65	0.75-3.62	0.2
	No	28 (40)	42 (60)			
Apgar score at 5 min	Yes	19 (65.5)	10 (37.5)	3.23	1.32-7.85	0.001
	No	30 (37)	51 (63)			
Resuscitation required	Yes	32 (51.6)	30 (48.4)	1.96	0.89-4.21	0.09
	No	17 (35.4)	31 (64.6)			
Metabolic abnormalities	Yes	6 (37.5)	10 (62.5)	0.71	0.23-2.11	0.5
	No	43 (45.7)	51 (54.3)			
USG cranium	Yes	16 (30.8)	36 (69.2)	0.33	0.15-0.73	0.01
	No	33 (56.9)	25 (43.1)			
CT brain	Yes	39 (40.6)	57 (59.4)	0.27	0.08-0.93	0.03
	No	10 (71.4)	4 (28.60			
EEG	Yes	38 (39.6)	58 (60.4)	0.17	0.04-0.68	0.006
	No	11 (78.6)	3 (21.4)			
HIE	Yes	31 (55.4)	25 (44.6)	2.48	1.14-5.37	0.02
	No	18 (33.3)	36 (66.7)			
Unknown causes	Yes	7 (36.8)	12 (63.2)	0.68	0.24-1.88	0.45
	No	42 (46.2)	49 (53.8)			

DISCUSSION

In present study, seizures most commonly occurred in 81% term babies with male preponderance (65.5%). These findings were similar to the studies of Anand et al.[9] About 54.5% had normal birth weight. Neonates were more affected with subtle and myoclonic seizures (44.5%) within 24hrs of life. However subtle seizures pattern reported more common in some studies like Mizrahi et al and Scher et al.[10,11] HIE was found to be the most associated etiological factor for neonatal seizures in about 48.2% cases. Similar observations were also made by Anand et al.[9]

In the present study, frequency of seizures, foetal distress, Apgar score at 5 min, need for resuscitation, EEG and USG findings, and etiology were found be highly significant with the adverse outcome. These observations were in accordance with previous studies.[6,12,13] Birth weight, type and onset of seizures, Apgar score at 1 min and gestational age were found to be not significant with adverse outcome. Similar findings were reported by Anand et al.[9] In his study mode of delivery, Apgar score at 1min, resuscitation maneuver, seizure type, neurological examination at onset of seizure were found to be no significance with adverse outcome.

In this study, neurological development was assessed by Hammersmith neurological examination (HINE) scale and Bayley (composite score equivalents) scale.[7,8] They were used to assess different developmental stages of brain during follow up period.

Implementation of HINE at different stages of follow up facilitates earlier detection of the problem and intervention at the regional level.[14] In this study HINE scale was used to assess neurological development at 4th, 8th and 12th month follow up period. Neurologic abnormality was found in 40.7% and 36.4% cases at 4th and 8th months of age respectively. The intervention done during the follow up period in the above cases was physiotherapy. On further follow up at 12th month percentage of cases with abnormality was reduced to 33.6%.

Bayley scales of infant and Toddler development (Bayley) have been widely used to assess neurodevelopment of children from 1 to 42 months of age.[8] The third edition of the Bayley scales (Bayley-III) includes a motor scale, which is commonly used as a test of motor function. In this study Bayley scale was used to assess cognition, language, motor skills, socio-emotional status and adoptive behavior at I year of age. Authors found cognitive developmental delay in 10.9% cases, language delay in 20%, motor delay in 5.5%, socio-emotional delay in 30% (n=33) had, and adoptive behavior delay in 31.8% cases.

In present study, overall 33.6% cases had developmental delay with mortality in 11.8% and lost to follow up in 10% cases. The reported rate of mortality in the literature is 9-15%.[15]

CONCLUSION

The findings of the study conclude that neonates suffered with multiple seizures (mostly subtle and myoclonic) within 24 hours of neonatal period had shown poor neurological outcome. HIE was the most common cause for poor neurological outcome with elevated perinatal mortality. Other significant risk factors were Apgar score at 5 minute, need of resuscitation at the time of birth. EEG and CT scan were considered as good predictors for the poor neurological outcome.

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