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Short Term Outcome and Predictors of adverse outcome of Neonatal Seizures

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ABSTRACT

Introduction: It is important to identify the early predictors of adverse outcome neonatal seizures to provide advanced care and to prevent complications. Hence, the present study was conducted to ascertain short term outcomes of neonatal seizures and percentage of mortality and severe neurological impairments and to assess significance of demographic, perinatal, clinical and etiological parameters as predictors of short-term outcome.

Methodology: This retrospective hospital record survey was conducted at Special Newborn Care Unit (SNCU), Department of Pediatrics, Govt. R.D.B.P Jaipuria Hospital, Jaipur, Rajasthan among Neonates admitted in SNCU with clinical diagnosis of Neonatal seizures during last two years (from 1st May, 2018 to 28th Feb.,2020). Medical records of the hospital were assessed and relevant demographic details, significant maternal (antenatal) history, perinatal history like Apgar score, need for advanced resuscitation, time of onset, duration of seizure, presence of status epilepticus etc were thoroughly evaluated. Short-term outcomes were categorized as Favorable and Adverse Neurodevelopmental Outcome.

Results: Most of the neonates with seizures were discharged with no or mild neuro impairment (66%). Mortality and adverse neurodevelopmental outcome was among 17%. Most common cause of mortality in neonatal seizures was BA HIE (76.5%) followed by IVH (11.8%) and brain malformation (11.8%). Most common cause of severe neuro impairment was HIE (76.5%). Other causes were meningitis (11.8%), hypoglycemia (5.9%) and IVH (5.9%). Adverse neuro-developmental outcome was significantly associated with Pre term birth (51.9%), Small for date subjects (83.3%) and Low birth weight (51.3%), one minute APGAR score ≤6 (43.7%) and five-minute APGAR score ≤6 (50%), seizure onset within 24 hours of birth (51.2%), status epilepticus (54.5%), severe abnormality on neuro examination (52.6%) and severe findings on cranial imaging (49%).

Conclusion: Scrutiny of factors like Pre term birth, Low birth weight, small for date, one minute APGAR score ≤6, 5 minute APGAR score ≤6, seizure onset within 24 hours of birth, status epilepticus, severe findings on neuro examination or on cranial imaging, can help in early identification of neonates at risk of adverse neuro-developmental outcome and initiate timely intervention for these neonates.

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Key words: Neonatal seizures, Status Epilepticus, Cranial ultrasound

1. INTRODUCTION

A seizure is a paroxysmal behaviour caused by hyper synchronous discharge of a group of neurons[1]. Neonatal seizures (NS) by definition occur within the first 4 weeks of life in a full-term infant and up to 44 weeks from conception for premature infants.[2] These neonatal seizures are most frequent during the first 10 days of life.[3]

The incidence of neonatal seizures is hard to define, since the majority of epidemiological studies derive from clinical observation alone that is known to be often unreliable.[4] The incidence of seizure varies from 1.5-3.7/1000 live birth, while in NICU it can be up to 5/1000 live birth.[5,6]

Neonatal seizure observed to be associated with various adverse neurodevelopmental outcomes that may predispose baby to cognitive, behavioral or epileptic complication later in life. Several prognostic factors for adverse outcome of seizure are well known, namely brain immaturity, abnormal cranial ultrasonography (USG) findings, low Apgar score, early onset of seizure or prolonged duration of seizure.[5] Etiology and gestational age are one of the most important factors affecting outcome. The time of onset of seizure also correlates with its etiology and prognosis.

Neonates with seizures are at an increased risk of mortality, and the survivors are at risk of neurological sequelae as developmental delay, epilepsy and cognitive impairment. The mortality rate can go up to 27% and commonly occurring in neonates with hypoxic ischemic encephalopathy.[7,8]

It is important to identify the early predictors of adverse outcome to provide advanced care and to prevent complications. Hence, careful evaluation of such newborns especially at the time of discharge from SNCU holds utmost importance because indicators like neurological examination and neuro imaging suggest good or poor outcome. The present study is directed towards finding the short term outcomes of seizures in form of mortality, neuro-impairment and/or abnormal neuroimaging among survivors at the time of discharge and predictors of adverse outcome of Neonatal Seizures. So the objectives of the study were to ascertain short term outcomes of neonatal seizures and percentage of mortality and severe neurological impairments amongst new born with seizures and to assess significance of demographic, perinatal, clinical and etiological parameters as predictors of short-term outcome.

2. MATERIALS AND METHODS

This retrospective hospital record survey- cross-sectional in design was conducted at Special Newborn Care Unit (SNCU), Department of Pediatrics, Govt. R.D.B.P Jaipuria Hospital (Attached with RUHS College of Medical Sciences), Jaipur, Rajasthan among Neonates admitted in SNCU with clinical diagnosis of Neonatal seizures from 1st January, 2021 to 31st July, 2021. Purposive sampling, a type of non-probability sampling was used. These 100 subjects were recruited from all the neonates having clinically diagnosed seizures during last two years (from 1st May, 2018 to 28th Feb.,2020) considering the following criteria for inclusion and exclusion.

- Inclusion criteria:

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I. Neonates (age up to 28 days), irrespective of gender.
II. In-born neonates of the hospital and out-born neonates who were transferred to the hospital were included.
III. Neonates admitted in SNCU with clinical diagnosis of seizures between 1st May, 2018 to 28th Feb., 2020.

- Exclusion Criteria:

I. Neonates for whom complete data was not available from records.
II. Neonates who by virtue of their parents left against medical advice (LAMA)/ were shifted to other hospitals or those who expired before specific etiology and short-term outcome could be determined were not undertaken for study.

After obtaining ethical clearance from Institutional Ethical Committee (IEC) and medical superintendent's permission to assess hospital records, Medical records of the hospital were assessed in semi-structured, pre-tested anonymized form protecting the rights of privacy and confidentiality of subjects. Relevant demographic details, significant maternal (antenatal) history, perinatal history like Apgar score, need for advanced resuscitation etc. were thoroughly evaluated. Apgar score was considered as suggestive of birth asphyxia as ≤6 at 5 mins. Gestational age assessment and Physical examination were done according to New Ballard Score.[9] History characterizing seizure namely time of onset, duration, presence of status epilepticus etc.

Values of Routine chemistries, including blood sugar, sepsis screen including total leucocyte count, absolute neutrophil count, C-reactive protein, micro ESR, serum electrolytes such as sodium, calcium, magnesium were recorded. Lumbar puncture, arterial blood gas analysis, TORCH screen and screen for inborn errors of metabolism were done wherever indicated. Neurological assessment and cranial ultrasound of the subject were done when they were fit for discharge with following Discharge Criteria:[10]

Seizure free for at least 3 consecutive days and

1. Normal vital signs including respiratory rate <60 breaths/min; axillary temperature 36.5°C- 37.4°C (97.7°-99.3°F) in open crib.
2. Physical examination reveals no abnormalities requiring continued hospitalization.
3. Regular urination; stool×1.
4. At least 2 uneventful, successful feedings.

USG cranium findings were considered severely abnormal when there was IVH of degree 3 or 4, severe hypoxic changes or Resistance index (RI) <0.55 after 24 hrs., periventricular leukomalacia, intraparenchymal hemorrhage or brain malformations. For neuro-developmental assessment of pre-term and full term neonates, Newborn neurologic Examination, American Academy of Neurology[11] was used. In HIE babies Sarnat staging of Hypoxic ischemic encephalopathy[12] and Thompson's Score[13] was used to clinically predict the neuro developmental outcome. The following categories of short-term outcome were defined for the subjects: (a) Favorable Neurodevelopmental Outcome, which included normal neurological examination and /or mild muscle tone+/reflex abnormalities; (b) Adverse Neurodevelopmental Outcome, which included death, severe neurological impairment with or without abnormal cranial ultrasound.

All data thus collected were entered into MS Excel sheet, cleaned and verified. Categorical variables were summarized as frequency and proportion and were analyzed using the Chi-square test. Quantitative Data were expressed as mean and standard deviation. All

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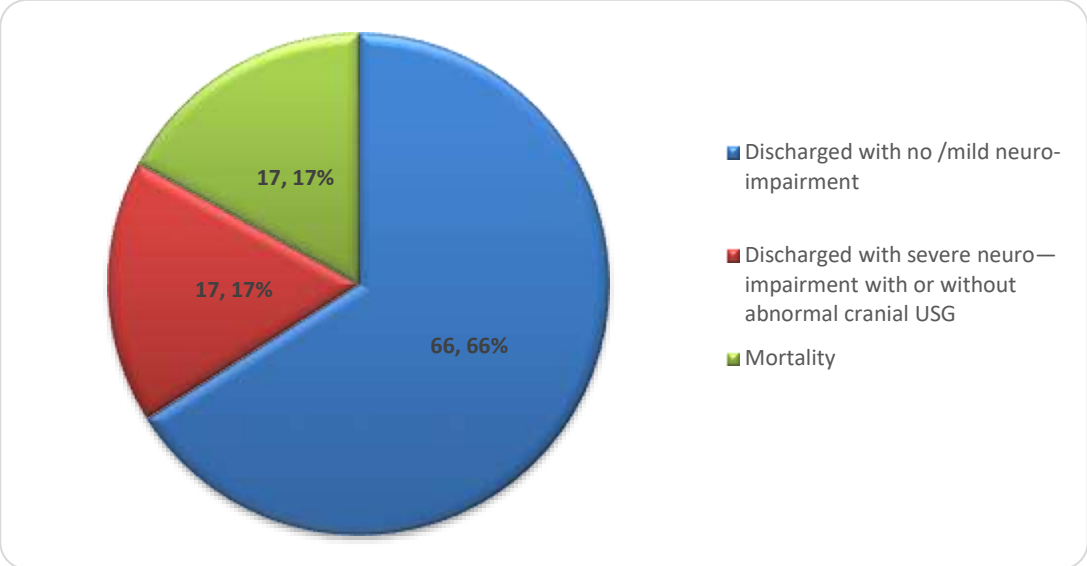
statistical analysis was done using Epi info version 7.2.1.0 statistical software. A p-value < 0.05 was considered as statistically significant.

3. RESULTS

In this study out of 100 participants, most of the neonates with seizures were discharged with no or mild neuro impairment (66%). 17% neonates had severe neuro impairment or abnormal cranial USG. Death occurred in 17% of neonates with seizures. [Graph-1]

Graph 1: Distribution of Study Subjects According to Short Term Outcome



Most common cause of mortality in neonatal seizures was BA HIE (76.5%) followed by IVH (11.8%) and brain malformation (11.8%). No mortality was seen among cases of hypoglycemia, meningitis and hypocalcemia. Total proportion of severe neuro-impairment among neonatal seizures was 17%. Most common cause of severe neuro-impairment was BA HIE (76.5%). Other causes were meningitis (11.8%), hypoglycemia (5.9%) and IVH (5.9%). [Table-1]

Table 1: Association of Short Term Outcome of Neonatal Seizures with etiological Factors

Etiological factor	Death		Severe Neuro-impairment		Mild/ No neuro-impairment		Total
	N	%	N	%	N	%	
BA HIE	13	21	13	21	36	58	62
Hypoglycemia	0	0	1	4.5	21	95.5	22
Meningitis	0	0	2	25	6	75	8
Brain malformation	2	100	0	0	0	0	2
IVH	2	50	1	25	1	25	4
Hypocalcemia	0	0	0	0	2	100	2
Chi-square = 26.665 with 10 degrees of freedom; P = 0.003 (S)							

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Most common cause of mortality as well as neuro impairment was BA HIE. Hypocalcemia has the best neurological outcome showing no/mild neuro impairment in both cases (100%) followed by hypoglycemia, with most cases showing no/mild neuro impairment (95.5%). Patient with meningitis also mostly had no/mild neuro impairment (75%) and 2 (25%) had severe neuro impairment. Death occurred in 21% of cases with HIE while 21% had severe neuro impairment. Death was highest in patients with brain malformation (100%) and IVH (50%). Brain malformation had the poorest neurological outcome. Although death (outcome variable) is most commonly associated with brain malformations and IVH (exposure variables), however most common cause of death (high mortality association) in neonatal seizure is HIE. [Table-1]

Table 2: Association of Baseline Variables with Adverse Neurodevelopmental Outcome

Baseline Variables		Favorable neuro developmental outcome		Adverse neuro developmental outcome		P value
		N	%	N	%	
Gestational age	**Full Term**	53	72.6	20	27.4	0.040
	Pre-Term	13	48.1	14	51.9	
Intra uterine growth	**AGA**	64	72.7	24	27.3	<0.001
	SGA	2	16.7	10	83.3	
Mode of delivery	**NVD**	47	64.4	26	35.6	0.079
	AVD	0	0	2	100	
	LSCS	19	76	6	24	
Meconium stained liquour (MSL)	**No**	42	68.9	19	31.1	0.591
	Yes	24	61.5	15	38.5	
Birth weight	**<2.5 Kg**	19	48.7	20	51.3	0.048
	≥2.5 Kg	43	70.5	18	29.5	
Gender	**Female**	24	67.9	13	32.1	0.972
	Male	42	66.7	21	33.3	

Factors significantly associated with adverse neurodevelopmental outcomes were Gestational age, Intra uterine growth and birth weight. Adverse neuro-developmental outcome was significantly higher among pre term subjects (51.9%) as compared to full term subjects (27.4%), ($p<0.05$). significantly more among Small for date (83.3%) as compared to appropriate for age neonates (27.3%), ($p<0.001$), significantly more among Low birth weight subjects (51.3%) as compared to normal birth weight neonates (29.5%), ($p<0.05$). Adverse neuro-developmental outcome was seen more in neonates delivered by AVD (100%) and NVD (35.6%) as compared to neonates delivered by LSCS (24%), however this difference was not found to be statistically significant ($p=0.079$). No significant association was found between short term outcome of neonates with seizure and meconium-stained liquor ($p>0.05$). Favorable neuro-developmental outcome was almost similar in males and females, the difference was not found to be statistically significant ($p>0.05$) [Table-2, Graph-2]

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Graph 2: Association of Baseline Variables with Adverse Neurodevelopmental Outcome

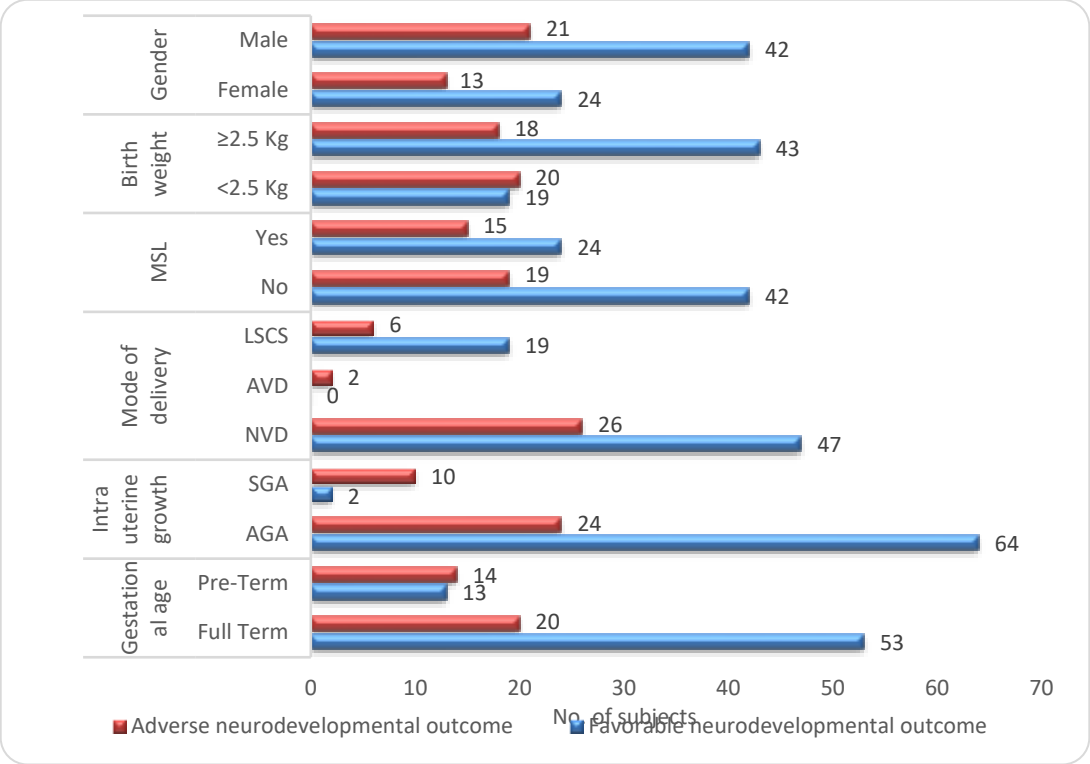

Table 3: Association of Perinatal Variables with Adverse Neurodevelopmental Outcome

		Favorable neuro developmental outcome		Adverse neuro developmental outcome		P value
		N	%	N	%	
Need for advanced resuscitation at birth	**No**	29	76.3	9	23.7	0.137
	Yes	37	59.7	25	41.3	
APGAR 1 MIN	**≤6**	36	56.3	28	43.7	0.012
	>6	30	83.3	6	16.7	
APGAR 5 MIN	**≤6**	35	56.5	27	43.5	0.018
	>6	31	81.6	7	18.4	

Adverse neuro-developmental outcome was seen more in neonates who needed advanced resuscitation at birth (41.3%) as compared to neonates who did not need advanced resuscitation at birth (23.7%), this difference was however not found to be statistically significant (p>0.05). Adverse neurological outcome was seen significantly more in neonates with one minute APGAR score ≤6 (43.7%) as compared to APGAR score >6 (16.7%), (p=0.012). Adverse neuro-developmental outcome was seen significantly more in neonates with 5 minute APGAR score ≤6 (50%) as compared to APGAR score >6 (18.4%). [Table-3, Graph-3]

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Graph 3: Association of Perinatal Variables with Adverse Neurodevelopmental Outcome

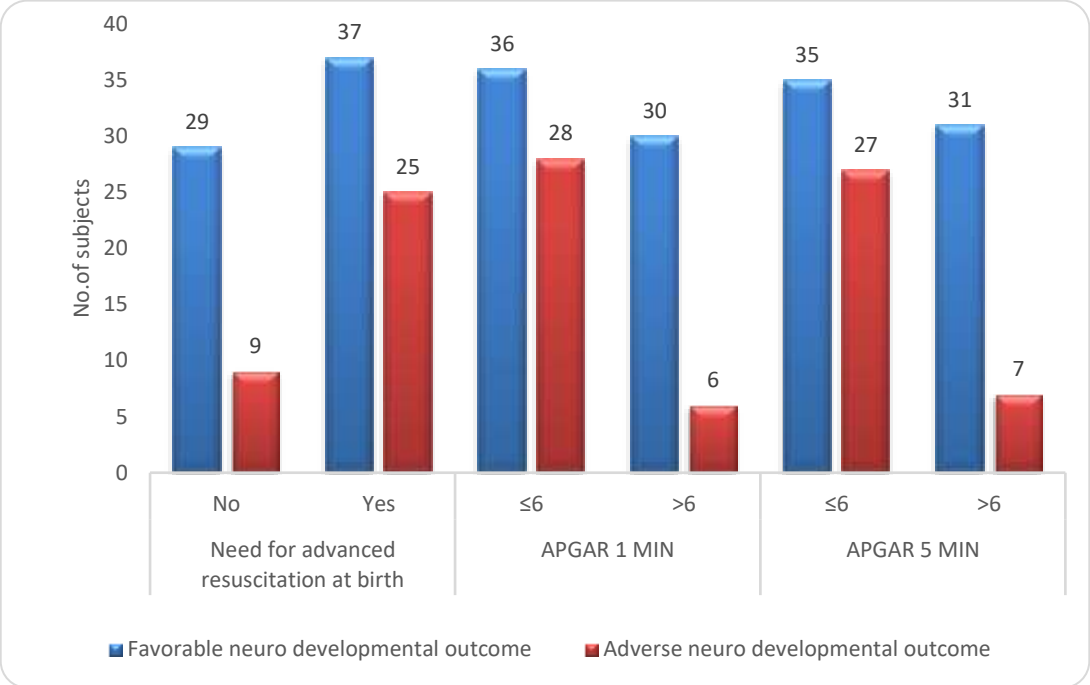

Table 4: Association of Clinical Characteristics with Adverse Neurodevelopmental Outcome

Clinical Characteristics		Favorable neuro developmental outcome		Adverse neuro developmental outcome		P value
		N	%	N	%	
Time of onset of seizure	Within 24 hrs	21	48.8	22	51.2	0.003
	After 24 hrs	45	78.9	12	21.1	
Status Epilepticus	Absent	41	91.1	4	8.9	< 0.001
	Present	25	45.5	30	54.5	
Neuro examination (at time of discharge from SNCU)	Mild / normal	48	77.4	14	22.6	0.004
	Severe	8	47.4	9	52.6	
Cranial ultrasound	Normal/Mild	41	80.4	10	19.6	0.004
	Severe	25	51	24	49	

Adverse neuro-developmental outcome was seen significantly higher in neonates with seizure onset within 24 hours of birth (51.2%) as compared to neonates with seizure onset after 24 hours of birth (21.1%), ($p<0.05$), significantly higher in neonates with status epilepticus (54.5%) as compared to neonates without status epilepticus (8.9%), ($p<0.001$), significantly more in neonates with severe abnormality on neuro examination (52.6%) as compared to neonates mild / normal features on neuro examination (22.6%), ($p<0.05$). Adverse neuro-developmental outcome was seen more in neonates with severe findings on

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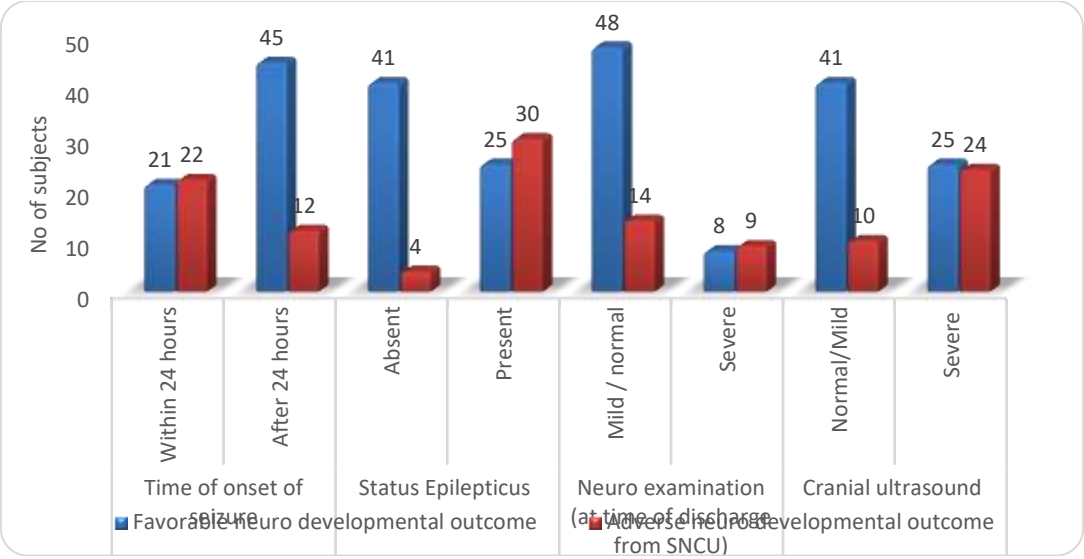
cranial ultrasound (49%) as compared to neonates with normal / mild findings (19.6%), this difference was found to be statistically significant (p=0.004). [Table-4, Graph-4]

Graph 4: Association of Clinical Characteristics with Adverse Neurodevelopmental Outcome



4. DISCUSSION

In this study, mortality was 17% and most of the neonates with seizures were discharged with no or mild neuro impairment (66%) and 17% neonates had severe neuro impairment or abnormal cranial USG. In study of Abhishek CK et al [14] mortality was 28.4% in neonates with seizures. Among the 232 enrolled infants, 125 had a normal outcome and 14 had mild functional disability (59.9%), and 55 (23.7%) survived with one or more neurodevelopmental impairments and mortality was 16.4% in study of Lai YH et al. [15] Singh SD. et al [16] in their study found that mortality was 13.67%. Mortality rates was found 32.51% in preterm neonates in study of Momen HA et al [17]. Hur YJ et al [18] found that Favorable outcomes were observed in 67.2% and unfavorable outcomes in 32.8% infants and mortality rate was 6.1%.

In our study, most common cause of mortality in neonatal seizures was BA HIE (76.5%) followed by IVH (11.8%) and brain malformation (11.8%). No mortality was seen among cases of hypoglycemia, meningitis and hypocalcemia. Nair BK et al's study [19] found that the causes of seizures were HIE, meningitis, and IC bleed in 60%, 26.67%, and 13.33% of the patients, respectively among the expired patients. The leading causes of death were multi-organ failure accompanying bronchopulmonary dysplasia, sepsis and severe asphyxia in study of Hur YJ et al [18]

In our study the most common cause of mortality in neonatal seizures was birth asphyxia associated HIE (76.5%) followed by IVH (11.8%) and brain malformation (11.8%). In present study IVH and brain malformations were associated with much higher proportion of mortality being 50% and 100% respectively, whereas HIE was the most common cause as most of our study population includes Birth asphyxia associated HIE. This could be explained by the fact that seizures are usually associated with severe grades of these two etiologies and that etiology and its severity are said to be the biggest predictor of outcome. No mortality was

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seen among cases of hypoglycemia and hypocalcemia. Amar et al (2005)[20] found that the most common causes of neonatal deaths were severe birth asphyxia seen in 9(42.8%) neonates followed by IVH in 5 (23.8%), septicemia in 4(23.8%) and meningitis in 3 (14.2%) neonates. Abdul Naseer Abdul Bari et al (2017)[21] found the causes of death as birth asphyxia (47.6%) IVH (23.8%) and meningitis (14.28%). Hailu Tazebew Amare et al (2019)[22] found that most common cause of death was PNA with HIE (perinatal asphyxia with HIE).

In our study adverse neurodevelopmental outcome was found to be significantly associated with pre term, Small for gestational age (SGA), Low birth weight. Adverse neurological outcome was seen more in neonates with one minute APGAR score ≤6 (43.7%) as compared to APGAR score >6 (16.7%), more in neonates with five minute APGAR score ≤6 (50%) as compared to APGAR score >6 (18.4%), more observed in neonates with seizure onset within 24 hours of birth (51.2%) as compared to neonates with seizure onset after 24 hours of birth, more in neonates with status epilepticus, more in neonates with severe abnormality in neuro examination & more observed in neonates with severe findings on cranial ultrasound (49%) as compared to neonates with normal / mild findings. No significant association was found between short term outcome of neonates with seizure and meconium-stained liquor ($p>0.05$). Favorable neuro-developmental outcome was almost similar in males and females, the difference was not found to be statistically significant ($p>0.05$). Anand V et al (2014)[23] found that mortality and severe neurological impairment after neonatal seizure is associated with prematurity, LBW, low Apgar score at 5 min, etiologies like meningitis, sepsis, severe HIE, brain malformations, grade 3 or 4 IVH or intracranial hemorrhage, seizure onset <24 hours, presence of status epilepticus, severely abnormal radiological and EEG findings. Hur YJ et al [18] found that unfavorable outcome was more among pre terms (42.9%) as compared to full term (28.8%), more among cesarean delivery (37.7%) as compared to spontaneous (25%), significantly higher among status epilepticus (72.6%) as compared to no status epilepticus (27.4%) and significantly higher among APGAR score <7 at 5 minutes (61.9%) as compared to APGAR score >7 at 5 minutes (28.8%). Similar findings were observed in other studies by Singh SD. et al [16] and Lai YH et al [b] where they found that low Apgar scores at one and five minutes and early onset of seizure were prognostic factors for poor outcome.

5. CONCLUSION

This study revealed that mortality and adverse neurodevelopmental outcome was among 17% and most common cause of mortality as well as neuro impairment was BA HIE. Study concluded that scrutiny of factors like Pre term birth, Low birth weight, small for date, one minute APGAR score ≤6, 5 minute APGAR score ≤6, seizure onset within 24 hours of birth, status epilepticus, severe findings on neuro examination or on cranial imaging, can help in early identification of neonates at risk adverse neuro-developmental outcome and initiate timely and individualized intervention for these neonates.

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