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Original Research Article

Clinical profile, outcome and clinical indicators for poor prognosis in full term babies born with severe birth asphyxia: study from tertiary care hospital from western India

Pareshkumar A. Thakkar[1]*, Paresh Valia[1], Niyati Parmar[2], Bakul Javadekar[1], Ukti P. Thakkar[3]

[1]Department of Pediatrics, [2]Department of Community Medicine, Medical College and SSG Hospital, Vadodara, Gujarat, India.
[3]VIP Physiotherapy Clinic, Vadodara, Gujarat, India

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***Correspondence:**
Dr. Pareshkumar A. Thakkar,
E-mail: drpareshthakkar123@gmail.com

ABSTRACT

Background: The World Health Organization describes birth asphyxia as failure to initiate and sustain breathing at birth. The aim of the study was to study the clinical profile and outcome at 3 months of age of full term babies born with severe birth asphyxia and to analyze risk factors associated with adverse outcome.
Methods: This was a prospective observational study carried out over period of 12 months in year 2015-16. All full-term babies born with severe birth asphyxia (n = 45) during four months period were enrolled and were followed up for 3 months. Severe birth asphyxia was defined as APGAR score 3 or less at 1 minute. Baseline characteristics, clinical profile and outcome were noted. HIE was graded as per Sarnat and Sarnat staging. Neurological Assessment at 7th day and on discharge was done and children were assessed by Amiel Tison Scale at 3 months. Multivariate analysis by linear regression was done to find risk factors associated with adverse outcome.
Results: Of total 45 babies with SBA, 35 developed HIE, of which 13 (28.8%) were in HIE grade II and 13 (28.8%) were in HIE III. Mortality found was 20% while 28.5% of survivors had abnormal neurological outcome at 3 months. Multivariate analysis of risk factors shows that abnormal neurological findings on 7th day of life, APGAR ≤ 6 at 10 minute and HIE grade II or more were associated with abnormal outcome (p = 0.01). The risk factors associated with mortality were multiorgan dysfunction, difficult to control seizures, APGAR ≤4 at 10 minute (p = 0.07).
Conclusions: Full term neonates with severe birth asphyxia has significant mortality and significant number of survivors has abnormal neurological outcome at 3 months of age. Presence of certain clinical indicators is associated with increased risk of adverse outcome.

Keywords: Outcome**,** Prognosis, Risk factors, Sever birth asphyxia

INTRODUCTION

The World Health Organization describes birth asphyxia as failure to initiate and sustain breathing at birth.[1] WHO estimates in the developing countries 3% of all infants (3.6 millions) suffer from moderate to severe birth asphyxia, of which 23% (840,000) die and approximately the same numbers develop serious sequelae. Asphyxia accounts for 23% of neonatal deaths globally, and 8% of all deaths in children under five years of age.[2] India, being a developing country, has high infant mortality rate (IMR), in which neonatal mortality rate (NMR) has a

major contribution. Survivors of birth asphyxia are at risk for neurodevelopmental sequelae including motor and cognitive disabilities.[3-7] One of the best population studies of asphyxia in a developing country reported that 18% of survivors of mild to moderate birth asphyxia had neonatal encephalopathy and permanent severe neurologic impairment.[8] Infant with hypoxic ischemic encephalopathy (HIE) suffer neurological sequelae in later life.[9-12] HIE is a common cause of mental retardation, cerebral palsy and other neurodevelopmental disorders.

Parents of surviving asphyxiated infants are greatly concerned about the future of their newborns. Despite the vast advances in the pathophysiology of asphyxia, no definite criteria have been determined for identifying the prognosis in these patients. Explaining prognosis is an important part of clinical management. The severity of perinatal asphyxia can be graded by Sarnat and Sarnat staging system in which Stage-1 has excellent prognosis while stage-3 has high mortality and poor neurological outcome. Outcome in patient of stage 2 can be much variable which may range from mild, moderate, or severe developmental delay or even deaths in few cases. So explaining prognosis in such case is at times difficult. Some study have reported predictive factors for neurodevelopmental outcome in infants with HIE.[13-15]

Various authors have tried to study biochemical parameter like pH, base deficit, lactate, LDH and modalities like EEG and MRI for their association with poor outcome. It is not possible to carry out such investigations especially in resource limited settings like in developing countries. In this study we have tried to analyze certain "clinical" risk factors or indicators for their possible association with adverse outcome in such cases, so that more precise prognostication can be done. This should be of help in prognostication as well as for vigilant monitoring during post-natal follow up of at risk individuals.

We carried out this study with objectives of to study the clinical profile and outcome at 3 months age of full term babies born with severe birth asphyxia and to analyze the risk factors associated with adverse outcome.

METHODS

The present study was carried out at Intramural Neonatal Nursery of Department of Pediatrics at Medical College SSG Hospital, Vadodara, Gujarat, India. This was prospective observational study carried out over period of 12 months from 1st August, 2015 to 31th July, 2016. Babies were enrolled after assessing inclusion and exclusion criteria. We included all consecutive full term babies born at our institute with severe birth asphyxia with APGAR score 3 or less at 1 minute from 1st December, 2015 to 31th March, 2016. Babies who delivered elsewhere and referred to our hospital, major congenital malformations including CNS malformations, Preterm babies (< 37 week of gestation), birth weight < 1,800 gm, severe hyperbilirubinemia bordering on kernicterus or requiring exchange transfusion, pyogenic meningitis, refusal of parental consent were excluded from the study.

A complete clinical assessment and a detailed neurological examination were done daily till discharge. Patient information was obtained and recorded in study profoma. Information was collected prospectively by attending daily visits. This includes demographic data, maternal information, APGAR score at 1, 5 and 10 minutes, mode of delivery, details of resuscitation, duration of IPPR, birth weight, gestational age, gender, need for mechanical ventilations, presence and details of seizures, grades of HIE, mortality, duration of hospital stay, clinical profile, morbidities during NICU stay, requirement of inotropes etc. Gestational age was assigned by ultrasound dating, if this was not available, by date of last menstrual period, and if that also was unavailable then by New Ballard scoring system. ANC was considered as complete when minimum 3 visits were taken. All the babies were treated as per our NICU protocols by maintaining euthermia, maintaining normal oxygenation and ventilation, maintaining normal tissue perfusion, maintaining normal blood glucose, Ca++, treatment of seizures and by providing nutrition.

Newborn was said to have "intractable seizures" when seizures persisted after appropriate and optimum trial of initial two anti-convulsion drug, i.e. phenobarbitone and phenytoin. Difficult to control seizures: were defined as continued occurrence of an unacceptable quantity of seizures despite reasonable treatment. i.e. if after midazolam drip seizure could not be controlled. Multiorgan dysfunction was defined as involvement of organ of two or more systems. Abnormal clinical neurological findings persisting beyond First 7th days of life (which included abnormalities of muscle tone, posture like hypotonia, rigidity and weakness) were carefully noted.

HIE was graded in first 24 hours by Sarnat and Sarnat classification. All newborn were periodically and regularly re-evaluated. The child was assigned higher grade if subsequently child showed manifestation of higher grade of HIE by Sarnat and Sarnat staging. Only clinical elements of Sarnat and Sarnat staging were used, as EEG was not done in all asphyxiated babies. Poor prognostic factors like repeated seizures, difficult to control seizures, multi organ dysfunction, requirements of inotropes, abnormal neurological findings after 7th day or at discharge (like hypotonia, rigidity, weakness), APGAR score of ≤ 4 at 10 minutes or later, assisted ventilation for >24 hours, hypoglycemia, polycythemia, severity of HIE (SARNAT stage 2 or above) and persistent feeding difficulties were analyzed.

On discharge, babies were assessed for abnormal neurological signs like tone abnormalities, moros reflex,

feeding difficulty etc. head circumference and weight at birth were noted and monitored monthly till 3 months follow up. Babies were followed up in high risk newborn clinic. Neuromotor assessment was done at 3 months by Amiel Tison scale.[16] Deep tendon reflexes, abnormal persistence of primitive reflexes, like ATNR; Moro reflex, automatic walking, fisting, cortical thumb etc. were also recorded. Neurosensory evaluation was done in form of hearing and vision assessment. Head circumference and weight gain were monitored and were compared with standard WHO charts. The outcome was classified as favorable (normal neurodevelopment) or adverse (death or abnormal neurological findings).

Statistical analysis

Data was entered into an MS Excel spreadsheet and then imported and analyzed in statistical software MedCalc 12.5.0 (trial version). The obtained results were described by tables and statistical charts and compared between groups. The analysis of patient demographics and baseline outcome variables was done by using descriptive statistics (frequencies and percentages for categorical variables) and analytical statistics were expressed as means (± standard deviation) or medians for continuous variable. Categorical data was compared using chi square analysis. Multivariate analysis by linear regression was done for analyzing the risk factors associated with mortality and abnormal neurological outcome. P-value of <0.05 was considered as statistically significant.

This is study was approved by Institutional Ethics Committee and valid written informed consent was obtained from parents.

RESULTS

The present study was conducted over period of 12 months from August 2015 to July 2016 at intramural NICU, Medical College Baroda & SSG hospital. During this study period full term babies born with severe birth asphyxia during four months periods from December 2015 to March 2016 were enrolled.

Total 66 babies who met inclusion criteria were screened, of which 21 were excluded. Among excluded babies, 19 babies were premature, 1 had pyogenic meningitis and 1 had major congenital malformation. Total 45 patients with severe birth asphyxia were enrolled in our study. During this period there were total 2019 live births, of which 66 newborns suffered severe birth asphyxia, so the incidence of SBA was 33 per 1000 live births. Full term babies instead of A full term baby during this period was 1838 so incidence of SBA amongst full term babies found was 24.4 per 1000 full term live birth.

Of 45 patients who suffered from SBA, 35 patients developed Hypoxic ischemic encephalopathy (HIE), so the proportion of HIE among SBA babies was 77%. Of total 1838 full term live birth 45 babies had SBA, of which 35 babies developed HIE, so the incidence of HIE found was 19.1 per 1000 live birth.

Table 1: Baseline characteristics.

	(n = 45)
Gestational age (weeks) (mean±SD)	38.62±1.1
Birth weight (gms) (mean±SD)	2540±365
Gender	
Male	25/45 (55.5%)
Weight category	
AFD	39/45 (86.6%)
SFD	06/45 (13.4%)
ANC taken	
Yes	13/45 (28.9%)
Duration of IPPR	
≤30 sec	13/45 (28.8%)
30 sec-60 sec	8/45 (17.7%)
60sec-120 sec	11/45 (24.7%)
>120 sec	13/45 (28.8%)
APGAR <5	
At 1 minute	1/45 (100%)
At 5 minute	12/45 (26.6%)
At 10 minute	4/45 (8.8%)

Table 2: Morbidities found in study group.

Morbidities	Percentage (%)
RDS	16/45 (35.5%)
Acute kidney injury	20/45 (44.4%)
Shock	15/45 (33.3%)
Mechanical ventilation	19/45 (42.2%)
Multiorgan dysfunction	11/45 (24.4%)
HIE	35/45 (77.7%)
Sepsis	25/45 (55.5%)
DIC	7/45 (15.5%)
Seizure	28/45 (62.2%)
Hypoglycemia	0/45 (0%)
Hypocalcaemia	3/45 (6.6%)
Apnea	2/45 (4.4%)
NEC	1/45 (2.2%)
Polycythemia	3/45 (6.6%)
Persistent feeding difficulty	17/45 (37.7%)

Clinical profile and outcome

Ratio of male and female neonates was almost equal in our study group. Baseline characteristics of the study group is described in Table 1. Mean gestational age of the patients was 38.6 weeks. In our study group, 25 out of 45 (55.6%) were low birth weight. The mean birth weight was 2540 gm. Most of the patients 39 out of 45 (86%) were AFD amongst SBA. Majority of the mothers (71.10%) of SBA babies had not taken or had taken incomplete ANC. In our study group, 13/45 (29%) had APGAR score of < 5 at 5 minute, and 4/45 (9%) had an

APGAR < 5 at 10 minutes of age. 46% of babies required <1 min duration of IPPR.

Morbidities during NICU stay

The morbidity profile of study subjects has been described in Table 2. Common morbidities in study group were respiratory distress syndrome in 35%, acute kidney injury in 44%, shock in 33%, and multi-organ dysfunction in 24%.

Table 3: Characteristics of patients with respect to HIE grades.

	No HIE	HIE I	HIE II	HIE III
HIE staging	10/45	9/45	13/45	13/45
APGAR score				
≤4 at 5 minute	0/10	0/9	5/13	7/13
≤4 at 10 minute	0/10	0/9	0/13	4/13
Duration of IPPR				
<30 sec	5/10	5/9	3/13	0/13
30-60 sec	2/10	1/9	4/13	1/13
60-120 sec	3/10	2/9	2/13	4/13
>120 sec	0/10	1/9	4/13	8/13
Duration of encephalopathy among survivors				
<3 days	0/10	6/9	1/12	0/5
3-7 days	0/10	3/9	3/12	0/5
7-14 days	0/10	0/9	5/12	1/5
>14 days	0/10	0/9	3/12	4/5
Duration of NICU among survivors				
<10 days	9/10	8/9	2/12	0/5
10-20 days	1/10	1/9	8/12	1/5
>20 days	0/10	0/9	2/12	4/5
Mean±SD	6.7±1.2	7.1±1.4	14±2.11	21±3.4
Mortality	0/10	0/9	1/13	8/13
Abnormal neurological findings at 7th day	0/10	0/9	5/12	5/5
Abnormal neurological findings at 3 month	0/10	0/9	5/12	5/5
Inadequate weight gain and head growth	0/10	0/9	5/12	5/5

Hypoxic ischemic encephalopathy

Out of 45 patients with severe birth asphyxia 35 developed HIE. Characteristics of patients with HIE has been described in table 3 and is compared with patients who did not develop HIE. All patients with HIE grade III had APGAR of ≤ 4 at 10 minutes. Those who needed IPPR for longer duration developed higher grade of HIE (p value = 0.0012). Out of 13 babies who required IPPR <30 sec, 5/13(38%) did not developed HIE and 5/13 (38%) developed HIE grade I, while out of 13 babies who required IPPR more than 2 min, 8/13(61.5%) developed HIE grade III. Patients who required longer duration of IPPR and had low APGAR score at 5 minutes and 10 minutes developed higher grades HIE. The patients who had higher grade of HIE remained in encephalopathy for significantly longer duration and had longer NICU stay.

Table 4: Baseline characteristics of study subjects and outcome.

	Normal outcome n = 26	Abnormal outcome n = 19	p-value
Gender			
Male	14 (53.9%)	11 (57.9%)	0.97
Female	12 (46.1%)	08 (42.1%)	0.97
Gestational age (weeks)			
37	6 (23.0%)	3 (15.9%)	0.83
38	9 (34.6%)	2 (10.5%)	0.13
39	6 (23.0%)	7 (36.8%)	0.49
40	5 (19.4%)	7 (36.8%)	0.33
Birth weight (kg)			
≤ 2	3 (11.5%)	3 (15.8%)	0.98
2-2.5	10 (38.5%)	9 (47.4%)	0.77
>2.5	13 (50.0%)	7 (36.8%)	
Weight category			
AFD	23 (88.5%)	16 (84.2%)	0.98
SFD	3 (11.5%)	3 (15.8%)	0.98
Antenatal care			
Yes	9 (34.6%)	4 (21.0%)	0.50
No	17 (65.4%)	15 (79.0%)	0.46
APGAR at 5 minute			
≤6	14 (53.8%)	10 (52.6%)	0.82
>6	12 (46.2%)	9 (47.4%)	0.82
APGAR at 10 minute			
≤6	2 (7.6%)	10 (52.6%)	0.002
>6	24 (93.4%)	9 (47.4%)	0.001
IPPR duration			
≤30 sec	12 (46.1%)	1 (5.3%)	0.008
30-60 sec	6 (23.0%)	2 (10.5%)	0.49
60-120 sec	6 (23.0%)	5 (26.3%)	0.92
>120 sec	2 (07.9%)	11 (57.9%)	0.0009

Majority of babies without HIE and grade I HIE could be discharged early. While HIE grade III (80%) babies had longer duration of NICU stay. Highest mortality was found with HIE grade III (89%) while there was no mortality in HIE grade I. All newborn in HIE grade III had abnormal findings on neurological assessment when assessed on 7th day of life. HIE grade III had 100% abnormal neurological outcome. Babies with grade I HIE and no HIE had good neurological outcome at 3 months of age. Inadequate weight gain and head growth was associated with abnormal outcome at 3 months of age.

Those babies with an APGAR of ≤ 4 at 10 minutes had an abnormal neurological outcome.

Table 5: Clinical risk factors and outcome.

Risk factors (variable)	Standard error (SE)	p-value
Repeated seizure	0.25	0.494
Difficult to control seizure	0.172	0.183
Multiorgan dysfunction	0.26	0.342
Inotropes	0.306	0.682
Abnormal neurological findings on 7th day	0.29	0.018
HIE Grade ≥ 2	0.258	0.029
Ventilation >24 Hrs	0.37	0.173
Polycythemia	0.241	0.887
APGAR ≤6 At 10 min	0.166	0.002
Persistent feeding difficulty	0.335	0.800

Table 6: Risk factors and mortality.

Regression equation			
Independent variables (Constant)	Std. error	$r_{partial}$	P value
APGAR ≤ 4 at 10 min	0.1234	0.4376	0.007
Difficult to control seizure	0.1280	0.3852	0.020
Persistent feeding difficulty	0.2488	-0.1806	0.292
HIE grade ≥2	0.1919	0.02627	0.879
Requiring inotropes	0.2277	0.2065	0.227
Multiorgan dysfunctions	0.1929	0.3041	0.071
Polycythemia	0.1791	0.06184	0.720
Repeated seizures	0.1854	0.1361	0.428
Requiring ventilation	0.2752	0.1123	0.514

Analysis of risk factors associated with adverse outcome

We analyzed the risk factors and checked their possible association with adverse outcome. 'Adverse outcome' means patient who either died or who had abnormal neurological outcome at 3 months of age. We checked possible association of certain baseline characteristics like birth weight, gestational age and other shown in Table 4 for their association with adverse outcome. In our study we did not find statistically significant association between gestational age, birth weight, gender and antenatal care with adverse outcome. APGAR at ≤6 at 10 minutes and duration of IPPR more than 120 seconds were significantly associated with abnormal outcome.

The multivariate analysis shows abnormal neurological finding on 7th day of life, APGAR ≤6 at 10 minute and HIE of grade ≥2 were the risk factors significantly associated with adverse outcome. We analyzed the possible association of following clinical parameters for their association with outcome of mortality. The multivariate analysis shows multi-organ dysfunction, difficult to control seizures, APGAR ≤4 at 10 minute were the risk factors significantly associated with mortality.

DISCUSSION

Birth asphyxia is one of the major causes of perinatal mortality and morbidity, especially in developing countries. A number of antenatal, intranatal and postnatal factors are responsible for birth asphyxia and its outcome.

In our study, we found significant incidence of SBA and HIE and such patients had significant morbidities and mortality. We also found certain clinical indicator to predict adverse outcome in babies born with severe birth asphyxia. Abnormal neurological finding on 7th day of life, APGAR ≤6 at 10 minute and HIE grade II or more where associated with abnormal outcome. The risk factors associated with mortality were Multi-organ dysfunction, difficult to control seizures, APGAR ≤4 at 10 minute.

Various studies have quoted varying incidence of birth asphyxia ranging from 18.6/1000 live birth to 112/1000 live births.[17-21] The difference in the incidence can be explained by the different methodology adopted in various studies and the type of the health facility. Referral hospitals having higher number of high risk delivery had more incidence of birth asphyxia compare to primary health centre. However this incidence does not reflect the true incidence as most of the data were hospital based and was of single centre, which does not reflects the true incidence in general population. Mortality in other studies range from 10% to 45%.[22-26] In our study we had mortality of 20 %. The varying rates of mortality may be due to type of patients based on high risk pregnancy, late referral in case of obstructed labour, type and level of NICU care.

The studies have shown significant number of survivor with severe birth asphyxia developed neuro-developmental handicaps on follow up. The study by Boskabadi et al followed patients till 24 months of age and assessed baby by Denver-II developmental test found 28% of patients had developmental delay. In the study by Klinger et al they found 25% of patients had neuromotor deficit on follow up. Hatami et al found 30% of survivors had developmental disorder in follow up till 5 years of age.[27] However various studies like De Vriesetalb and Polat M et al did long term follow up of up to 2 to 3 years had significant number of patients with abnormal neurological outcome. This emphasizes the need for careful neurodevelopmental evaluation and comprehensive care in survivors of severe birth asphyxia. In our study we have followed up patients only till 3 month of age.

Many authors have studied the risk factors for the development of birth asphyxia; these are various antenatal, intrapartum and obstetric risk factors for development of birth asphyxia. Few authors have also studied risk factors for unfavorable or adverse outcome in babies who had suffered severe asphyxia at birth. These can be maternal, fetal, neonatal clinical indicators, various biochemical parameters like pH and base deficits. EEG and MRI also have been reported as useful indicators in predicting outcome. Various authors have noted increasing severity of HIE was associated with poorer outcome. The low APGAR score at 5 minute and 10 minute, need of adrenaline during resuscitation, low pH have been linked to poorer outcome.

The study by Hayakawa et al found low APGAR score at 5 minute, need of adrenaline during resuscitation were associated with poor outcome. In laboratory parameters they found low pH and base excess and high level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine kinase (CK) with poor outcome compared to babies with good outcome. Glass et al found the clinical neonatal seizures were independently associated with abnormal neurological outcome on follow up. They also noted abnormal findings with adverse outcome. In our study we also noted difficult to control seizures associated with adverse outcome.[29]

In our study we have mainly focused on clinical parameters as risk factors for predicting abnormal neurological outcome. We have not studied the biochemical parameters like pH, base excess, MRI and EEG findings. Currently Sarnat and Sarnat staging of HIE gives prognostication. Grade I HIE has quite good prognosis while grade III HIE has poor prognosis including very high mortality. Presence or absence of these additional risk factors analyzed in this study should be of help in prognostication and in prediction of favorable or unfavorable outcome. However the findings of this study needs to be reconfirmed by a separate prospective study utilizing these risk factors for the assessment of the outcome in birth asphyxiated children.

Limitation of the study was that it included only full term babies with (birth weight >1800 grams) with asphyxia. We have not included pre-term babies. For defining asphyxia we have used NNF definition and have not done biochemical investigations like arterial blood pH. In our study we have mainly focused on clinical parameters as risk factors for predicting adverse outcome. We have not studied the biochemical parameters like pH, base excess and other tools like MRI and EEG. We could not study long term outcome because of limited time period.

CONCLUSION

Full term neonates who suffered severe asphyxia at birth has significant mortality and significant number of survivors has abnormal neurological outcome at 3 months of age. HIE grade 2 or more, abnormal neurological findings at 7th day, APGAR score of ≤ 6 at 10 min are the risk factors associated with adverse outcome. Difficult to control seizures, multiorgan dysfunction, APGAR score of ≤ 4 at 10 minute are associated with high risk of mortality.

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