

Research Article

A study of multiorgan dysfunction in asphyxiated neonates

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ABSTRACT

Background: Perinatal asphyxia is an important cause of neonatal mortality, morbidity and late sequelae in developing countries like India. Each year 4 million neonates die worldwide, representing 38 % of all deaths of children less than 5 years of age. It is a study of the clinical profile, the frequency and pattern of organ involvement and the impact of different organ system involvement on early neonatal morbidity and mortality in asphyxiated neonates.

Methods: The study was conducted in Level-III NICU of Department of Pediatrics, S P Medical College, Bikaner. 190 asphyxiated neonates were studied after due approval from Ethics committee and parental consent. The clinical and Biochemical parameters were analyzed and classified each of the organ system dysfunction as per the criteria defined. Multiple organ dysfunction is defined as involvement of two or more than two organ system.

Results: Multiple organ dysfunction occurred in 63.1% infants and 27.6% died during the study; Central Nervous System (CNS) was most frequently involved (69.4%). Severe CNS injury (42 infants i.e. 22.1%) always occurred with involvement of other organs, although moderate CNS involvement was isolated in 90 infants. Renal involvement occurred in 52.1%, pulmonary in 44.2%, cardiac in 48.4% infants. Respiratory involvement having 53.3% of mortality had maximum of all other organ system involvement. Involvement of Two organ system occurred in 39 infants as compared to three and four organ system involvement in 44 and 37 infants respectively. Four organ system involvements accounted 72.9% mortality whereas two and three organ system involvement contributed 20.5% and 38.6% respectively. Three and Four organ system involvement had significant statistical association to mortality; p value <0.05 and <0.0001 respectively.

Conclusions: Multiorgan Dysfunction (MOD) remains an essential entity of perinatal asphyxia. The result further delineates the clinical spectrum of Multi organ dysfunction and emphasizes the need of global management in asphyxiated new born babies.

Keywords: HIE (hypoxic ischemic encephalopathy), MOD, Birth asphyxia

INTRODUCTION

Perinatal asphyxia is an important cause of neonatal mortality, morbidity and late sequelae in developing countries like India. Each year 4 million neonates die worldwide, representing 38 % of all deaths of children less than 5 years of age.¹ 23% of neonatal deaths in low-income countries are due to birth asphyxia.¹ Among the complications of birth asphyxia, HIE and multi organ failure are the most dreaded complications. Now there is

a consensus that multiple organ dysfunctions is a constant feature of neonatal post asphyxial syndrome.² It is important to identify those who are destined to have a good outcome so as to avoid subjecting this group to therapeutic interventions that may be potentially toxic. In developing countries like India, early recognition of multi organ dysfunction may affect the management of these neonates, therefore this prospective study of asphyxiated neonates using clinical and biochemical criteria of multiple organ was conducted with objectives: To

evaluate the clinical profile and the frequency, pattern of organ involvement and the impact of different organ system involvement on early neonatal morbidity and mortality in asphyxiated neonates.

METHODS

Patients

The study covered 190 asphyxiated hospital born babies admitted to the NICU during December 2013 to September 2014. The neonates were identified by using any one of the criteria.³

1. Signs of fetal distress as indicated by one of following
 - Fetal bradycardia (<100 beats/min);
 - cord arterial blood or blood gas analysis within first hour after birth indicated by a base deficit >16 mmol/l or umbilical artery pH<7;
 - Thick meconium stained liquor.
2. Apgar score <6 at 5 minute of life.
3. Patient required Positive Pressure Ventilation before sustained respiration occurs.
4. First cry delayed for five minute.
5. Neurologically abnormal in first two hr. of life.
6. Dysfunction in one or more organ system.

Baby born outside PBM hospital and baby with congenital anomalies were excluded. Data about the birth events, Apgar score, antenatal data, maternal history were collected and entered to the prepared proforma. At the time of enrolment a written consent was taken from the guardians. A detailed history was elicited. A thorough clinical examination was performed with special attention to various systems at the zero hour. A baseline investigation profile and sepsis screening was evaluated in all cases within the 1st 12 hrs of life. And then the neonate was followed prospectively up to the discharge and daily progress was monitored. On discharge the neurological status of the baby, treatment advised was recorded.

Central nervous system evaluation

A detailed neurological examination was done on day one. The clinical course was followed, sarnat & sarnat staging was done without EEG according to the clinical signs observed.

Central nervous system dysfunction:^{3,4}

- Seizure,
- Abnormal low or increased neuromuscular tone,
- Intra cranial hemorrhage,

- Abnormal myocardial finding

Renal evaluation

Urine output was monitored daily for the first 7 days. Baby with urine output <1ml/kg/hr was labelled as oliguric and subjected to a fluid challenge test of 20 ml/kg N/2+D10. If 30 min after the challenge oliguria persist, IV furosemide 2mg/kg was administered. If oliguria still persist, baby was diagnosed oliguric ARF (acute renal failure). A day three serum creatinine level was obtained.

Renal dysfunction:^{3,4}

- Anuria or oliguria (<1 ml/kg/hr) for 24 hours or more, and a serum creatinine concentration >100 mmol/l; or
- Anuria/oliguria for >36 hours; or any serum creatinine >125 mmol/l; or
- Serial serum creatinine values that increased postnatally;
- Hematuria and proteinuria >+1 quantitation in successive sample renal tubular acidosis.

Respiratory system evaluation

Evaluation was on the basis of respiratory distress, need for O₂ supplementation, need for mechanical ventilation or the presence of meconium aspiration syndrome. A day one Chest X RAY was done in all patients. ABG (Arterial blood gas analysis) was done when indicated.

Pulmonary dysfunction:^{3,4}

Need for ventilator support with oxygen requirement >40% for at least the first four hours after birth

- Ventilator dependent respiratory distress or hood requirement >24 hr (including meconium aspiration).

Cardiovascular system evaluation

A daily examination was done to detect any murmur, arrhythmias, and signs of congestive heart failure. A day one ECG was done in all patients. In all cases having murmur and any other abnormal cardiac finding, echocardiography was carried out. ECG abnormalities were graded as per Jedeikins criteria.¹⁰

CVS dysfunction:^{3,4}

- Hypotension treated with an inotrope for more than 24 hours to maintain blood pressure within the normal range, or;
- Electrocardiographic evidence of transient myocardial ischaemia;
- Congestive heart failure not associated with structural heart disease or abnormal fluid status.

Gastro intestinal system evaluation

Change in abdominal girth and consistency was monitored. The presence of GIT bleed, abdominal distension was monitored. An X-ray FPA and USG abdomen was done in all probable cases. ALT, AST enzymes levels was obtained on day one. And the course of enzyme profile was monitored for the 1st 7 days. The day of initiation of enteral feeding was noted.

Git dysfunction:^{3,4}

- Abdominal distension and GI Bleeding,
- Necrotizing enterocolitis
- Alanine Aminotransferase >100 IU/l

Metabolic evaluation

A daily blood sugar monitoring was done to detect any hypoglycemia. Random Blood sugar <40mg/dl was defined as hypoglycemia. Sodium <130mg/l was defined as Hyponatremia, serum potassium >5meq/l was defined as Hyperkalemia. And a serum calcium <7.5mg/dl was defined as Hypocalcemia.

Hematologic evaluation

All infants were screened for thrombocytopenia. Any bleeding tendencies, signs of DIC (disseminated intravascular coagulation), Purpura were noted during the stay in hospital.

RESULTS

General data

Out of 190 neonates, 66.9% were males while 33.1% were female. Full term babies comprised 64.7%. 63.6% babies were having birth weight more than 2.5kg. Primi mother accounted 57.8%. 61.6% babies were delivered through normal vaginal route while LSCS and assisted delivery contributed 28.4% and 10% respectively. MSL was found in 42.1% of cases followed by decreased fetal movement (15.2%), abnormal lie (13.1%), oligo and polyhydramnios (11%), PIH (9.7%), obstructed labour (7.3%) and APH (2.6%). None of any natal as well as antenatal insult was documented in 23.1% of cases. The 5 min Apgar score ≤3 was found in 30% of asphyxiated babies.

Characteristic of organ involvement

CNS was affected in 69.4% asphyxiated neonates and was found to be most frequently affected organ system. All CNS involved asphyxiated neonates showed hypoxic ischemic encephalopathy either grade II or III as per Sarnat and Sarnat staging. 82.5% asphyxiated neonates with CNS dysfunction had seizure. 44.3% showed imaging changes (out of 143 neonates) while another 34.12% had EEG abnormalities (out of 144 neonates).

78.9% babies having CNS dysfunction presented seizure within 6 hour of delivery. Tonic type of seizure was most commonly documented (63.3%) followed by subtle type in 27%.

Renal involvement was noted in 52.1% cases. All asphyxiated neonates with renal involvement had raised creatinine level. Azotemia was documented in 80.8% cases. 21.2% asphyxiated neonates presented with oliguric renal failure; another 24.2% showed proteinuria and 13.1% had hematuria. 5.7% asphyxiated neonates developed acute kidney injury requiring renal replacement treatment.

CVS involvement

48.4% asphyxiated neonates had cardiovascular involvement. All asphyxiated neonates with cardiovascular dysfunction required inotrope support. ECG abnormalities were documented in 67.3% neonates having CVS involvement. Murmur was noted in 16.3% neonates. Two neonates presented heart failure. Severity of asphyxia was associated with worsening of ECG abnormalities. 78.5% of Grade III ECG changes occurred in babies with severe asphyxia (5 min Apgar score ≤3).

Respiratory system was affected in 44.2% asphyxiated neonates. Eighty asphyxiated neonates with Respiratory involvement required mechanical ventilation in the first 12 hr of life. Meconium aspiration syndrome was noted in 25.3% asphyxiated neonates. 73.3% asphyxiated neonates with respiratory involvement had chest x-ray abnormalities and another 42.2% had low blood pH. Eleven asphyxiated babies developed pulmonary hemorrhage.

Gastrointestinal system was least commonly involved organ system in 4.7% cases. All babies with GIT dysfunction were associated with multiorgan dysfunction where more than three organ systems were affected.

Metabolic involvement

Hypoglycemia was noted in seven asphyxiated neonates. 10.5% were hyperkalemic. Hypocalcemia (52.1%) was most frequently observed metabolic abnormalities followed by hyponatremia (42.6%).

Hematological involvement

13.6% asphyxiated neonates had anemia. Thrombocytopenia was documented in 27.8% cases. 13.6% asphyxiated neonates had elevated Prothrombin time. 7.8% developed Disseminated intravascular coagulation and 6.8% neonatal Hyperbilirubinemia.

Multiple organ involvement

Single organ system involvement was documented in 26.8% cases while neonates at risk of MOD. In other studies that only concerned to a specific organ system,

the relative frequency of involvement got Multiorgan dysfunction in 63.1%. MOD with two and three organ system involvement was found in 20.8% and 23.2% cases respectively while severe MOD in which all four organ system were affected was found in 19.5%. 84.2% of MOD occurred in baby having severe asphyxia while 45% babies with less severe asphyxia (APGAR score >3) did not develop MOD. CNS was most common, accounting 51% cases with single organ involvement,

which was followed by Renal in 39.2%. Two organ systems involvement was documented in 20.8% babies. CNS-RENAL Involvement was found to be most frequently noted combination accounting for 43.5%. 23.2% neonates were having MOD with three organ system involvement. The most frequently documented organ system involvement combination was CNS-RS-CVS (43.2%) followed by CNS-RS-RENAL (31.8%).

Table 1: Relation of risk factors with outcome.

Factors	No.	MOD (120)	P Value	Mortality (52)	P Value
Wt<2.5kg	69	47 68.1%	0.5	24 34.7%	0.03
Primi Parity	115	79 68.7%	0.019394	30 26.4%	= 0.75883
<37wk Gestation	67	46 68.7%	<0.05	25 37.3%	0.023254
Lscs/Assisted mode	73	44 62.8%	>0.05	16 22%	>0.05
MSL	80	55 68.7%	0.17	22 27.5%	0.69
Abnormal Lie	25	15 60%	0.72	7 28%	<0.05
Oligo/Poly Hydramnios	21	16 76.2%	0.18	10 47.6%	0.02
Eclampsia	18	10 55.5%	0.48	2 11.1%	0.10
Five Min Apgar≤3	57	46 80.7%	=0.0006	45 78.9%	= 0.0000

Table 2: Multiorgan dysfunction and mortality in asphyxiated neonates.

Asphyxiated neonates	No.	%	Expired	
			No.	%
Asphyxiated neonates with MOD	120	63.1%	52	43.3%
Two ORGAN	39	32.5%	8	20.5%
>Two ORGAN	81	67.5%	34	41.9%
Asphyxiated neonates without MOD	70	36.9%	0	0
Total	190	100%	52	27.6%

P value <0.00001

Perinatal data and outcome

LBW, Prematurity and Severe asphyxia (5 min APGAR ≤3) were significantly associated with mortality (Table 1).

Characteristics of organ involvement and outcome

CNS dysfunction had 34.8% mortality while Renal, CVS; Respiratory system had 41.4%, 44.5% and 53.3% mortality respectively. 63.1% developed MOD and 27.6% died during the study period. No mortality was observed in asphyxiated neonates without MOD. Mortality in asphyxiated neonates was significantly associated with occurrences of MOD with P value <0.00001 (Table 2). The relation of characteristics of organ dysfunction to mortality was shown in Table 3. The mean duration of stay in NICU of Babies without evidence of MOD was 5.2 days while babies with MOD had 9.8 days mean length of stay in NICU.

Table 3: Organ dysfunction with outcome in asphyxiated neonates.

	No.	Mortality	P value
CNS Involvement			
HIEII/III	132	49 37.2%	<0.00001
Seizure	109	24 22%	=0.055
Abnormal imaging*	63*	4* 6.3%	<0.05
Abnormal EEG**	49*	5* 10.20%	<0.05
Renal dysfunction			
Raised creatinine	99	41 41.4%	<0.000001
Oliguria	21	6 28.5%	=0.02
Hematuria	13	3 23%	>0.05
Proteinuria	27	8 29.6%	>0.05
Azotemia	80	36 45%	<0.00001
Need of RRT	11	9 81.8%	<0.05
CVS Dysfunction			
Inotropes support	92	41 44.5%	<0.05
Abnormal ECG	62	27 43.5%	=0.0004
Respiratory dysfunction			
Need for ventilation	80	45 56.2%	=0.0000
MAS	23	12 52%	<0.05
Abnormal Chest X-ray	67	24 35.8%	>0.05
Abnormal blood Ph	42	24 57%	=0.001
Pulmonary Hemorrhage	11	8 72.7%	<0.05
Hematological abnormalities			
Abnormal PT	29	13 44.8%	<0.05
DIC	20	11 55%	=0.0003

*, **not carried out in all patients

DISCUSSION

90% of the study neonates showed one or more than one organ system dysfunction although 63.5% neonates had MOD. 84.2% of MOD occurred in baby having severe asphyxia (5min. APGAR ≤ 3). There was variability in the reported incidence of MOD with other studies. It might be explained by the difference in criteria for studies of MOD, (a) the varied spectrum of cases of "intrapartum asphyxia" from mild i.e. with or without HIE during the neonatal period to the severest end of the intrapartum asphyxia, (b) the differences in the definition of MOD with respect to the number of organs included in its definition, (c) the criteria of "organ/system", and the definition of each organ/system.⁵⁻⁸ In addition, our finding also indicate five minute APGAR score along with other risk factors of perinatal asphyxia may help to identify neonates at risk of MOD. In other studies that only concerned to a specific organ system, the relative frequency of involvement got probably skewed towards the organ system evaluated due to the most sensitive definition of dysfunction. Our finding had a balanced definition of involvement of all organ system. The recent consensus statement also suggested that MOD is a criterion to suggest intrapartum timing but is not a specific parameter.⁸ Sarnat and Sarnat reported that those who entered stage III, signs of stage II persisted more than 7 days and whose EEG fails to revert to normal either died or had significant neurologic impairments.⁹ Our results confirmed the observation that there was significant relationship between stage of Encephalopathy and outcome.

Tubular dysfunction in asphyxiated neonates has been identified by means of marker such as β -2 microglobulin, Retinol binding protein, myoglobin.⁶ We have considered renal involvement only in presence of clinically significant clinical criteria which is comparable to those used for other organ system. A significant association between clinical sign of HIE and neurological deficit with persistent oliguria had been reported.⁶ The association of mortality was found significance statistically for RRT, azotemia, oliguria and raised creatinine levels in our study.

Although the fetal and neonatal myocardium seems to be resistant to hypoxia, heart failure was the main recognized manifestation of myocardial dysfunction after perinatal asphyxia in early studies.¹¹ We have only 2 case of heart failure. 67.3% of those neonates who require inotropic support had ECG changes suggestive of myocardial ischemia. The actual myocardial dysfunction was underestimated due to lack of pathologic studies. Pulmonary complications are meconium aspiration syndrome, pulmonary hemorrhage, pulmonary hypertension, surfactant disruption requiring oxygen therapy, mechanical ventilation or extracorporeal membrane oxygenation.¹² The specific mechanism of respiratory distress was not well isolated, various of these factors were reinforcing each other.

APGAR was the only perinatal factor related to the number of organ affected and severity of organ involvement.¹³ Other studies also found a relation of APGAR and mortality and MOD after perinatal asphyxia.

Limitation of the study is, a generally accepted definition of asphyxia was lacking and many other indicators were used to define it. It is possible that mild cases of asphyxia might be missed. No control populations were studied. The definition criteria of organ system dysfunction were a bit arbitrary.

CONCLUSION

Multiple organ dysfunction remains an essential entity of perinatal asphyxia. Our results further delineate the clinical spectrum of Multiorgan dysfunction and emphasize the need of global management in asphyxiated neonates. The new therapeutic modalities of HIE must carefully evaluate possible side effects on other organ system and the changes in pharmacokinetics of drugs due to on-going organ system dysfunction must be concerned.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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