Spectrum of Multi-Organ System Involvement in Perinatal Asphyxia at a Tertiary Care Hospital in Southern India - A Descriptive Study

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ABSTRACT

BACKGROUND

Perinatal asphyxia (PA) is an important cause of neonatal morbidity, mortality, and neurologic handicap in children. Dysfunction of organs other than central nervous system is often recognised after perinatal asphyxia and manifests as hypoxic ischaemic insults to heart, lungs, kidneys and bowel. The purpose of this study was to assess the spectrum of multi-organ system involvement in perinatal asphyxia.

METHODS

This observational, descriptive study was conducted at SVRRGGH (Sri Venkateswara Ramnarayan Ruia Government General Hospital) - Tirupati from October 2010 to September 2011 and has Institutional Ethics Committee approval (Regd. No: 58647, Dt: 20 / 11 / 2010). After considering the inclusion and exclusion criteria, 204 neonates diagnosed with perinatal asphyxia who got admitted in our newborn intensive care unit (NICU) were included in this study.

RESULTS

In the present study, we had 118 (57.89 %) male babies and 86 (42.11 %) female babies. The mean birth weight was 2640 +/- 460 grams. Infants of birth weight 2500 - 4000 grams (appropriate for gestational age - AGA) accounted for 202 (98.96 %). Major maternal risk factors in this study were MSAF (meconium-stained amniotic fluid (66/204, 32.4 %), PIH (pregnancy induced hypertension) and Eclampsia (26/204, 12.7 %) and PROM (premature rupture of membranes) (26/204, 12.7 %). In the present study, we found higher mortality (19/117, 16.2 %) in babies born to multiparous mothers. Respiratory system involvement was seen in 80 (39.2 %) infants. Renal involvement was observed in 58 (27.5 %) infants. Acute renal failure was diagnosed in 22 (10.8 %) cases. CVS (cardiovascular system) involvement was seen in 56 (27.5 %) cases where as GIT (gastrointestinal tract) involvement was found in 32 (15.68 %) cases.

CONCLUSIONS

Epidemiological research is needed to accurately estimate the contribution of birth asphyxia to perinatal morbidity and mortality, especially in community settings where the burden of disease, due to high proportion of unattended deliveries, is likely to be larger than the hospital setting.

KEYWORDS

Perinatal Asphyxia, Neonatal Intensive Care Unit, Hypoxic Ischaemic Encephalopathy, Multi Organ Dysfunction, Cardiovascular System

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BACKGROUND

Perinatal asphyxia (also known as neonatal asphyxia or birth asphyxia) is the medical condition resulting from deprivation of oxygen to a newborn infant that lasts long enough during the birth process to cause physical harm, usually to the brain. It is also the inability to establish and sustain adequate or spontaneous respiration upon delivery of the newborn. Perinatal asphyxia is a major public health problem. As per the latest estimates, PA accounts for 9 % (i.e. 0.8 million) of total under-5 mortality (i.e. 8.8 million) worldwide, being one of the three most common causes of neonatal deaths along with prematurity and bacterial infections. Of a total of 2.7 million stillbirths globally, approximately 1.2 million occur during intrapartum period, largely owing to asphyxia.[1] As per NNPD (National Neonatal and Perinatal Database), 9.5 % of babies require some form of resuscitation. National neonatology forum of India (NNF) has suggested that birth asphyxia should be diagnosed when 'baby has gasping and inadequate breathing or no breathing at 1 minute.' It corresponds to one-minute APGAR (appearance, pulse, grimace, activity and respiration) score of 3 - 6. In 1952, Dr Virginia Apgar devised a scoring system that was a rapid method of assessing the clinical status of the newborn infants at 1 minute of age and the need prompt intervention to establish breathing.[2] Hypoxic ischaemic encephalopathy (HIE) is defined as neonatal encephalopathy with intrapartum hypoxia in the absence of any other abnormality. Infants with severe encephalopathy frequently have an adverse outcome. The outcome of those with moderate encephalopathy is less certain.

The Sarnat grades of encephalopathy are commonly used.[3] Babies with HIE stage 1 have 100 % survival and no or minimal deficits if any. Mortality in babies with HIE stage 2 can vary from 10 - 15 %. 50 % of babies with HIE stage 3 die and the remainder usually have sequelae. Acute hypoxia usually affects all the vital organs and not just the brain but may occasionally occur without major dysfunction of other organs. Multi system involvement may include acute bowel necrosis, renal failure, hepatic injury, cardiac damage, respiratory complications or haematological insult. This requires testing over the early neonatal period (within 24 hours).[4] Manifestations of hypoxic ischaemic encephalopathy were seen in approximately 1.4 % of all babies. PA was responsible for 28.8 % of all neonatal deaths. Apart from neonatal deaths, asphyxia is responsible for life-long neuromotor disability in a large number of children.[5]

Asphyxia can cause damage to almost every tissue and organ of the newborn baby, the target organs for dysfunction due to asphyxia insult being the brain, heart, lungs, kidneys, liver, bowel and bone marrow. The degree of severity of the asphyxia determines the number of organs damaged, and the severity of damage to the organs involved.[6,7,8] Perinatal asphyxia remains an important cause of neonatal mortality, morbidity and late sequelae especially in a developing country like India.

Objective

To assess the spectrum of multi-organ system involvement in perinatal asphyxia.

METHODS

This observational, descriptive study was conducted at SVRRGGH - (Sri Venkateswara Ramnarayan Ruia Government General Hospital) - Tirupati from October 2010 to September 2011 and has Institutional Ethics Committee approval (Regd. No: 58647, Dt: 20/11/2010). All intramural babies (babies born within premises of hospital) with perinatal asphyxia delivered at Government Maternity Hospital, Tirupati whose APGAR score was less than 6 at 1 minute and 5 minutes were included in the study. Neonates with major systemic congenital malformations, birth weight less than 2500 grams; gestational age less than 37 weeks and those babies who had culture positive sepsis were excluded from this study.

All term neonates admitted in neonatal intensive care unit of Department of Paediatrics, SVRRGGH - Tirupati with history suggestive of perinatal asphyxia with 5 minute APGAR score of less than 6 or babies with delayed initiation of respiration of more than 5 minutes with evidence of hypoxic ischaemic encephalopathy at admission (for babies where APGAR score was not available) were included in the study.

Among 366 neonates admitted in our NICU with perinatal asphyxia, 126 cases came culture positive for sepsis on day 5 of admission who were excluded from the study. 18 cases were discharged against medical advice and another 18 cases who did not turn for follow up were also excluded from the study population. Hence, a total of 204 cases were included in this study.

Detailed birth history and examination findings were recorded as per the pre-designed and pre structured proforma. Necessary investigations to identify the multi organ dysfunction like complete blood count (CBC), blood urea, creatinine, liver enzymes, prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), X-ray chest, arterial blood gases (ABG), echocardiography (ECG) etc. as per the protocol were done. Other investigations were done as necessary. Babies were monitored and treated as per standard protocol according to the clinical condition.

Organ Dysfunction was Defined as Follows

Central Nervous System

Evidence of hypoxic ischaemic encephalopathy according to and classified as per Sarnat and Sarna staging. Brain is the most common organ involved in birth asphyxia and its involvement manifests as hypoxic ischemic encephalopathy. Encephalopathy can be mild (HIE stage 1), moderate (HIE stage 2) and severe (HIE stage 3).

Renal failure

Oliguria < 1 ml/kg/hour for more than 24 hours or serum creatinine of more than 1.2 mg/dl. Blood samples for serum creatinine were obtained at around 48 hours of age.

Respiratory System
Hypoxia with or without hypercapnia or need for oxygen to maintain spo2 > 92 % for > 24 hour or requirement for mechanical ventilation.

Cardiac Dysfunction
Signs of poor perfusion like prolonged capillary refill time, poor pulses, tachycardia with or without hypotension or inotrope requirement to maintain normal perfusion or unexplained metabolic acidosis with base excess of more than 5 mEq/L.

Gastrointestinal Evaluation
Evidence of necrotising enterocolitis (NEC) in the form of gastrointestinal (GI) bleeding, abdominal distension, gastrointestinal residues, and X-ray showing signs of NEC.

Hepatic Dysfunction
Elevation of aspartate amino transferase (SGOT) or alanine amino transferase (SGPT) of more than 100 IU/L. Blood samples were taken between 2nd & 5th day of life.

Haematological Dysfunction
PT (Prothrombin time) INR > 1.5 & platelet count less than 1 lakh/mm3. Blood samples were taken between 2nd & 5th day of life.

Statistical Analysis
Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) software version 17.0. Data analysis was done by descriptive statistics as frequency (number) and percentage. Comparison was done by applying frequency and percentage. Percentage of involvement of individual organs was calculated (Table - 4.). Chi square value, P-value and Fisher exact test were applied as per the applicability (Table - 3.). Significance was assessed at 5 % (P < 0.05). A P-value of 0.05 was considered statistically significant. Microsoft Word and Excel were used to generate tables.

RESULTS

During the 1-year study period, out of 204 asphyxiated babies fulfilling the preformed inclusion criteria, we had 118 (57.89 %) male babies and 86 (42.11 %) female babies. The mean birth weight was 2640 +/- 460 grams. Infants of birth weight 2500 - 4000 grams (Appropriate for gestational age - AGA) accounted for 202 (98.96 %) and those more than 4000 grams (large for gestational age - LGA) were 2 (1.04 %). Major maternal risk factors in (Table - 1) this study was MSAF (meconium stained amniotic fluid) (66/204, 32.4 %), PIH (pregnancy induced hypertension) and eclampsia (26/204, 12.7 %), PROM (premature rupture of membranes) (26/204, 12.7 %), prolonged 2nd stage of labor (14/204, 7.9 %), abruptio placenta (6/204, 2.9 %), oligohydramnios (6/204, 2.9 %), per vaginal bleeding (7/204, 3.4 %), and fever in 3rd trimester (4/204, 1.96 %). In about 22.1 % (45/204) cases, no maternal risk factors found. In the present study, 24.5 % of mothers of study population were aged less than 20 years and the mortality in these asphyxiated babies was 34 %. Whereas the mortality in babies whose mothers age group between 20 - 30 years was 5.1 % (7/137) and 35.3 % (6/17) in babies whose mothers aged > 30 years. In the present study, we found higher mortality (19/117, 16.2 %) in babies born to multiparous mothers. In babies of primiparous mothers the mortality was 12.6 % (11/87) (Table - 2).

The P value 0.47; was not significant. We found high mortality (44.44 %, 16/36) among the babies born through assisted delivery and the babies who were resuscitated with IPPV (16/76, 21.1 %). In this, the P value is 0.048; significant (Table - 2). In the present study decreased APGAR score (< 4) at 5 minutes was found in 30 cases and the mortality in these cases was 76.7 % (23/30). P value is < 0.001; significant (Table - 3). Since the study group included all those with perinatal asphyxia (204 cases), 100 % of cases had CNS (central nervous system) involvement (Table - 2). According to Sarnat and Sarnat's staging of HIE (hypoxic ischaemic encephalopathy) 74, 97 and 33 infants were classified into stage 1, 2 and 3 respectively (Table - 2). Clinical seizures were found in 120 infants.

Basic Perinatal Characteristics/ Clinical Variable of Study Population		Frequency Number (%)
Gender (n = 204)	Male	118 (57.89)
	Female	86 (42.11)
Birth weight (grams) (n = 204)	2500 - 3000	98 (48.14)
	3001 - 3500	80 (39.22)
	3501 - 4000	24 (11.60)
	> 4000	2 (1.04)
Maternal age (years) (n = 204)	< 20	50 (24.5)
	20 - 30	137 (67.2)
	> 30	17 (8.3)
Parity of mothers (n = 204)	PRIMIPARA	87 (42.6)
	MULTI PARA	117 (57.4)
Maternal risk factors (n = 204)	MSAF	66 (32.4)
	PIH & Eclampsia	26 (12.7)
	PROM	26 (12.7)
	Prolonged 2nd stage of labor	14 (6.9)
	Abruptio placenta	6 (2.9)
	Fever in 3rd trimester	4 (2)
	Decreased fetal movements	4 (2)
	Oligohydramnios	6 (2.9)
	Per vaginal bleeding	7 (3.4)
	No risk factors	45 (22.1)
Mode of delivery (n = 204)	NVD (Normal vaginal delivery)	114 (55.9)
	LSCS (Lower segment Caesarean section)	54 (26.5)
	Assisted (Forceps/Vacuum)	36 (17.6)
Resuscitation (n = 204)	Minimal	128 (62.7)
	IPPV (Intermittent Positive pressure ventilation)	76 (37.3)
APGAR score (< 4) (n = 204)	At 1 minute	174 (85.3)
	At 5 minutes	30 (14.7)

Table 1. Clinical Variables of (Both Maternal and Neonates with Perinatal Asphyxia) Present Study Population

In HIE stage 1, we found no mortality. In HIE stage 2, the mortality was 9.3 % (9/97) and in HIE stage 3, we found highest mortality 63.6 % (21/33) (Table - 2). Only 12 cases among HIE stage 3 were survived with neurological sequelae. In our study, out of 204 cases, we noted respiratory system involvement in 80 (39.2 %) infants. Renal involvement was observed in 58 (27.5 %) infants. Acute renal failure was diagnosed in 22 (10.8 %) cases. CVS (cardiovascular system) involvement was seen in 56 (27.5

%) cases where as GIT (gastrointestinal tract) involvement was found in 32 (15.68 %) cases. In the present study, haematological abnormalities were found in 40 (19.6 %) babies. In our study group, we found metabolic derangements with clinical manifestations in 51 (25 %) infants (Table - 2).

Among the metabolic derangements, hyperkalaemia was found in 11 cases followed by hypoglycaemia in 10 babies, hypocalcaemia in 8 babies and hyponatremia in 8 babies (Table - 3). Overall mortality in our study was observed to be 14.71 % (30/204) while 85.29 % (174) infants survived.

Basic Perinatal / Clinical Characteristics		Frequency (No.)	Survived No. (%)	Expired No. (%)	Statistics
Maternal age (years)	< 20	50	33 (66)	17 (34)	Chi Square is 30.6423, P value is 0.00001. Significant.
	20 - 30	137	130 (94.9)	7 (5.1)	
	> 30	17	11 (64.7)	6 (35.3)	
Parity	PRIMI	87	76 (87.4)	11 (12.6)	Chi Square is 0.5143, P value is 0.473283. Not Significant.
	Multiparous	117	98 (83.8)	19 (16.2)	
Mode of delivery	NVD	114	106 (93)	8 (7)	Chi Square is 31.311, P value is 0.00001. Significant
	LSCS	54	48 (88.9)	6 (11.1)	
	Assisted (Forceps/Vacuum)	36	20 (55.6)	16 (44.4)	
Resuscitation	Minimal	128	114 (89.1) p	14 (10.9)	Chi Square is 3.8898, P value is 0.04858. Not Significant
	IPPV	76	60 (79)	16 (21)	
APGAR score < 4	At 1 minute	174	167 (96)	7 (4)	Chi Square is 107.6529, P value is 0.00001. Significant
	At 5 minutes	30	7 (23.3)	23 (76.7)	
HIE (Sarnat and Sarnat staging)	Stage 1	74	74 (100)	0 (0)	Fisher exact test value is 0.00001, Significant.
	Stage 2 & 3	130	100 (77)	30 (23)	

Table 2. Distribution of Outcome (Survived/Expired) According to Basic Perinatal / Clinical Characteristics of Present Study Population

Spectrum of Systemic Involvement in Perinatal Asphyxia Cases		Frequency Number (%)
CNS (n = 204)	HIE	204 (100)
	Clinical seizures	120 (58.9)
	Haemorrhage (CNS)	9 (4.4)
Respiratory system (n = 80)	Respiratory distress	51 (63.8)
	MAS	29 (36.3)
CVS (n = 56)	Hypotension (Requiring inotropes)	30 (53.6)
	Clinical murmur	26 (46.4)
Renal system (n = 58)	ARF	22 (38)
	Oliguria	36 (62)
GIT (n = 32)	Gastrointestinal bleeding	12 (37.5)
	Abdominal distention	11 (34.4)
	Altered gastric aspirate	9 (28.1)
Haematological system (n = 32)	With bleeding manifestations	19 (59.4)
	Without bleeding manifestations	13 (40.6)
	Thrombocytopenia	18 (56.25)
	Abnormal PT/APTT	1 (3.1)
Metabolic complications (n = 51)	Hypoglycaemia (RBS < 40 mg/dl)	10 (19.6)
	Hyperglycaemia (RBS > 120 mg/dl)	12 (23.5)
	Hypocalcaemia (Serum Ca < 7.5 mg/dl)	8 (15.7)
	Hyponatremia (Serum Na < 130 mEq/L)	8 (15.7)
	Hyperkalaemia (Serum K > 5 mEq/L)	13 (25.5)

Table 3. Distribution of Present Study Population According to Spectrum of Systemic Involvement

DISCUSSION

Despite the advances in management of perinatal asphyxia, the incidence remains unacceptably high. The pattern and distribution frequency of each organ system involvement in our study slightly differ from previous studies of Perlman JM et al. (1989),[8] Ana Martin et al.[9] (1995) and Akmal Laeeq Chishty et al.[10] (2001). Ana Martin et al. documented single organ involvement in 26 % and two or more than two organs involved in 56 % of infants in their study. They found 18 % of asphyxiated newborns with no signs of organ dysfunction in their study. They found CNS involvement in 72 % infants, followed by renal involvement in 42.1 %, respiratory system 26 %, and CVS involvement in 29 % of cases in their study. Perlman JM et al. reported single organ involvement in 23 % of infants, two organs involvement in 34 %, three organs involvement in 9 % and 34 % of infants with no evidence of organ injury after asphyxial insult. They found a different pattern of systemic involvement with 50 % infants had renal involvement; one third of cases had CNS involvement followed by CVS and respiratory systems accounting for 25 % each. On the other hand, Akmal Laeeq Chishty et al. found CNS involvement in all cases (100 %), two organs involvement in 20 %, three organs in 17 % and more than 3 organs involvement in 51 % infants in their study. In our study, we found single organ involvement (CNS) in 100 % cases, two organ systems involved in 39.2 %, three organs involved in 28.4 % and more than 3 organs involved in 32.4 % of infants. Next to CNS (100 %) involvement, we found respiratory (39.2 %), renal (28.4 %), CVS (27.5 %), metabolic (25 %) and haematological (15.7 %) manifestations in our study population. In the present study, CNS involvement (HIE) was observed in 100 % cases (contributed by HIE stage 1 (36.3 %), HIE stage 2 (47.5 %) and HIE stage 3 (16.2 %). Ana Martin et al. study documented CNS involvement in the form of HIE in 72 % of infants with 41 %, 21 % and 10 % infants classified under HIE1, HIE2 and HIE 3 respectively. Perlman JM et al. observed CNS involvement in 37 % of infants second to renal involvement. Akmal Laeeq Chishty et al. also found 100 % CNS involvement in the form of HIE and 27 %, 51.5 % and 21.5 % case being contributed by HIE stage 1, 2 and 3 respectively (Table - 4). Ana Martin et al. reported respiratory system involvement in 26 % cases. Perlman JM et al. reported respiratory involvement in 23 % cases. We found 39.2 % infants with respiratory system involvement in our study population. Ana Martin et al. reported 42 % cases with renal involvement and observed significant association between renal failure, HIE stage 3 and respiratory failure. Perlman JM et al. documented renal abnormalities in approximately 50 % of infants (Table - 4). Oliguria was seen in 40 % of infants. Elevated creatinine levels were noted in 17 %. In the present study, acute renal involvement (27.45 %) was associated with a mortality of 44.74 % in our study. Oliguria was seen in 12 (42.85 %) infants, out of which 8 infants developed acute renal failure indicating that oliguria can be taken as an early sign of renal failure. In this study, we have considered renal involvement only in the presence of clinically significant dysfunction. Ana Martin et al. (1995) documented the overall incidence of cardiac involvement as

29 %. A transient systolic murmur was noted in 15 (21 %) infants, and the electrocardiogram showed signs of myocardial ischemia in 14 (19 %). Akmal Laeeq Chishty et al. (2001) observed hypotension in 29.5 % cases. Perlman JM et al. (1989) observed 28 % of the infants with CVS involvement. In the present study, CVS involvement was seen in 27.5 % with mortality of 62.07 %. Clinical signs of hypotension like weak peripheral pulse and prolonged capillary filling time, requiring use of inotropes (26.47 %) as an indicator of mild CVS involvement are observed and comparable with earlier studies. Ana Martin et al. 35 (1995) noted GI involvement in 29 % of infants and GI bleeding in 76 % of the infants. Akmal Laeeq Chishty et al. (2001) noted GI complications including gut haemorrhage as hematemesis or haemorrhagic aspirate in 27.5 % cases and persistent feeding intolerance (> 72 hours) in 8 % of cases. In the present study, gastrointestinal involvement was seen in 15.68 % of infants and mortality of 56.25 %. NEC was not found in any of the infants in the study. Akmal Laeeq Chishty et al. (2001) observed hypoglycaemia in 27.6 %, metabolic acidosis in 77 %, hyperbilirubinemia in 24 % and hypocalcaemia in 12 % of infants. In the present study, we observed 10.78 % (11 infants) of asphyxiated neonates to have metabolic disturbances like hyponatremia in 8.83 %, hyperkalaemia in 40.2 %, hypocalcaemia in 12.75 % and hyperglycaemia in 49 % of the infants. The findings of the present study correlates well with earlier studies. Shankaran S et al.[11] noticed haematological involvement in 10 (35.71 %) of 28 infants with severe perinatal asphyxia. In the present study, haematological involvement was the least common system to be affected. We observed haematological involvement in 40 (19.6 %) of asphyxiated neonates. Haematological abnormalities are prominently seen in preterm babies and less commonly in term and as the present study evaluated only term infants, this could be the reason for the difference in the result. In previous studies, the definitions of dysfunction for each organ evaluated were based on the different criterion i.e., mild biochemical involvement without clinical involvement was considered in some studies but only severe failure was the criterion in other. In the present study, we have assessed the organ involvement depending upon the clinical presentations specific for each organ system involvement along with some basic biochemical parameters. Therefore, the relative frequency of organ involvement was probably deviated towards those organs evaluated with the most sensitive definitions of dysfunction in each study giving a different pattern of distribution of organ dysfunction in them.

CNS Involvement	Akmal Laeeq Chishty et al.[92] (2001)	Ana Martin et al.[35] (1995)	Present Study
Hypoxic ischaemic encephalopathy (Sarnat and Sarnat stages)	100	72	100
Stage - 1	27	41	36.3
Stage - 2	51.5	21	47.5
Stage - 3	21.5	10	16.2

Table 4. Distribution (%) of HIE Cases (According to SARNAT and SARNAT Staging) Comparison Among Different studies

This study is an attempt to recognise clinically the systemic involvement following asphyxia. Collectively looking back into our data, at this point, we found that multi organ involvement following perinatal asphyxia can be used as a clinical guideline for predicting morbidity and mortality in asphyxiated newborns.

Organ System Involved	Perlman et al. (1989) %	Akmal Laeeq Chisty et al. (2001) %	Ana Martin et al. (1995) %	Present Study %
CNS	33	100	72	100
Respiratory	25	--	26	39.2
Renal	50	--	42	28.4
CVS	28	29	29	27.5
GIT	--	27.5	29.1	15.7
Haematologic	--	--	--	15.7

Table 5. Comparison of Different Organ Systems Involvement among Different Studies

It was clear from our study that, as the number of organs involved went on increasing, the morbidity and mortality observed was also significantly higher.

CONCLUSIONS

Multi organ dysfunction is a common finding in babies with birth asphyxia. Morbidity and mortality correlates directly with stage of HIE. Cardiac and renal dysfunction in babies with perinatal asphyxia is associated with poor outcome. Mortality increases proportionately with the number of organs involved. Epidemiological research is needed to accurately estimate the contribution of birth asphyxia to perinatal morbidity and mortality, especially in community settings where the burden of disease, due to high proportion of unattended deliveries is likely to be larger than the hospital setting. There is a tremendous need to study this clinical entity with a larger sample size and for a longer duration at more centres in India to give some new dimensions and guidelines for practicing paediatricians.

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