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Original Research Article

Spectrum of multi-organ system involvement in perinatal asphyxia in neonatal intensive care unit department of Pediatrics, King George hospital, Visakhapatnam, Andhra Pradesh, India

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ABSTRACT

Background: The objective of the current study to find out the maternal risk factors associated and spectrum of involvement of multiorgan dysfunction in perinatal asphyxia.
Methods: This is a prospective study comprises of 102 asphyxiated neonates. At the time of admission blood samples were taken for complete blood picture, random blood sugar, serum electrolytes, septic screen & blood culture. For the assessment of the central nervous system a neurosonogram would be carried out in all asphyxiated new-borns. Computed tomography scan was done who had abnormal neurosonogram. Chest x ray was done for all respiratory cases. Echocardiogram was done for cardiac assessment. Renal system evaluated by serum creatinine and urine output.
Results: Of these 102 babies, 59 were males and 43 were females. Major risk factors in the study were meconium stained amniotic fluid cases, eclampsia, pregnancy induced hypertension, premature rupture of membranes and prolonged second stage of labour. central nervous system (CNS) involvement occurred in all 102 (100%) neonates. Hypoxic ischemic encephalopathy was the most common presentation of CNS involvement. Respiratory involvement was noted in 42 (41.5%). Renal involvement was seen in 27 (26.5%). Cardiovascular system involvement was observed in 26 (25.5%). Gastrointestinal involvement was observed in 16 (15.68%). Hematological abnormalities were seen in 14.7%.
Conclusions: Multiorgan dysfunction is common in neonates with perinatal asphyxia. Overall mortality was 24.5%, which clearly indicates the need for early detection of maternal risk factors, better obstetric management and the prompt resuscitator measures.

Keywords: Hypoxic ischemic encephalopathy, Multiorgan dysfunction, Perinatal asphyxia

INTRODUCTION

Perinatal asphyxia is an insult to the fetus or newborn due to a lack of oxygen and/ or a lack of perfusion to various organs of sufficient magnitude and duration to produce more than fleeting functional and/ or biochemical changes.

It is associated with tissue lactic acidosis. If accompanied by hypoventilation, it also may be associated with hypercapnia. The American Academy of pediatrics has proposed that the term perinatal asphyxia defined as cord umbilical artery pH <7.0 with a base deficit>10meq/litre, neurologic manifestations suggestive of hypoxic ischemic encephalopathy and multi organ system dysfunction.[1]

The incidence of perinatal asphyxia is about 1.0 to 1.5% of live births in most centers and is inversely related to gestational age and birth weight, lowering considerably in later gestation. Asphyxia at a pathophysiological level, is the simultaneous combination of both hypoxia and hypoperfusion, which impairs tissue gas exchange, leading to tissue acidosis.

Multiple Organ Involvement

Multisystem involvement likely results from diving reflex, the redistribution of fetal cardiac output away from the skin and musculoskeletal beds and non-vital viscera (kidneys, gastrointestinal tract, liver) to the heart, brain and adrenal glands.[2]

Central nervous system

Four neuropathological processes have been associated with perinatal asphyxia, primary subarachnoid hemorrhage, hypoxic-ischemic encephalopathy (HIE) in term newborns, periventricular leukomalacia and periventricular and intra-ventricular hemorrhage in premature newborns.

Renal system

Kidneys are very sensitive to oxygen deprivation, renal insufficiency may occur within 24 hours of a hypoxic ischemic episode, which if prolonged, may even lead to irreversible cortical necrosis.

Cardiovascular system

Heart failure was the main recognized manifestation of myocardial dysfunction after perinatal asphyxia in early studies. Other recognized complications include cardiogenic shock and hypotension, functional tricuspid incompetence, arrhythmia and myocardial ischemia.

Respiratory system

The pulmonary effects of asphyxia include increased pulmonary vascular resistance, pulmonary hemorrhage, pulmonary edema, secondary hyaline membrane disease and meconium aspiration syndrome.

Gastrointestinal tract system

Gastrointestinal damage might include injury to the bowel wall, which can be mucosal or full thickness and even involve perforation. The asphyxiated infant is at risk for bowel ischemia and necrotizing enterocolitis.

Hematological system

Asphyxiated infants often have a low red cell volume. Disseminated intravascular coagulation is well recognized complication of birth asphyxia.

Metabolic disorders

Metabolic abnormalities like hypoglycemia, hypocalcemia, hyponatremia, Inappropriate secretion of antidiuretic hormone, hypoxemia and acidosis.

Hepatic system

Following the asphyxia insult the liver metabolism may be deranged which can be evident by abnormal serum hepatic enzymes. If total liver failure occurs, it is usually a bad prognostic sign.

The aims and objectives of this study to find out the maternal risk factors associated with birth asphyxia to find out the clinical spectrum of neonates admitted with birth asphyxia in neonatal intensive care unit, Department of Pediatrics, King George Hospital, Visakhapatnam, Andhra Pradesh, India and to find the extent of involvement of different organ systems in cases of birth asphyxia and its impact on outcome.

METHODS

This is a prospective study conducted in neonatal unit, department of pediatrics, King George Hospital, Visakhapatnam from August 2018 to October 2018.

Inclusion criteria

- All term babies with birth asphyxia were taken into study.
- All babies with Apgar <6 at 1 minute and 5 minutes were taken in to the study.

Exclusion criteria

- Neonates with major systemic malformations.
- Those weighing <2000 grams
- Gestational age <37 weeks
- All culture positive birth asphyxia cases.

Among 135 cases that had got admitted in neonatal unit of King George Hospital, Visakhapatnam with birth asphyxia, 15 cases were culture positive after admission which were excluded from the study,9 cases were discharged against medical advice,9 cases did not turn up for follow up study. Hence this study comprises of 102 asphyxiated neonates as per the inclusion and exclusion criteria.

A detailed history would be elicited, and examination performed at the time of admission. The neonatal clinical course followed up prospectively and the data so obtained would be recorded on the proforma. Blood samples were taken for complete blood picture, random blood sugar, serum electrolytes, septic screen and blood culture.

For the assessment of the central nervous system, a detailed neurologic examination would be performed

daily and any features of central nervous system injury eg. seizures, abnormal tone would be noted. Sarnat HB et al, Sarnat MS et al would be used to classify the neurologic status clinically.[3] In order to provide objective evidence of central nervous system injury a neurosonogram would be carried out on day seven of life in all asphyxiated newborns. Computed tomography scan was done for all babies who were abnormal on neurological examination and who had abnormal neurosonogram. At the time of onset of convulsions, random blood sugar and serum calcium levels were checked, if they were normal given injection Phenobarbitone loading dose (20 mg/kg) if convulsions persists after15 minutes considered mini bolus (10 mg/Kg) up to 40 mg/kg, assess seizures control after every 15 min of end of bolus. If seizures persist injection phenytoin (20 mg/kg) given and assessed seizure control after 30 minutes. If seizures persist, injection Lorazepam (0.05mg/Kg/dose) was given. If convulsions persist, injection Midazolam (0.15 mg/kg/dose) followed by infusion starting with 1mcg/Kg/minute up to maximum of 18mcg/kg/min given. If seizures persist considered alternative drugs (pyridoxin, sodium valproate, lignocaine). 10% calcium gluconate 6-8 mg/kg/day was added to the maintenance intravenous fluids for all birth asphyxia cases for 3 to 5 days. Babies were discharged on oral phenobarbitone. All babies were followed at first month of life, if central nervous system examination is normal oral phenobarbitone was stopped. If central nervous system examination is abnormal, oral phenobarbitone was continued and electroencephalogram (EEG) was repeated.

Respiratory system clinically assessed on the basis of presence of respiratory distress, need for oxygen supplementation, need for mechanical ventilation and the presence of meconium aspiration syndrome. Chest x ray was done for all cases and arterial blood gas analysis would be done for all infants who require mechanical ventilation.

Cardiovascular system would be examined daily to look for heart murmurs, hypotension and shock. Echocardiogram was done for cases with upper limb and lower limb oxygen saturation difference, clinical murmur on auscultation, and abnormal chest x ray. For the evaluation of renal system, urine output would be monitored daily, oliguria defined as urine flow of <1ml/kg/hr for 24hrs.Serum creatinine estimation would be done on day 3 and if the value found >1mg/dl would be considered as evidence of renal injury. Gastrointestinal system would be assessed by looking for any abdominal distension, altered gastric aspirate and gastro intestinal bleeding.

RESULTS

Among the 102 babies admitted there were more male babies (59) compared to female babies (43) as shown in the (Figure 1).

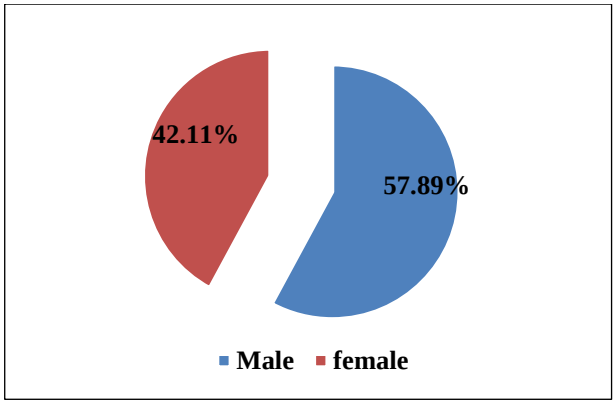

Figure 1: Sex distribution of cases.

Most of the newborns were between 2.5 to 3 kgs accounting approximately half of the newborns as shown in (Figure 2).

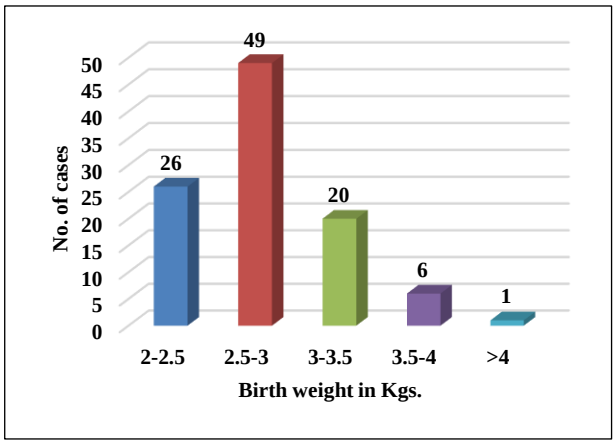

Figure 2: Distribution of cases according to birth weight.

Table 1: Maternal risk factors and risk of perinatal asphyxia.

Maternal risk factors	No. of cases
Meconium stained amniotic fluid	33
Pregnancy induced hypertension and eclampsia	13
Premature rupture of membrane	7
Prolonged second stage of labor	13
Abruptio placentae	3
Fever in 3rd trimester	2
Decreased fetal movements	2
Oligohydramnios	3
Per vaginal bleed	4
No risk factors	22

Meconium stained amniotic fluid, pregnancy induced hypertension, eclampsia, premature rupture of membranes, prolonged second stage of labor were major maternal risk factors associated perinatal asphyxia

accounting approximately more than half of the babies as shown in (Table 1).

Mortality was more in multipara (14 of 58) compared to primigravida (11 of 44) as shown in (Figure 3).

Table 2: Mortality in relation to mode of delivery.

Mode of delivery	No. of cases	Mortality	Percentage
Normal vaginal delivery	57	12	21.05
Lower segment caesarian section	27	5	18.5
Assisted (forceps/vacuum)	18	8	44.4
Total	102	25	

Table 3: Resuscitation details and outcome.

Resuscitation details	No. of cases	Survived	Expired
Minimal resuscitation	64	54	10
Intermittent positive pressure ventilation	38	23	15
Total	102	77	25

Table 4: Organ dysfunction in relation to APGAR scoring system.

APGAR score at 5 min	No. of neonates	Organ dysfunction
4-6	78	23 (30%)
<4	24	24 (100%)

Highest incidence of mortality was seen in babies who were resuscitated with intermittent positive pressure ventilation (60%) than with minimal resuscitation with significant p value (0.048) as shown in (Table 3). While all the neonates with severe birth asphyxia (APGAR <4) had evidence of organ dysfunction, only 1/3rd. of neonates with moderate asphyxia demonstrated evidence of organ dysfunction as shown in (Table 4).

Highest mortality is observed in neonates with hypoxic ischemic encephalopathy (HIE) stage–III (72%) compared to stage-I (0%) with a significant p value (<0.001) as shown in (Table 5). The spectrum of involvement of nervous system in present study was mentioned in Table 6.

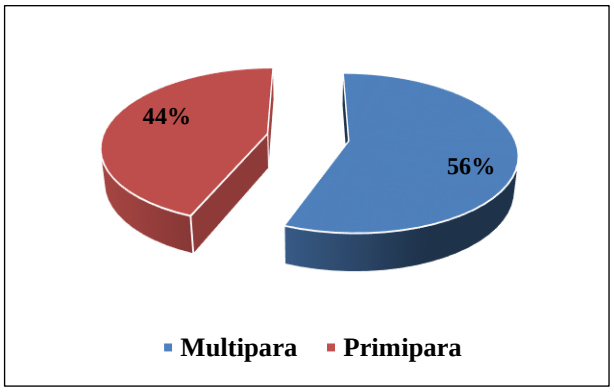

Figure 3: Mortality in relation to parity of mother.

Table 5: Mortality in relation to hypoxic ischemic encephalopathy staging.

Staging	No. of cases	Survived	Expired(percentage)
Hypoxic ischemic encephalopathy -I	35	35	0
Hypoxic ischemic encephalopathy-II	43	37	7 (28%)
Hypoxic ischemic encephalopathy -III	24	6	18 (72%)

All the neonates had hypoxic ischemic encephalopathy, half of them had seizures and very few had hemorrhage as shown in (Table 6). Respiratory system was involved in 42 (41.5%) neonates in present study. There was approximately 50% of mortality in those who affected with this system.

The mortality was more in those affected with meconium aspiration syndrome as shown in (Table 7). Renal involvement was seen in 27 (26.5%) infants. Acute renal failure was observed in 40.7% of cases with renal involvement.

Table 6: Spectrum of involvement of central nervous system.

Central nervous system involvement	No. of cases	Percentage
Hypoxic ischemic encephalopathy	102	100
Clinical seizures	60	58.88
Hemorrhage	5	4.9

Table 7: Respiratory system involvement in perinatal asphyxia.

Respiratory system	No. of cases	Survived	Expired
Respiratory distress	26	15	11
Meconium aspiration syndrome	16	5	11
Total	42	20	22

Table 8: Renal system involvement in perinatal Asphyxia.

Renal system	No of cases	Survived	Expired
Acute renal failure	11	3	8
Oliguria alone	16	10	6
Total	27	13	14

Approximately 50% of babies had mortality with renal involvement with significant p value (<0.001) as shown in (Table 8).

Cardiovascular system involvement was observed in 26 (25.5%) infants. Neonates with cardio vascular involvement were noted to have significantly high mortality rate (69.2%). Use of inotrope was associated with significant mortality in present study as shown in (Table 9).

Table 9: Cardiovascular system involvement in perinatal asphyxia.

Cardiovascular system	Number of cases	Survived	Expired
Hypotension requiring inotropes	17	3	14
Clinical murmur	9	5	4
Total	26	8	18

Mortality was more with the involvement of gastrointestinal system with approximately 50% of babies had mortality with significant p value (0.013) as shown in (Table 10).

Hematological abnormalities were seen in 14.7% of babies in present study. Out of the 15 babies affected 10 had no bleeding manifestations and 5 had bleeding manifestations. Metabolic derangements with clinical manifestation occurred in 11babies. Out of 102 infants studied, seven had hyperkalemia, while five babies had hypoglycemia, four babies had hypocalcemia and four had hyponatremias. Most common organs involved were central nervous system (102) and least common affected were gastrointestinal system (16) as shown in (Figure 4).

Table 10: Gastrointestinal involvement in perinatal asphyxia.

Gastrointestinal system	No of cases	Survived	Expired
GI bleeding	6	1	5
Abdominal distention	5	2	3
Altered gastric aspirate	5	4	1
Total	16	7	9

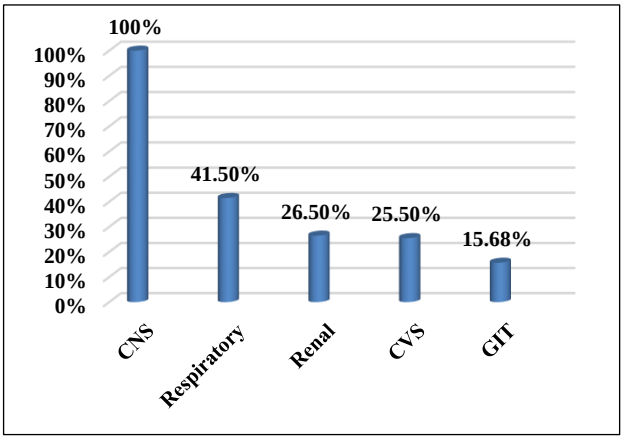

Figure 4: Overall organ involvement.

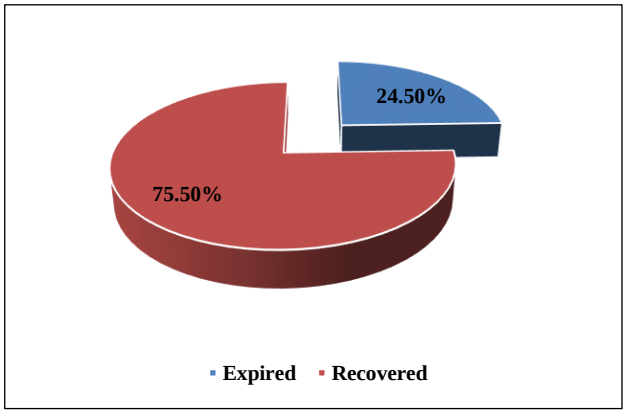

Figure 5: Total number of cases and outcome.

In the present study, mortality increased with increase in number of organs involved, 32% when more than four organs involved compared to 12% when one organ involved as shown in table 11. Overall mortality was

observed to be 25(24.5%), while 77(75.5%) neonates had survived as shown in (Figure 5).

DISCUSSION

Perinatal asphyxia is an important cause of neonatal mortality and morbidity and accompanied by multiorgan dysfunction in many cases.

The present study included 102 neonates. Our sample size was similar to studies by Mohammed LH et al, and Martin-Ancel A et al.[4,5]

In present study , 58% were male babies and 42% were females with male to female ratio being 1.37 :1. These results were similar to studies by Futrakul S et al, Parkash J et al, and Das N et al, and Mohammed LH et al, this male predominance probably reflects negligence and lack of care for female babies in country like India.[4,6,7]

In present study perinatal asphyxia was more common in babies delivered vaginally (74%), compared to those delivered by lower segment caesarian section (26%). Mortality was more in babies delivered by vaginally (26%) compared to lower segment caesarian section (18%). Mortality was still more with assisted vaginal delivery (44%) compared to normal vaginal delivery (21%). this could be the result of difficult deliveries being carried out by vaginally and poor obstetric care. present study results were similar to previous studies by Mohammed LH et al, and Singh KS et al.[4,8]

In the present study, it was observed that meconium stained amniotic fluid (32%), pregnancy included hypertension (PIH) and eclampsia (12%), Prolonged labour (12%) were the major maternal risk factors associated with perinatal asphyxia. Our results suggest that meconium staining was the commonest risk factor for perinatal asphyxia. these results were similar to studies by Ross MG et al, Shrestha M et al, and Mohammad LH et al.[4,9,10]

In the present study, authors observed single organ involvement in 59% infants, two organs were involved in 14.8%, while three organs involvement was seen in 10% of the infants and more than three organs involved was observed in 25.4%. In a similar study by Shah P et al, one organ dysfunction in 5% of cases, two organ dysfunction in 25% of cases ,three organ dysfunction in 33% of cases and four organ dysfunction in 37% of cases.[11] Another similar study by Bennet L et al, one organ dysfunction in 47% of cases, two organ dysfunctions in 17% of cases, three organ dysfunctions in 13% of cases and four organ dysfunctions in 12% of cases.[11] Perlman JM et al, showed single organ involvement in 23% of infants, two organs involvement in 34% and three organs were involved in 9% of the infants and 34% infants with no evidence of organ injury after asphyxia insult.[12] Shankaran S et al, and others observed single organ involvement in 25%, 11% having involvement of two organ system, three organs were involved in 18% neonates,38% in four organ systems that included pulmonary, central nervous system, cardiac and renal systems.[13]

In present study, central nervous system involvement was seen most frequently (100%) followed by respiratory system (41.5%), renal (26.5%), cardiovascular system (25.5%), gastrointestinal system (15.68%) while hematological system was the least commonly involved (14.7%).The study by Martin-Ancel A et al, found central nervous syatem involvement in 72% of the infants, followed by renal system (42.1%), pulmonary involvement (26%) and cardiac involvement (29%).[5] Perlman JM 13 observed a different pattern with renal involvement in 50% of the infants, central nervous system involvement one-third of the cases and cardiovascular and pulmonary abnormalities in 25% each. Chishty AL et al, found encephalopathy in all cases similar to present study.[14]

In previous studies, the definitions of dysfunction for each organ evaluated were based on the different criterion, mild biochemical involvement without clinical involvement was considered in some studies but only severe failure was the criterion in other. Whereas in the present study, authors 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. This study is an attempt to recognize clinically the systemic involvement following asphyxia. In the present study, 34% babies had stage-I hypoxic ischemic encephalopathy (HIE), 42% had stage-II HIE and 23% had stage-III HIE, according to Sarnat HB et al, and Sarnat MS et al. Similar study by Martin-Ancel A et al, showed 41% infants had stage-I HIE, 21% had stage-II HIE and 10% had stage-III HIE. Another similar study by Chisty AL et al, observed that 27% of infants were in HIE stage-I, 51.5% in HIE stage-II and 21.5% in HIE stage-III.[3,5,14]

In the present study respiratory system was the second most common involved 42% next to central nervous system. Respiratory distress was the most common symptom seen in 62% of infants. Although respiratory distress in most of the infants disappeared by the end of one to two days, ten neonates needed mechanical ventilation, which signified the severity of pulmonary involvement. This incidence of respiratory involvement was higher as compared to the earlier studies. Since, it was not possible in present study to have serial arterial blood gas measurements for all infants even the transient tachypnea of newborn was taken as a clinical sign of respiratory involvement, which might have led to such a high incidence of pulmonary involvement in the present study. Similar studies with respiratory system being

second most common system was seen in studies by Pattar RS et al, (63%), Shah P et al, (86%), and Shankaran S et al, (85%).[11,14,15]

In the present study, renal involvement was seen in 26.5% of neonates with perinatal asphyxia and was associated with a mortality of 51% in present study. This was the third most common system affected next to pulmonary system in present study. In this study, authors have considered renal involvement only in the presence of clinically significant dysfunction. Ana Martin et al, showed 42% renal involvement.[5] Perlman JM et al, documented renal abnormalities in approximately 50% of the infants.[13] Other studies which report predominant renal dysfunction [4,5,8]

In the present study, cardiovascular system involvement was seen in 25% with mortality of 69%. Clinical signs of hypotension like weak peripheral pulse and prolonged capillary filling time, requiring use of ionotropes as an indicator of mild cardiovascular system involvement is observed. Martin-Ancel A et al, documented the overall incidence of cardiac involvement as 29%.[5] Chisty AL et al, observed hypotension in 29.5% cases.[14] Perlman JM et al, observed 28% of the infants with cardiovascular system involvement.[12]

In the present study, gastrointestinal involvement was seen in 15% of asphyxiated neonates. Ana Martin et al 5 noted gastrointestinal system involvement in 29% of infants. Chisty AL et al, noted gastrointestinal complications in 27.5% cases.[14]

In the present study, authors observed 20 infants of asphyxiated neonates to have metabolic disturbances like hyponatremia in 20%, hyperkalemia in 35%, hypocalcemia in 20% and hypoglycemia in 25%of the neonates. The findings of the present study correlates well with earlier studies. Chisty AL observed hypoglycemia in 27.6%, metabolic acidosis in 77%, hyperbilirubinemia in 24% and hypocalcemia in 12% of infants.[15]

In the present study, authors observed hematological involvement in 14% of asphyxiated neonates. Hematological 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 compared to by Shankaran S et al, who showed hematologic involvement in 35% of babies with severe perinatal asphyxia.[13]

In the present study, overall mortality was 24.5% which was similar to studies by Singh KS et al, (27%) and Mohammad LH et al (40%).[4,8]

Finally, multiorgan involvement following perinatal asphyxia can be used as a clinical guideline for predicting morbidity and mortality in asphyxiated newborns. It was clear from present study that, as the number of organs involved went on increasing, the morbidity and mortality observed was also significantly higher.

Limitations of present study are a generally accepted definition of asphyxia is lacking and many different clinical markers have been used to suggest that asphyxia has occurred. The inclusion criteria in this study was based on the presence of clinical markers and it is possible that infants with mild asphyxia with changes in bio-chemical markers like umbilical cord pH were missed. There is no control population for this study and dysfunction of organ systems were defined depending upon more on the clinical presentations than the sensitive special investigations.

CONCLUSION

Perinatal asphyxia still remains a major cause of morbidity and mortality during neonatal period in India. Overall mortality was 24.5%, which clearly indicates the need for early detection of maternal risk factors, better obstetric management and the prompt resuscitatory measures.

Prolonged Apgar scores at 5, even at 10, 15, 20 minutes duration were the best clinical predictors of morbidity and mortality during an asphyxial insult. Meconium stained amniotic fluid, pregnancy induced hypertension, premature rupture of membranes, prolonged second stage of labor were the most frequently observed maternal risk factors associated with asphyxia.

Presence of fetal distress antenatally, prolonged low Apgar score, more than two organ systems involvement, central nervous system involvement with multisystem dysfunction, prolonged seizures not controlled by single drug therapy and severe central nervous system damage (hypoxic ischemic encephalopathy- III) were well recognized clinical markers of poor neurological outcome and higher mortality in perinatal asphyxia.

The results of this study highlight the varied clinical picture of multisystem involvement in asphyxiated newborn infant and indicate the need for global management of these infants. There is a tremendous need to study this clinical entity with a larger sample size and for a longer duration at more centers in India to give some new dimensions and guidelines for practicing pediatricians.

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

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