Open Access Journal
International Journal of Medical Research and Pharmaceutical Sciences
Volume 4 (Issue 4): April 2017 ISSN: 2394-9414
DOI- 10.5281/zenodo.569909 Impact Factor- 3.109

ONE YEAR LONGITUDINAL STUDY OF TERM NEONATES WITH PERINATAL ASPHYXIA AND MULTI ORGAN DYSFUNCTION: AN OBSERVATIONAL STUDY

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Keywords:
Multi organ dysfunction; Perinatal asphyxia; Hypoxic ischemic encephalopathy.

Abstract

Introduction – Perinatal asphyxia is an important cause of permanent brain damage. It can result in neonatal mortality, multi organ dysfunction or long term disability in the form of cerebral palsy or mental retardation.

Material and Methods – 100 term neonates with birth asphyxia admitted in the neonatal intensive care unit (NICU) of a tertiary care hospital were included in the study. Signs and symptoms of various organ dysfunction were assessed alongwith relevant laboratory investigations. Babies were followed up every three months for a period of one year after the discharge. Appropriate statistical tests were applied to the data collected.

Results – 76% cases developed multi organ dysfunction (at least one organ dysfunction in addition to central nervous system). Central nervous system (CNS) was affected in all cases followed by respiratory failure in 58%. At the end of one year; 29% babies were normal, 33% developed neuro motor delay, while 30% had expired. 8% cases were lost to follow up. The severity of HIE (Hypoxic ischemic encephalopathy) and the number of organ system involved had a significant association with poor outcome i.e. mortality or neuro developmental delay ($p<0.001$).

Conclusion – Involvement of more than one organ was seen in majority of cases in our study. Poor outcome was more likely in babies with multi organ dysfunction and/or with higher degree of encephalopathy.

Introduction

Perinatal asphyxia is the state of decreased oxygen delivery to the fetus or neonate resulting in inadequate tissue perfusion. World Health Organization has defined birth asphyxia as 'failure to initiate and sustain breathing at birth' and with an Apgar score of less than 7 at one minute of life. The American Academy of Pediatrics (AAP) has described asphyxia as APGAR score below 3 at five minutes associated with cord pH of less than 7.0, presence of neurologic dysfunction and evidence of multiorgan dysfunction.[1]

Perinatal asphyxia is one of the most common causes of neonatal deaths worldwide. Global incidence of perinatal asphyxia has been reported to be 1% to 1.5%.[2] Of the 2.7 million stillbirths globally, asphyxia accounts for 1.2 million deaths during the intrapartum period.[3] In India, about 20% of neonatal deaths are attributed to asphyxia and intrapartum complications. It is the third most common cause of neonatal deaths in our country after prematurity and infections.[4] Death may occur in the neonatal period itself or there may be neuromotor disability resulting in lifelong handicaps in a large number of children.[5] The impaired gas exchange during an asphyxial insult results in decreased perfusion to the various organ systems. There is a redistribution of blood flow to the vital organs like brain, heart and adrenals known as the 'diving reflex'. Asphyxia can cause damage to almost every organ of the newborn body especially brain, heart, lungs, kidneys, liver and gastro-intestinal tract (GIT). The number of organ systems involved is directly related to the degree of asphyxia.[6]

The present study is an attempt to evaluate the involvement of multiple organ systems in cases of perinatal asphyxia and to assess the outcome both immediate and through follow up. There are not many studies on the effects of asphyxia on various organ systems of the neonate other than the central nervous system (CNS) and even lesser

Volume 4 (Issue 4): April 2017 ISSN: 2394-9414
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literature on follow up especially in the Indian population. Considering all these points, this study tries to evaluate the effects of asphyxia on multiple organs and its immediate and delayed outcome in our native population.

Materials And Methods

Study Design

This study was conducted in the Neonatal Intensive Care Unit (NICU) of Department of Paediatrics, Patna Medical College and Hospital, Patna, India over a one year period from April 2011 to April 2012. It included all term neonates born with a history of difficulty in initiation of respiration at birth and an APGAR score below 5 at five minutes of life, or need for resuscitative effort with positive pressure ventilation (PPV) for more than one minute, or neonates with delayed cry at birth and examination findings suggestive of hypoxic ischemic encephalopathy at the time of admission (in cases where Apgar score was missing). Babies with major congenital malformations, or gestational age below 37 weeks from the last menstrual period, or birth weight below 2000 grams were excluded from the study.

A total of 100 neonates were included in the study. All neonates included in the study were examined in detail and relevant history with examination findings were recorded according to the predesigned proforma. All these babies were observed during their NICU stay and signs and symptoms of involvement of various organ systems were noted. All babies were treated as per standard protocol. Apart from the routine investigations like complete blood count, serum electrolytes, renal and liver function tests; these babies were subjected to specialised investigations pertaining to the organ system affected. Informed consent from the parents and approval from the ethical committee was taken for the study.

Criterion for Organ dysfunction was as follows:

Central nervous system – Clinical features of Hypoxic Ischemic Encephalopathy (HIE) as described under Sarnat & Sarnat staging.[7]

Respiratory – Need for supplemental oxygen to maintain Spo2 ≥ 92% for >24 hrs, or need for mechanical ventilation, or hypoxia and/or hypercapnia.

Cardio vascular system - Evidence of hypoperfusion in the form of prolonged capillary refill time, weak pulses, hypotension, or inotrope requirement for maintenance of normal blood pressure.

Renal- Anuria or Oliguria with urine output <1ml/kg/hr for >48 hrs of life and/or Serum creatinine ≥ 1.2 mg/l at 48 hrs of age.

Gastro intestinal tract- Signs and symptoms of necrotising enterocolitis (NEC) in the form of abdominal distension, GI bleed, with radiological evidence.

Hepatic- An elevation of SGOT/SGPT ≥ 100 U/L at 48 hrs of age.

Hematological- Thrombocytopenia with platelet count < 1 lac / cmm, or Elevation of PT with INR> 1.5 at 48 hrs of age.

Ascertainment of outcome

Immediate outcome was assessed on the basis of course of stay in the NICU with the surviving babies being stabilised and shifted to step down and then discharged. Trivandrum Development Screening Chart was used for assessing neuromotor milestones and findings were recorded.[8] Delayed outcome, as per this proforma, meant cases with neuro-developmental delay and it was determined from the records of neonatal follow up and from re-admissions. All discharged babies were evaluated for neurological development every 3 months till the age of one year and the evaluation was done by the pediatrician in the out-patient department.

Statistical analysis

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Birth weight was expressed as Mean with standard deviation. For the purpose of statistical analysis, outcome was converted into a dichotomous data; good outcome (normal infants) and poor outcome (neuro-developmental delay, expired and attrition). Chi square analysis was done to test for association between various parameters and outcome. An independent sample t test was used for comparison of birth weight difference in the outcome groups. A logistic regression model was applied to examine the relationship between perinatal data and organ involvement. A 'p value' of less than 0.05 was considered significant. All statistical tests were done using IBM SPSS (statistical package for social sciences) version 23.

Results

A total of 100 babies were included in this study. Out of this 74 were males and 26 females. Majority of the babies (96%) were term and delivered through vaginal route (NVD), while only four per cent were born by lower segment caesarean section (LSCS). Most of the cases in our study were outborn (81%), and 19% were born in our hospital. The percentage of institutional delivery was 37%, whereas 63% babies were born at home. The mean birth weight was 2617 grams with a standard deviation of 326 grams. While 44 out of 100 babies were admitted on first day of life, 51% were admitted on day two and five babies were admitted beyond that.

Central nervous system was involved in 100% cases with respiratory system involvement in 58% followed by cardio vascular system dysfunction in 42% cases followed by other organ systems in lesser percentage of cases (Fig. 1.). While 24% babies had involvement of a single organ system, 41% had two organ systems involved and the rest (35%) had three or more organ dysfunction. 76% cases developed multi organ dysfunction (involvement of at least one organ system other than the CNS). On the basis of Sarnat & Sarnat staging,[7] the majority (56%) of cases developed HIE II, 23% had features of HIE III and the remaining babies (21%) did not progress beyond HIE I stage. Among cases who survived the neonatal course, at NICU discharge all system effects other than the central nervous system had resolved. Babies were followed up regularly for a period of one year during which 8% cases were lost to follow up. At the end of one year, 29 % babies had normal outcome, 33% developed neuro developmental delay while 30% had expired. The outcome of neonates with respect to the number of organ systems involved and the stage of HIE has been depicted in Tables 1 and 2, respectively.

A Chi-square test of independence was calculated comparing the staging of HIE in good and poor outcome cases. A significant interaction was found [$\chi^2(2) = 58.68$, $p<0.001$]. Increase in the number of organ system involvement was associated with poor outcome [$\chi^2(2) = 63.04$, $p<0.001$]. Institutional delivery resulted in a significant number of good outcome cases as compared to deliveries at home [$\chi^2(1) = 31.36$, $p<0.001$]. Outcome had no significant relationship with gender [$\chi^2(1) = 0.53$, $p<0.46$] or mode of delivery [$\chi^2(1) = 0.03$, $p<0.85$].

An independent sample t-test was carried out to compare the difference in birth weights of the two outcome groups (good and poor). A mean difference of 80 grams was found but it was not significant [$t(98)=1.121$, $p=0.265$].

A logistic regression analysis was conducted to predict outcome (good or poor) using following predictors: gender, birth weight, setting (institutional vs home) and type (normal vaginal delivery vs LSCS) of delivery, staging of HIE, and organ system involvement. A test of full model against a constant only model was statistically significant, indicating that the predictors as a set reliably distinguished between poor and good outcome (chi square=98.34, $p<0.001$ with df=6). Nagelkerke's R^2 of 0.894 indicated a strong relationship between prediction and grouping. Prediction success overall was 97%. The Wald criterion demonstrated that only staging of HIE ($p=0.035$) and organ system involvement (0.001) made a significant contribution to prediction; while other parameters were not a significant predictor. Exp(B) value indicates that when organ system involvement is raised by one unit (one organ system) the odd's ratio is 318 times as large and therefore neonates with two organ involvement are 318 more times likely to suffer a poor outcome as compared to their counterparts with dysfunction of single organ system. Similarly for staging of HIE, the odd's ratio was 27 times as large.

Discussion

Perinatal asphyxia is an important cause of neonatal mortality and, morbidity which may be life long, disabling and in many cases it is accompanied by dysfunction of other organ systems as well. In the present study, there was involvement of multiple organs in 76% cases, while 24% babies developed HIE without accompanying multi organ

Volume 4 (Issue 4): April 2017 ISSN: 2394-9414
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dysfunction. There was a mortality of 30%. A favourable outcome was seen in 29% subjects only and 33% had neurodevelopmental delay on follow up.

In the present study we had included 100 neonates. Similar sample size was there in studies conducted by Mohammad et al, (n=100),[9] and Anna martin et al,(n=72).[10] Pattar et al, (n=57),[11] Hankins et al, (n=46),[12] and Phelan et al, (n=57)[13] had smaller samples while Shah et al, (n=130),[14] Singh et al, (n=190)[15] had larger sample size. There were 74 males against 26 females in our study sample, thus a male female ratio of 2.84:1. This highly skewed ratio could be explained by the higher admission rate of male neonates in our hospital compared to their female counterparts. Similar pattern was observed in studies conducted at S.N. Medical College, Bagalkot, Karnataka with male female ratio of 2.44:1[11] and S. P. Medical College, Bikaner, Rajasthan having a male female ratio of 2.03:1.[15] This male predominance in the various studies conducted in India possibly reflects the negligence and lack of care for female babies due to the deep rooted gender bias in our society.

The majority of neonates (96%) in our study were delivered vaginally and only 4% were born through LSCS. In other studies also the percentage of babies with asphyxia born vaginally was higher compared to those delivered by LSCS.[9, 15] This may be the result of difficult deliveries being carried out vaginally with lack of timely intervention and poor obstetric care. Similar explanation holds true as 64% of neonates in our study were delivered at home without even basic medical facilities and no monitoring.

Perinatal asphyxia is an important cause of permanent brain damage which may result in either death during the neonatal period itself or disabling sequelae like cerebral palsy or mental retardation. In our study there was involvement of the CNS in all cases. Similar finding with 100% affection of CNS was seen in studies conducted by Mohammad et al and Hankins et al.[9, 12] Hypoxic ischemic encephalopathy (HIE) is the manifestation of CNS dysfunction in asphyxia. There are three grades of encephalopathy, HIE I, HIE II and HIE III with increasing severity. Babies in Stage one encephalopathy have 100% survival with no or minimal sequelae. HIE stage II has good outcome in 80% cases. HIE III has the worst prognosis with 50% mortality and the rest with severe sequelae.[7] In the present study the majority of babies were in stage II (56%) and similar outcome was found, with HIE I patients having the best prognosis and survival in all cases without any disability. Among HIE II cases, only 16% were normal. Stage III encephalopathy had 100% poor outcome with 87% mortality and 13% sequelae. The severity of HIE correlated well with poor outcome and the interaction was found to be statistically significant, which was in agreement with the findings of other studies.[10, 17]

After the CNS, kidneys are the second most commonly affected organ in asphyxia.[6] However, the frequency of other organ involvement varies in the published literature. In the present study the respiratory system was involved in 58% cases and was the most frequently organ affected apart from the CNS. Similar finding with respiratory system being the second most common organ involved was seen in studies conducted by Pattar et al, (63%),[11] Shah et al, (86%)[14] and Shankaran et al, (85%).[16] Other studies reported predominant renal dysfunction.[9,10,15]

In our study, babies who were stabilised and subsequently discharged were followed up every three months for a total duration of one year. The period of follow up ranged from two years[14] to five years[17] in few studies but the majority of them had no data on outcome following discharge. An assessment of neuro motor development was carried out at each follow up visit. Our study reported an overall mortality of 30% which was similar in studies conducted by Singh et al, (27%) [15] and Mohammad et al, (40%).[9] In the present study, at the end of one year, 29% babies were normal while 33% had neurodevelopmental delay. In the study conducted by Shankaran et al, 50% neonates had normal outcome after five years, [17] while Shah et al, reported 35% cases to be normal at the end of two year follow up.[14]

Perinatal asphyxia affects the CNS most commonly but all organ systems are vulnerable to the asphyxial insult. Systemic hypoxia ischemia poses the risk of damage to every organ and thus multi organ dysfunction is a part of the clinical spectrum of asphyxia.[6]In this study single organ system involvement was seen in 24 % of the patients, while 76 % patients had involvement of two or more organs**.**Percentage of multi organ dysfunction which was reported in other studies was similar and it ranged from 63% to 82%.[9-11, 15] However, severe brain injury can occur without involvement of multiple organs as reported by Phelan et al.[13]

Among the babies with single organ dysfunction majority had normal outcome. Among cases with affection of two organs, 63% had developed neuro-developmental delay. Babies with affection of three or more organs had the worst prognosis with 83% mortality and the rest suffering from developmental delay. As is evident, multiple organ involvement adversely affects the prognosis and is directly correlated with poor outcome in such babies. Mohammed et al, found that 100% of babies with four or more organ involvement had expired and 86% of cases with three organ involvement had a fatal outcome.[9] Pattar et al, reported in their study that 32 % of cases with four or more organ system involvement had expired while 38% left against medical advice.[11] A mortality of 73% was seen in babies with four or more organ involvement in the study by Singh et al, while three organ involvement had a fatal course in 38% cases.[15] However, Study by Shah et al, did not find any relation between multi organ dysfunction and outcome.[14]

The following limitations should be considered while interpreting the results of this study. First, lack of a consensus on definition of asphyxia may result in discrepancies in the inclusion criteria of various studies. Secondly, no control population was studied. Also, the criteria for organ involvement varied in different studies.

Conclusion

To conclude our study reiterated the fact that multi organ dysfunction is a common association in babies with asphyxia. Mortality as well as long term sequelae were directly correlated with the degree of HIE and increased proportionately with the number of organ system involved.

Conflicts of Interest

The authors have indicated that they have no potential conflicts of interest to disclose.

Acknowledgement

We are grateful to Dr. Vijendra Nath Jha, M.D. Psychiatry for statistical assistance and thoughtful criticism during the preparation of this manuscript..

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Volume 4 (Issue 4): April 2017 ISSN: 2394-9414
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Figure 1

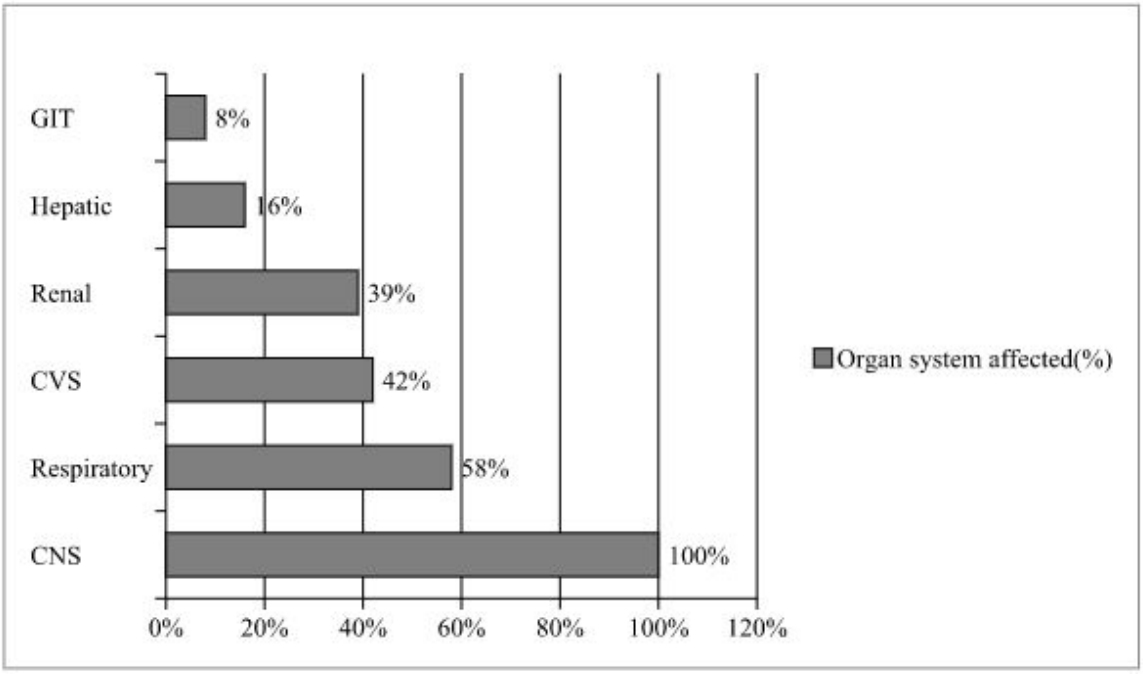

Fig. 1.Frequency of Organ system involvement in term neonates with perinatal asphyxia (GIT- gatro intestinal tract; CVS- cardio vascular system; CNS- central nervous system).

Table 1. Multiorgan dysfunction and its outcome.

	Outcome			
Number of organs involved	Normal	NDD*	Expired	Attrition
One (N=24)	22	2	0	0
Two (N=40)	7	26	0	7
Three or more (N=36)	0	5	30	1
Total (N=100)	29	33	30	8

*NDD- Neuro developmental delay

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International Journal of Medical Research and Pharmaceutical Sciences
Volume 4 (Issue 4): April 2017 ISSN: 2394-9414
DOI- 10.5281/zenodo.569909 Impact Factor- 3.109

Table 2. HIE[#] severity and outcome

	Outcome			
HIE severity	Normal	NDD*	Expired	Attrition
HIE I (N=21)	20	0	0	1
HIE II (N=56)	9	30	10	7
HIE III (N=23)	0	3	20	0
Total	29	33	30	8

[#]HIE – Hypoxic ischemic encephalopathy; *NDD- Neuro developmental delay