Original Articles

Correlates of mortality among hospital-born neonates with birth asphyxia

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ABSTRACT

Background. Birth asphyxia is a major cause of neonatal mortality. An understanding of the determinants of mortality among asphyxiated neonates will help formulate effective management protocols.

Methods. One hundred and fifty consecutive neonates with birth asphyxia (apnoea or gasping respiration at 1-minute of age) were prospectively studied. The association of the outcome variable, namely, mortality before discharge, was documented in relation to a number of clinically important risk factors.

Results. The neonatal mortality of 24.7% (37/150) among asphyxiated neonates was 34.5-times compared to that of the non-asphyxiated population ($p<0.001$). The mortality rates in preterm- and term-asphyxiated neonates were 47.8% and 6%, respectively ($p<0.0001$). The relative risk of mortality increased progressively with increasing birth-weight. On univariate analysis, prematurity, low birth-weight, respiratory distress, severity of asphyxia, hypoxic–ischaemic encephalopathy, apnoea, acidosis and seizures were found to be significant risk factors of death. However, on step-wise regression analysis, prematurity emerged as the most significant determinant of mortality. The highest positive predictive value (58.3%) for mortality was documented for hypoxic–ischaemic encephalopathy.

Conclusion. A significant reduction in mortality among asphyxiated neonates will require aggressive management of prematurity-related neonatal complications and hypoxic–ischaemic encephalopathy.

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INTRODUCTION

Birth asphyxia is a major cause of neonatal deaths in India, both in the community[1,2] and in hospitals.[3,4] Prevention is the most appropriate strategy but is not easy. Even in developed countries with advanced infrastructure for perinatal care, birth asphyxia continues to be a significant problem with an incidence of 1%–1.5%.[5] In India, the estimated incidence of birth asphyxia is higher—12%–16%.[1] Therefore, the management of the asphyxiated neonate is important.

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The broad aims for the care of infants with birth asphyxia are to prevent death and neuromotor sequelae. The long term outcome of asphyxiated neonates has attracted considerable attention and there are several studies on the risk factors and predictors of long term sequelae.[6–10] In contrast, the determinants of neonatal mortality are less well documented. Most studies have addressed the question of mortality in relation to individual correlates such as Apgar scores,[9–12] renal injury[13] or hypoxic–ischaemic encephalopathy (HIE).[6,14] Only one study has discussed the relative importance of a number of determinants of mortality in asphyxiated neonates.[15]

This prospective study was undertaken to determine the correlates of mortality in hospital-born newborns with asphyxia. A better understanding of the determinants of mortality in asphyxiated newborns will enable formulation of suitable management protocols and provide the basis for clinical trials of improved modalities for neonatal life-support measures.

PATIENTS AND METHODS

The obstetric services of the All India Institute of Medical Sciences, a tertiary care hospital in New Delhi, cater largely to 'high-risk' booked cases. The neonatal unit was providing level II facilities (organized special care services without critical care modalities) at the time of this study. A total of 2667 neonates were born at the hospital during a period of 19 months. Of these, 150 (5.6%) had birth asphyxia defined as gasping respiration or apnoea at 1-minute of age.[16] Eighty of them had moderate asphyxia (defined as gasping respiration at 1 minute), while the rest had severe asphyxia (defined as apnoea at 1 minute).[16] There were 83 term and 67 preterm infants.

All deliveries were conducted by resident(s) and/or consultant(s) of the obstetrics department. A resident from the neonatology unit was available for resuscitation of all newborns except 14. Events at birth, in particular, the respiratory status at 1 minute, were carefully timed and recorded. Resuscitation was performed according to the protocol of the unit.[17] The baby was examined after initial stabilization and the birth-weight recorded to the nearest 10 g. Gestation was confirmed clinically[18] to categorize babies into intrauterine growth categories (namely, appropriate-for-dates, small-for-dates, large-for-dates) based on the local charts.[19] Babies with severe asphyxia were transferred to the newborn intensive care unit. Those with moderate asphyxia were managed in the lying-in ward. The manifestations of HIE[14,20] were recorded every 24 hours. Respiratory distress (respiratory rate >60 per minute), with grunt or retractions (of more than 4 hours duration), seizures, apnoea (cessation of respiration for more than 20 seconds), acidosis ($pH<7.3$), congestive heart failure, hyperbilirubin-

aemia (serum bilirubin >15 mg/dl), hypoglycaemia (whole blood glucose <30 mg/dl up to 72 hours of age, and <40 mg/dl after that), polycythaemia (capillary haematocrit >70%), and hypothermia (rectal temperature <35 °C) were systematically looked for. The diagnosis of systemic sepsis was based on the clinical presentation, and the treatment was as per the judgement of the treating team substantiated by blood culture.

The management of neonatal problems was essentially the prerogative of the treating team based on the management guidelines followed in the department. Phenobarbitone was administered randomly as per an ongoing trial within 2 hours after birth and at 12, 36, 60 and 84 (±1) hours of age. Neonates with severe asphyxia received 20 mg/kg initially and 5 mg/kg/dose subsequently by the intravenous route. Those with moderate asphyxia were given 10 mg/kg as the initial dose, followed by 5 mg/kg/dose intramuscularly.

The outcome variable was death before discharge from the hospital. The causes of deaths were classified according to the modified Nakamura classification.[21,22] The data were analysed by Microstat and Epi info 5 softwares. The relative risks (RR) and attributable risks were estimated. Step-wise logistic regression analysis was done for variables found significant on univariate analysis using the BMDP statistical software.

RESULTS

Of the 150 neonates in the observational cohort, 37 (24.7%) died before discharge. In contrast, only 18 (0.7%) of the 2517 neonates without asphyxia died. Thus, asphyxiated newborn infants had a 34.5-fold risk of mortality compared to their non-asphyxiated counterparts (Table I). The population attributable risk of neonatal mortality due to birth asphyxia was 65.2%. The RR of mortality (95% confidence interval) in neonates with moderate and severe birth asphyxia were 15.7 (7.3–33.9) and 55.9 (32.5–96.2), respectively. Mortality among preterm- and term-asphyxiated neonates was 47.8% and 6%, respectively. The mortality rose with decreasing birth-weight in both the asphyxiated and non-asphyxiated subpopulations (Table I). However, the RR for mortality among infants with asphyxia was higher in the higher birth-weight categories, varying from 1.9 in infants weighing <1000 g, to 30.1 in those weighing >2999 g.

The primary causes of death were assigned as follows: perinatal hypoxia in 14 (37.8%), immaturity and hyaline membrane disease in 11 (29.7%), sepsis in 6 (16.2%), congenital malformations in 5 (13.5%) and other causes in one (2.7%).

Table II shows the analysis of various risk factors of mortality among the asphyxiated neonates. Prematurity, low birth-weight, (LBW), respiratory distress, severity of asphyxia, HIE, seizure(s), apnoea and acidosis were significantly related to mortality on univariate analysis. On step-wise logistic regression analysis, incorporating the variables found to be significant on univariate analysis, the following emerged as independent risk factors of mortality: prematurity, HIE, respiratory distress, acidosis and seizure(s) (Table III). The sensitivity, specificity and positive predictive values for death in the presence of these five variables are shown in Table IV. Respiratory distress and prematurity were the most sensitive, while seizure(s) and HIE were the most specific predictors of mortality. The positive predictive value of death was highest (58.3%) for HIE, followed by acidosis (55.3%) and seizures (50%).

DISCUSSION

In this hospital-based study, birth asphyxia emerged as a key determinant of newborn mortality. Asphyxiated infants had a 34.5-fold risk of dying as compared to non-asphyxiated infants. Nearly two-thirds of newborn deaths were attributable to birth asphyxia. Even those subjects who had gasping respiration at 1-minute (moderate asphyxia), had more than 15-fold risk of mortality compared to the non-asphyxiated infants. As expected, the RR among severely asphyxiated neonates (apnoeic at 1-minute) was much higher. Using the need for positive pressure ventilation as a criterion for asphyxia, MacDonald *et al.* reported an 88-fold risk of death in asphyxiated newborns compared to the non-asphyxiated (46.4% *v.* 0.52%).[15]

Several important factors need to be considered while comparing the mortality data of different studies. Firstly, there is no consensus on the definition of asphyxia.[22] Secondly, mortality depends on the gestation and birth-weight distribution of the cohort. If the study cohort includes a greater proportion of low birth-weight or preterm infants, the overall mortality will be high. Thirdly, mortality also depends on the quality of neonatal care at the unit concerned. This information is often difficult to assess from the published description. Within the confines of our definition and the setting, the mortality rate of 24.7% compares well with other reports. MacDonald *et al.* defined asphyxia as the need for positive pressure ventilation for over one minute and reported a mortality rate of 46.3%.[15] Scott reported a 52% mortality in neonates who were either apparent stillbirths or had no spontaneous breathing at 20 minutes.[10]

On univariate analysis, several well-known high-risk neonatal states including prematurity, low birth-weight, severity of asphyxia, respiratory distress, HIE and apnoeic spells emerged as significant determinants of mortality. On regression analysis,

TABLE I. Mortality among neonates with and without asphyxia at birth

Group	With asphyxia		Without asphyxia		Relative risk (95% CI)	p value
	n	Died (%)	*n*	Died (%)		
Overall	150	37 (24.7)	2517	18 (0.7)	34.5 (20.1–59.1)	<0.001
Birth-weight categories (g)						
<1000	11	9 (81.8)	14	6 (42.8)	1.9 (0.9–3.7)	ns
1000–1499	25	13 (52.0)	31	5 (16.1)	3.2 (1.3–7.8)	<0.05
1500–1999	29	7 (24.1)	95	2 (2.0)	11.5 (2.5–52.2)	<0.001
2000–2499	28	4 (14.3)	366	0	Undefined*	<0.0001
2500–2999	32	2 (6.2)	882	2 (0.2)	27.6 (4.0–189.5)	<0.01
>2999	25	2 (8.0)	1129	3 (0.3)	30.1 (5.3–172.3)	<0.01

CI confidence interval * undefined because there were no deaths due to asphyxia

TABLE II. Risk factors of mortality among neonates with birth asphyxia: Univariate analysis

Variable	Total (n=150)	Deaths (%) (n=37)	RR (95% CI)	p value
Prematurity				
No	83	5 (6.0)	7.9 (3.3–19.2)	<0.0001
Yes	67	32 (47.8)		
Low birth-weight				
No	56	4 (7.1)	4.9 (1.8–13.1)	<0.001
Yes	94	33 (35.1)		
Intrauterine growth categories				
Appropriate-for-dates	111	28 (25.2)		
Small-for-dates	30	9 (33.3)	0.8 (0.4–1.5)*	ns
Large-for-dates	9	0		
Respiratory distress				
No	76	4 (5.3)	8.5 (3.2–22.7)	<0.0001
Yes	74	33 (44.6)		
Severity of asphyxia				
Moderate	80	9 (11.2)	3.6 (1.8–7.0)	<0.0001
Severe	70	28 (40.0)		
HIE				
No	114	16 (14.0)	4.2 (2.4–7.1)	<0.001
Yes	36	21 (50.0)		
Seizure				
No	134	29 (21.6)	2.3 (1.3–4.1)	< 0.05
Yes	16	8 (50.0)		
Apnoea				
No	127	26 (20.4)	2.3 (1.3–4.1)	0.01
Yes	23	11 (47.8)		
Acidosis				
No	103	11 (10.7)	5.2 (2.8–9.6)	< 0.0001
Yes	47	26 (55.3)		
Maternal pethidine/sedation				
No	132	33 (25.0)	0.9 (0.3–2.2)	ns
Yes	18	4 (22.2)		
Foetal distress				
No	95	22 (23.1)	1.2 (0.6–2.1)	ns
Yes	55	15 (15.7)		
Meconium staining				
No	108	31 (30)	0.5 (0.2–1.1)	ns
Yes	42	6 (14)		
Hypothermia				
No	135	31 (22.9)	1.7 (0.8–3.5)	ns
Yes	15	6 (40.0)		
Hypoglycaemia				
No	111	28 (25.2)	0.9 (0.5–1.7)	ns
Yes	39	9 (23.0)		
Polycythaemia				
No	144	37 (25.6)	Undefined	ns
Yes	6	0		
Hyperbilirubinaemia				
No	112	25 (33.9)	1.4 (0.8–2.5)	ns
Yes	38	12 (31.5)		
Congestive heart failure				
No	133	31 (22.3)	1.5 (0.7–3.1)	ns
Yes	17	6 (42.8)		
Systemic sepsis				
No	134	30 (22.3)	1.0 (1.0–3.7)	ns
Yes	16	7 (43.7)		
Phenobarbitone use				
No	80	22 (27.5)	0.8 (0.4–1.4)	ns
Yes	70	15 (21.4)		

RR relative risk CI confidence interval *Small for dates *v.* rest
ns not significant HIE Hypoxic–ischaemic encephalopathy

TABLE III. Step-wise regression analysis of risk factors of mortality

Variable	Adjusted odds ratio (95% CI)
Prematurity	23.0 (3.8–139.7)
Hypoxic—ischaemic encephalopathy	7.3 (1.9–28.7)
Respiratory distress	6.0 (1.6–23.4)
Acidosis	5.0 (1.5–16.1)
Seizure	6.7 (1.0–40.8)

CI confidence interval

Table IV. Sensitivity, specificity and positive predictive value for the risk factors found to be significant predictors of death on multivariate analysis (using data from Table II)

Variable	Sensitivity	Specificity	Positive predictive value
Prematurity	86.5	69.0	47.8
Hypoxic–ischaemic encephalopathy	56.8	86.7	58.3
Respiratory distress	89.2	63.7	44.6
Acidosis	70.3	81.4	55.3
Seizure	21.6	92.9	50.0

All figures are percentages

however, prematurity was the most significant determinant of mortality among asphyxiated neonates with adjusted odds of 23 (Table III). As many as 86.5% deaths in asphyxiated infants occurred among preterm infants. MacDonald *et al.*[15] found the mortality among preterm- and term-asphyxiated neonates to be 64.5% (129/199) and 20.6% (31/149), respectively. Volpe determined mortality rates of 60% and 11% among preterm and term neonates with asphyxia, respectively, on the basis of several studies.[20] Other authors have also highlighted the importance of prematurity and low birth-weight as a major correlate of neonatal death in asphyxiated infants.[9,10]

Hypoxic–ischaemic encephalopathy and seizures indicate the presence of overt dysfunction of the central nervous system. These conditions are well known risk factors of mortality in asphyxiated neonates.[6,14,15] We had defined respiratory distress as a respiratory rate >60/minute with grunt or retractions. It was caused by a variety of conditions causing respiratory insufficiency such as hyaline membrane disease, myocardial dysfunction secondary to hypoxia and aspiration syndromes. These serious complications also affect the outcome of an asphyxiated neonate. Acidosis, a consequence of significantly altered homeostasis, itself perpetuates tissue injury and organ system dysfunction.

Although the mortality rate increased with decreasing birth-weight, the RR of death among asphyxiated *v.* non-asphyxiated neonates increased with increasing birth-weight. This indicates that the fatal impact of asphyxia was more in larger infants who otherwise had a good chance of survival. MacDonald *et al.* reported a similar pronounced impact of asphyxia on neonatal mortality among larger infants.[15] This suggests that specific interventions aimed at managing the consequences of asphyxial injury would have an impact on larger and more mature newborns. However, a major reduction in asphyxia-related deaths would depend on the prevention of preterm births and efficient management of the complications of prematurity. In developing countries, neither the incidence of prematurity nor the expertise to manage its complications is likely to improve significantly in the

near future. Hence, the possibility of an early breakthrough in reducing asphyxia-related neonatal mortality in these countries appears remote.

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The ^{13}C urea breath test to assess *Helicobacter pylori* infection in school children

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ABSTRACT

Background. The ^{13}C urea breath test was used in this study to establish it as a diagnostic tool as well as to assess the prevalence of *Helicobactor pylori* in a group of school children.

Methods and Results. In a group of 50 children studied, 82% were found to be positive for *H. pylori* by this test. The influence of diet in modifying the results of the test was also assessed. Relatively small errors were seen if adequate precautions were taken.

Conclusion. Epidemiological studies are required to further quantify the magnitude of the prevalence of *H. pylori* in the Indian setting.

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INTRODUCTION

Helicobacter pylori infection has been established as a major cause of chronic gastritis in adults.[1,2] It has been implicated in the genesis of gastric carcinomas[3] and the development of gastric and duodenal ulcers.[2,4] It is postulated that nearly 90% of the adult population in developing countries may be affected with the infection since childhood.[5,6] Earlier studies on Indians[7–10] using serology and endoscopic biopsy have shown a high incidence of *H. pylori* infection in small numbers of patients. Considering the high prevalence and possible implications of infection with *H. pylori*, there is a need to standardize the ^{13}C urea breath test in the Indian environment.

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