RESEARCH BRIEF

Predictors of Mortality in Neonates with Meconium Aspiration Syndrome

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Received: January 24, 2014; Initial review: February 28, 2014; Accepted: May 12, 2014.

Objective: To identify risk factors for mortality in neonates with meconium aspiration syndrome. **Methods**: All neonates (2004-2010) with meconium aspiration syndrome, irrespective of gestation were included. Risk factors were compared between those who died and survived. **Results**: Out of 172 included neonates, 44 (26%) died. Mean (SD) gestation and birth weight were 37.9 (2.3) weeks and 2545 (646g), respectively. Myocardial dysfunction [aOR 28.4; 95% CI (8.0-101); *P*<0.001] and higher initial oxygen requirement [aOR 1.04; 95% CI (1.02-1.07); *P*<0.001] increased odds of dying while a higher birth weight [aOR 0.998; 95% CI (0.997-1.00); *P*=0.005] reduced the odds of dying. **Conclusions**: Meconium aspiration syndrome is associated with significant mortality. Myocardial dysfunction, birth weight, and initial oxygen requirement are independent predictors of mortality.

Keywords: *Mortality, Neonate, Outcome, Prognosis, Risk factors.*

The most important consequence for a neonate born through meconium stained liquor (MSL) is Meconium aspiration syndrome (MAS), that occurs in 1-3% of live births [1,2]. It is an important cause of neonatal morbidity and mortality in otherwise healthy term and post-term infants, with a case fatality rate approaching 40% [3]. Only a few studies from developing countries have looked at the clinical profile of MAS, associated morbidities and predictors of mortality [4-6]. In this study, we aimed to evaluate the morbidity profile of neonates with MAS, and identify the risk factors that predict mortality during hospital stay in such neonates.

METHODS

This case-control study was conducted in a level III neonatal unit in Northern India. All inborn babies, irrespective of their gestational age and birth weight, with a diagnosis of MAS – born between January 2004 and December 2010 – were included. MAS was diagnosed when the neonate had respiratory distress in the presence of MSL with onset within first 24 hours of life, and a chest *X*-ray showed non-homogenous infiltrates with or without hyperinflation.

Babies born through MSL were managed as per NRP guidelines as modified from time to time [7]. Pediatric residents/neonatology trainees attended all deliveries with MSL and performed endotracheal suction if indicated. Babies who had significant respiratory distress were started on non-invasive ventilation, Continous Positive Airway Pressue (CPAP) or Non-invasive Mechanical Ventilation (NIMV), and mechanically ventilated whenever indicated. Inhaled nitric oxide was available only in the later part of the study period. Case records of the patients were retrieved. Ante-partum and intra-partum risk factors were recorded. Chorio-amnionitis was defined as intra-partum maternal fever of ≥37.8^{0}C with at least two of the four: fetal tachycardia (>180/min), uterine tenderness, maternal leucocyte count >15,000/mm^3 and foul smelling vaginal discharge. Risk factors were compared among survivors and those who died.

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For the purpose of the study, Persistent pulmonary hypertension of newborn (PPHN) was defined on the basis of labile oxygen saturation, a pre-and post-ductal oxygen saturation difference of >10% or pre-and post-ductal partial pressure of arterial oxygen (PaO_2) difference of >20 mmHg with or without the presence of echocardiographic evidence of PPHN. Diagnosis of PPHN on echocardiogram was based on the peak velocity of a tricuspid regurgitant jet with a peak pulmonary pressure gradient of >20 mmHg [8,9]. Hypotensive shock was defined as presence of low pulse volume, tachycardia, skin mottling and a capillary refill time >3 seconds along with a systolic blood pressure (BP) and/or a diastolic BP <5th centile [10]. A diagnosis of hypoxic ischemic encephalopathy (HIE) was made based on Sarnat and Sarnat staging in babies ≥36 weeks of gestation and Levene's staging in babies <36 weeks [11,12]. Myocardial dysfunction was diagnosed on the

basis of edema, third space fluid collection, hepatomegaly, S_3 gallop or cardiogenic shock, manifesting with capillary filling time (CFT) >3 seconds or low BP along with elevated Creatinine Phosphokinase – Muscle Brain (CPK-MB >75 IU/L). Renal dysfunction was defined as an elevated blood urea (>60 mg/dL) or serum creatinine (>1 mg/dL) in the presence of normal maternal renal function.

Data were entered in to SPSS software version 15 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using Chi-square test or Fisher Exact test. Numerical variables were tested for normality using the Kolmogorov – Smirnov test. Normally distributed numerical variables were compared using the Student-t test and those with a skewed distribution were compared using the Mann-Whitney U test. A univariate analysis followed by a multivariable logistic regression model (forward, step-wise) was done to identify factors that were significantly associated with mortality. Variables to be entered in the model were chosen primarily based on a biologically plausible association between the predictor and response variable; a correlation matrix was drawn to identify a strong prior relation between the variables; 1 variable was entered in the model for every 10 subjects with the outcome of interest. A '*P*' value of <0.05 was considered significant. The predictive ability of the model as a whole was calculated both by the conventional manner as well as using the concordance 'c' statistic.

RESULTS

One hundred and seventy neonates were diagnosed to have MAS during the study period and 44 (26%) of them died. Sixty (35%) neonates were mechanically ventilated; it was the initial mode in 42 (25%). Non-invasive ventilation was used in 44 (26%) neonates – in 24 (14%) as the primary mode, and in 20 (12%) as a weaning mode. Median age at onset of respiratory distress was 0 hour (IQR, 0 to 1 hour). The median durations of ventilation and oxygen supplementation were was 22 hours and 66 hours, respectively. Four out of 170 (2.3%) patients received surfactant therapy for MAS. The median duration of hospital stay among those who survived was 168 hours and the median time to mortality was 24 hours.

PPHN, hypotensive shock, HIE (all grades) and myocardial dysfunction was observed in 29 (17%), 37 (22%), 79 (46%) and 37 (22%) neonates, respectively. Inhaled nitric oxide was used for PPHN in one patient whereas sildenafil was used in 3 patients. HIE was mild in 25 (32%), moderate in 44 (56%) and severe in 10 (12%) neonates. Myocardial dysfunction manifested as cardiogenic shock in 31 (18%) neonates, tricuspid regurgitation murmur in 1 (0.6%) and only with elevated CPK-MB levels in the remaining 5 (3%). Pneumothorax was detected in 7 neonates (4%) while one baby (0.6%) had pneumomediastinum.

Risk factors of mortality are presented in ***Table* I**. Of the 18 putative risk factors that emerged significant in univariate analysis, 5 factors namely birth weight (in grams unit), Apgar score at 5 minute (in a scale of 1 to 10), initial oxygen requirement (FiO2 in % unit), and need for mechanical ventilation, and myocardial dysfunction were entered into the regression model. Myocardial dysfunction was chosen over presence of shock as both these variables had a high degree of correlation between them on a correlation matrix and based on a biological assumption that myocardial dysfunction would have preceded shock. The prediction model identified that presence of myocardial dysfunction and a higher initial oxygen requirement increased the odds of death whereas a higher birth weight reduced the odds of death in these neonates with every 1% increase in initial O_2 requirement increasing the odds of death by 4.4% in comparison to baseline. We also observed that for every 100 grams increase in birth weight, the odds of death decreased by 20% from the baseline risk (***Table* II**). This model as a whole had a sensitivity of 78%, specificity of 94%, positive predictive value of 83%, negative predictive value of 93%, a positive likelihood ratio of 13 and a negative likelihood ratio of 0.2. The concordance statistic (c-statistic) of the model was 0.95 (95% CI 91.6-98.9; $P<0.001$)

DISCUSSION

In this study on 170 neonates who developed MAS, one-fourth died. About half of the neonates had HIE whereas a significant number of neonates developed complications. Presence of myocardial dysfunction and a higher initial oxygen requirement independently increased the odds of mortality.

Previous studies have shown a wide range (5-40%) in the mortality among infants with MAS with recent studies showing lower (<15%) mortality rate [13-15]. A higher mortality rate observed in the current study could be related to higher proportion of small for gestational age (SGA) neonates. An association between intra-uterine growth retardation (IUGR) and MAS has been described earlier [5]. The emergence of myocardial dysfunction as an independent risk factor for death indicates the major role of cardiovascular instability in modifying the outcome in such neonates. This also emphasizes the need for aggressive and close cardiovascular monitoring and early vascular support in such neonates. Previous studies have observed PPHN, pneumothorax, birth asphyxia, need for respiratory support in the first 48 hours of life

TABLE I COMPARISON OF RISK FACTORS BETWEEN NEONATES WHO DIED *VS.* SURVIVORS

Risk factor	*Died (n=44)*	*Survived (n=126)*	*Odds ratio or MD (95% CI)*	*P value*
Gestation * (wk)	37.6 (2.5)	37.9 (2.2)	0.3 (-0.45–1.1)	0.45
Preterm (<37 wk)	12 (27)	25 (20)	1.7 (0.8–3.9)	0.17
Birth weight (g)*	2270 (500)	2641 (664)	371 (154–588)	0.001
Low birth weight (<2500g)	29 (67)	48 (38)	3.1 (1.5–6.5)	0.002
Females	24 (55)	45 (36)	2.2 (1.1–4.3)	0.02
Small for gestational age	20 (45)	34 (27)	2.3 (1.1–4.6)	0.02
Thick MSL (*n*=168)	36 (82)	98 (78)	1.2 (0.5–2.9)	0.6
Caesarean section	25 (57)	64 (51)	1.3 (0.6–2.5)	0.49
Non-vigorous at birth	39 (88)	87 (69)	3.5 (1.3–9.5)	0.01
Cord pH*	7.02 (0.2)	7.15 (0.1)	0.13 (0.05–0.2)	0.001
Apgar score at 1 min[#]	3 (1, 5)	5 (3, 7)	1.9 (1.1–2.7)	<0.001
Apgar score at 5 min[#]	6 (3, 8)	8 (7, 9)	1.9 (1.2–2.5)	<0.001
Age of onset of resp. distress (h) [#]	0 (0, 0)	0 (0, 1)	0.9 (-0.6–2.4)	0.23
Need for mechanical ventilation	33 (75)	27 (21)	11 (4.9–24.6)	<0.001
Initial oxygen requirement * (%)	88 (19)	57 (23)	-31.1 (-39– -23)	<0.001
Maximum oxygen requirement * (%)	95 (14)	62 (24)	-32.6 (-4– -24)	<0.001
Duration of ventilation (h)[#]	17 (10, 38)	52 (24, 84)	0.9 (-17.7 – 19.6)	0.92
Duration of oxygen supplementation (h)[#]	25 (10, 53)	72 (36, 120)	72.2 (19.0–125.4)	0.008
Initial PaO_2 (mm Hg)[#]	50 (43, 83)	60 (48, 104)	15.3 (-7.2 – 37.8)	0.18
Persistent pulmonary hypertension	17(39)	12 (10)	7.6 (3.2–18.3)	<0.001
Air leak	4 (9)	4 (3)	3.1 (0.7–12.8)	0.13
Hypotensive shock	30 (68)	7 (6)	36.4 (13.5–98.2)	<0.001
Hypoxic ischemic encephalopathy	33 (75)	46 (37)	5.2 (2.4–11.3)	<0.001
Seizure	11 (25)	15 (12)	2.5 (1.0–5.9)	0.04
Myocardial dysfunction	29 (66)	8 (6)	31.6 (12.1–82.2)	<0.001
Renal dysfunction	9 (20)	8 (6)	3.9 (1.4–10.9)	0.006

*MSL: meconium stained liquor; MD: mean difference; Values of *mean (SD); [#] median (IQR); rest all expressed as n (%).*

TABLE II MULTIVARIATE LOGISTIC REGRESSION MODEL FOR PREDICTING DEATH IN NEONATES WITH MECONIUM ASPIRATION SYNDROME

Variables	*β coefficient*	*Adjusted Odds ratio (95% CI)*	*P value*
Birth weight (g)	- 0.002	0.998 (0.997-1.00)	0.005
Initial oxygen requirement (%)	0.044	1.044 (1.02-1.07)	<0.001
Myocardial dysfunction	3.35	28.5 (8.0-101)	<0.001

Note: For binomial independent variable (Myocardial dysfunction) – 0 (no event) was taken as reference category; direction of the ß coefficient indicates the direction of the association

and the need for vasopressor support as independent predictors of mortality [5,15,16].

Our study has few limitations. First, PPHN and myocardial dysfunction were diagnosed primarily on the basis of clinical presentation, and were not always confirmed by echocardiography. Second, MAS associated mortality (cause-specific) could not be separated out of all-cause mortality due to the presence of various co-morbidities, especially HIE.

To conclude, MAS is associated with significant mortality during the hospital stay. Myocardial dysfunction and a higher initial oxygen requirement increased the odds of death whereas a higher birth weight decreases the odds of death.

WHAT THIS STUDY ADDS?

- Meconium aspiration syndrome in neonates is associated with high (26%) mortality.
- Myocardial dysfunction and higher initial oxygen requirement is associated with higher mortality whereas a higher birth weight is associated with decreased mortality.

Contributors: DL: Data collection and drafted the manuscript; VS: designed the study, performed the analysis, helped in drafting, and reviewed the manuscript; KM, SD and PK: supervised the study and critically reviewed the manuscript.
Funding: None; *Competing interests*: None stated.

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