Risk factors for mortality of preterm infants with meconium aspiration syndrome

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Abstract

ABSTRACT Purpose: Meconium aspiration syndrome as one of the devasting conditions which remains the major cause of neonatal morbidity and mortality. Preterm infants affected by this life-threatening disease did not get enough attention. The aim of this study was to identify risk factors associated with mortality of preterm infant hospitalized with meconium aspiration syndrome. Methods: We undertook a case-control study in a neonatal diagnosis and treatment center in China over a ten-year period. Preterm newborns affected by meconium aspiration syndrome with early onset of respiratory distress hospitalized in NICU were included. Variables were compared between the non-survival group and survival group. Logistic regression model was conducted to identify risk factors associated with mortality. Results: Totally 92 preterm infants were included, 31(33.7%) died. Their median gestational age was 33.4 weeks, and their mean birth weight was 1925.2 g. Female[19(61.3%) vs 18(29.5%), P=0.003], arterial blood pH[7.22(±0.13) vs 7.30(±0.12), p=0.008], persistent pulmonary hypertension[19(61.3%) vs 21(34.4%), P=0.014], and pulmonary hemorrhage[16(51.6%) vs 13(21.3%), P=0.003] were associated with an increased rate of mortality. In the logistic regression model, the risk of death were found to be statistically associated with the following three factors: Female [odds ratio (OR) 3.91; 95% confidence interval(CI) (1.37-11.16); P=0.011], persistent pulmonary hypertension [OR 3.12; 95% CI (1.10-8.89); P=0.033], and pulmonary hemorrhage [OR 4.36; 95% CI (1.53-12.45); P=0.006]. Conclusions: The MAS-associated fatality rates in preterm infant was significantly high. Female, persistent pulmonary hypertension, and pulmonary hemorrhage were considered independent predictors of MAS-associated mortality.

Risk factorsfor mortality of preterm infants with meconium aspiration syndrome

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Methods: We undertook a case-control study in a neonatal diagnosis and treatment center in China over a ten-year period. Preterm newborns affected by meconium aspiration syndrome with early onset of respiratory distress hospitalized in NICU were included. Variables were compared between the non-survival group and survival group. Logistic regression model was conducted to identify risk factors associated with mortality.

Results: Totally 92 preterm infants were included, 31(33.7%) died. Their median gestational age was 33.4 weeks, and their mean birth weight was 1925.2 g. Female[19(61.3%) vs 18(29.5%), P=0.003], arterial blood pH[7.22(±0.13) vs 7.30(±0.12), p=0.008], persistent pulmonary hypertension[19(61.3%) vs 21(34.4%), P=0.014], and pulmonary hemorrhage[16(51.6%) vs 13(21.3%), P=0.003] were associated with an increased rate of mortality. In the logistic regression model, the risk of death were found to be statistically associated with the following three factors: Female [odds ratio (OR) 3.91; 95% confidence interval(CI) (1.37-11.16); P=0.011], persistent pulmonary hypertension [OR 3.12; 95% CI (1.10-8.89); P=0.033], and pulmonary hemorrhage [OR 4.36; 95% CI (1.53-12.45); P=0.006].

Conclusions: The MAS-associated fatality rates in preterm infant was significantly high. Female, persistent pulmonary hypertension, and pulmonary hemorrhage were considered independent predictors of MAS-associated mortality.

Introduction

Meconium aspiration syndrome (MAS), a major cause of morbidity and mortality in neonatal intensive care unit, is characterized by early onset of respiratory distress in neonates born through meconium-stained amniotic fluid (MSAF) with compatible radiological findings which cannot be otherwise explained [1]. Rates of BPD vary from 0.78 to 3.6 per 1000 livebirth without born through MSAF, while the incidence of which is approximately 1.7% to 35.8% in infants born through MSAF [1-4]. MAS remains a life-threatening condition in neonatal intensive care unit throughout the world, with a case fatality rate ranging from 5% to 40%, along with short-term and long-term pulmonary and neurodevelopmental sequelae [1,5-7].

Over the years, studies have sought to quest the risk factors for the mortality of MAS. It was observed that required resuscitation in the delivery room, birth asphyxia, lower birth weight, higher initial oxygen requirement, persistent pulmonary hypertension, pneumothorax, and myocardial dysfunction possess a potential relation to increased mortality in MAS [8-10].

However, these risk factors were identified from term and post-term neonate population which were at higher risk of being affected by MAS. To our knowledge, little is known about factors contributing to MAS-associated mortality in preterm infants in the absence of enough cases. This study was designed to assess the risk factors with respect to increasing mortality in preterm neonates with MAS.

Methods

This is a retrospective case control study of preterm newborns with MAS admitted to the NICU of Children's Hospital of Chongqing Medical University, between Jan 1, 2010 and Jan 1, 2020. Preterm infants born through MSAF grade III and need mechanical ventilation support due to respiratory distress onset within first 24 hours of life were included. Preterm neonates with no need of ventilator support or/and with incomplete data were excluded.

Data from electronic medical records were procured, and were recorded using a standardized form: 1)maternal information (gestational age, delivery mode, disorders complicating pregnancy, antenatal steroid therapy); 2)neonatal data (weight, gender, 1-min and 5-min Apgar score, required resuscitation, duration of hospitalization, outcome); 3)treatment and complications (mechanical ventilation, persistent pulmonary hypertension, neonatal sepsis, shock, necrotizing enterocolitis, pneumothorax, pulmonary hemorrhage, intracranial

hemorrhage, myocardial injury, renal dysfunction, anemia, hypoglycemia).

MAS was defined as respiratory distress in an infant born through MSAF whose symptoms cannot be otherwise explained [1]. Persistent pulmonary hypertension of the newborn (PPHN) was defined as elevated pulmonary vascular resistance and right-to-left shunting at the ductus arteriosus based on echocardiography[11]. Pulmonary hemorrhage was defined as a nontraumatic gush of bloody secretion from the endotracheal tube associated with clinical deterioration as well as requiring increased ventilatory support[12]. Intracranial hemorrhage was depended on imaging manifestations, including intraventricular hemorrhage and intraparenchymal hemorrhage. Arterial blood gas analysis was done at the time of admission to the NICU. This study was approved by the Ethics Committee of the Children's Hospital of Chongqing Medical University (No: 2020-09).

Data analysis was performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Chi-square test or Fisher's exact test were used to analyze categorical variables, as appropriate, and T- Student test or Mann–Whitney U test were used to analyze continuous variables, as appropriate. Categorical variables were expressed as number of cases and percentages while continuous variables were expressed as mean +- standard deviation (SD) or median (range). A p value below 0.05 was considered as statistically significant. Variables that were statistically significant in the univariate analysis were entered into the logistic regression analysis to identify risk factors for mortality of MAS in preterm infants.

Results

95 preterm infants with confirmed MAS were screened during the ten years period (Jan, 2010 to Jan, 2020), 2 case were excluded owing to missing data, 1 case were excluded owing to extremely severe abdominal distension that his parents chose to give up, 92 preterm neonates were finally included, consisting of 31 non-survivors and 61 survivors. The total mortality in this study was 33.7%, while female account for 40% of all involved preterm infants. Their median gestational age was 33.4 weeks, while their mean birth weight was 1925.2 g. Among all the infants, 17 (18.5%) premature infants were small for gestational age.

Table 1 outlines the baseline features compared between the non-survival group and survival group. Risk was substantially higher among those were female. Compared with the survivors, infants in the non-survival group were more likely to be in need of resuscitation. In comparison with infants of non-chorioamnionitis mothers, infants of mothers affected by chorioamnionitis were more likely to die. Infants of mothers undergoing premature rupture of membranes(>18h) were more frequently seen in the non-survival group. Surfactant or inhaled nitric oxide were more likely to administrated in non-survival group. Conversely, compared with the survival group, the non-survival group were in lower birth weight and smaller proportion of small for gestational age. Mothers of infants in the non-survival group were less likely to experience cesarean section and suffer from gestational diabetes mellitus or pregnancy-induced hypertension. Potential of hydrogen (pH) value and partial pressure of arterial oxygen (PaO_2) were lower in the survival group compared with the non-survival group. The median durations of ventilation were 108 hours (survival group) and 48 hours (non-survival group), at the same time the median hospitalization stay of those who survived was 23 day, longer than that of those who dead (their median hospitalization stay was 2 days).

Complications were compared between the two groups showed in table 2. It is suggested that persistent pulmonary hypertension and pulmonary hemorrhage were statistically in correlation with mortality of MAS in preterm infants. Meanwhile, majority of complications listed such as sepsis, necrotizing enterocolitis, pneumothorax, intracranial hemorrhage, shock, patent ductus arteriosus, anemia, myocardial injury, and metabolic acidosis were more frequently seen in the non-survival group.

Table 3 shows the independent risk factors for mortality by multivariate regression analysis. The parameters included in the regression model were all variables significant in the univariate analysis, three risk factors were significantly associated with mortality of MAS in preterm infants: female (P=0.011), persistent pulmonary hypertension (P=0.033), and pulmonary hemorrhage (P=0.006).

Discussion

We found that the mortality rate of preterm infants with MAS was 33.7%, which was similar to that in the study of Louis et al [8]. As mentioned above, this life-threatening condition remains a relatively high case fatality rate. Identifying the specific prediction risk factors of poor prognosis might be helpful to improved survival of preterm infants affected by MAS.

In this study, persistent pulmonary hypertension was considered as an independent risk factor associated with mortality in preterm infants with MAS. It was reported that PPHN increased the risk of death in infants diagnosed with MAS in the study of Louis and colleague[8]. PPHN is more commonly associated with diverse lung pathologies including MAS, perinatal asphyxia, congenital diaphragmatic hernia, pneumonia and respiratory distress syndrome[13]. MAS cause parenchymal lung disease with variable degrees of chemical pneumonitis, surfactant inactivation and release of inflammatory mediators, leading to hypoxemia, acidosis and hypercapnia, ultimately results in pulmonary vasoconstriction[14,15]. In clinical MAS, persistent pulmonary hypertension of the newborn is the leading cause of death in MAS. The overall mortality of infants with PPHN has been reported to be 12%-29% [16-18].

Pulmonary hemorrhage was another independent risk factor associated with mortality in preterm with MAS in our study. It occurs mainly in preterm infants with severe respiratory distress syndrome. Risk factors for pulmonary hemorrhage include severity of associated illness, intrauterine growth restriction, prematurity, PDA, coagulopathy and surfactant therapy [12,19]. Meconium aspiration may lead to uneven airway obstruction and dysfunction of ventilation, finally result in pulmonary hemorrhage. Pulmonary hemorrhage is associated with significant high mortality, which is as high as 50% to 82% [20-22].

Female was found to be another risk factor associated with mortality in preterm infants with MAS in our study, whereas relevant evidence was insufficient. The development and prognosis of some neonatal diseases (eg, neonatal respiratory distress syndrome, glucose-6-phosphate dehydrogenase deficiency, and congenital diaphragmatic hernia) were considered gender-related [23-25]. Although we can't find any strong evidence to explain the effect of gender on increasing the rate of mortality in preterm infants with MAS. Our finding is meaningful and deserves further exploration in the future research.

Lin et al [10] analyzed 314 cases of MAS between 1995 and 2001, and found that infants who required resuscitation in the delivery room, with birth asphyxia, developed persistent pulmonary hypertension and pneumothorax were associated with increased mortality in MAS. Another retrospective study reported that myocardial dysfunction, birth weight, and higher initial oxygen requirement were independent predictors of mortality in neonates with MAS[8]. These above studies included infants irrespective of gestational age, additionally, our study included a relatively small quantity of patients, which may explain the different conclusions of our studies.

Our study has several limitations. The sample size of our study is relatively small. As a case–control study, the inherent shortcomings of a case-control design (eg, selection bias and recall bias) were difficult to avoid. Some of the patients were transferred to our center from other hospitals, and information with regard to the details of treatment protocols performed outside of our hospital were limited.

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