Risk Factors for Intraventricular Hemorrhage in Preterm Infants Born at 34 Weeks of Gestation or Less Following Preterm Premature Rupture of Membranes

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Objective: The objective of this study is to identify possible perinatal risk factors related to intraventricular hemorrhage (IVH) in preterm infants born at 34 weeks of gestation or less following preterm premature rupture of membranes (pPROM). *Methods:* A total of 292 preterm infants born at 34 weeks of gestation or less following pPROM were enrolled in the study, while 155 newborns with incomplete data, especially those that lack histological examination of the placenta, maternal details, and neonatal characteristics, have been further excluded. Finally, data of 137 preterm infants were included in the analysis. All infants underwent ultrasonographic screening for IVH. Thirty-three infants with IVH were considered as cases and 104 infants without IVH were considered as controls. The association between risk factors and IVH was evaluated by univariate and multivariate logistic regression analyses. *Results:* The incidence of IVH in preterm infants born at 34 weeks of gestation or less following pPROM was 24.1%, while the incidence of maternal chorioamnionitis was 43.8%. By univariate analysis, gestational age, birth weight, asphyxia resuscitation, maternal chorioamnionitis, fetal distress, amniotic fluid index, and latency of the rupture of membranes to birth were found to be significantly different between the 2 groups. By logistic regression analysis, lower gestational age, low birth weight, asphyxia resuscitation, and maternal chorioamnionitis were found to be independent risk factors for IVH. *Conclusion:* Lower gestational age, low birth weight, asphyxia resuscitation, and maternal chorioamnionitis are independent risk factors for IVH in preterm infants born at 34 weeks of gestation or less following pPROM. **Key Words:** Intraventricular hemorrhage—preterm infants—preterm premature rupture of membranes—risk factors.

Introduction

Intraventricular hemorrhage (IVH) is a common complication in prematurely born infants. Despite advances in neonatal and obstetric care in the last decade, IVH remains a frequent complication in premature infants. Survivors of severe grades of IVH frequently experience long-term consequences such as cerebral palsy, seizures, cognitive or learning disabilities, and other neurological deficits.[1] Preterm premature rupture of membranes (pPROM) is defined as the rupture of amniotic membranes with release of amniotic fluid before onset of labor before 37 weeks of gestation. Despite recent advances in perinatal care, pPROM continues to occur as an important obstetric

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Received July 3, 2015; revision received October 22, 2015; accepted December 10, 2015.

This work was supported by a grant from Jiangsu Province's Scientific and Technological Supporting Program (grant number BL2012058).

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.12.011

complication. pPROM is associated with early delivery and perinatal infections.[2] Further, it is a potential risk factor for brain injury in preterm infants such as IVH, periventricular leukomalacia (PVL), and other neurodevelopment impairments.[3,4] Studies have mainly focused on antenatal, perinatal, or postnatal causes of IVH in premature infants[5-7]; and risk factors that predict IVH in preterm infants following pPROM are hardly studied. Moreover, optimal management of pPROM remains uncertain and many controversies remain to be unresolved.[8] Hence, the present study aims to evaluate possible risk factors for IVH in preterm infants born at 34 weeks of gestation or less following pPROM.

Materials and Methods

The present study is a retrospective case–control study performed on preterm infants born at 34 weeks of gestation or less following pPROM for risk of IVH at the Division of Neonatology in the Department of Pediatrics of the Affiliated Hospital of Jiangsu University in China from January 2008 to December 2013. This study was approved by the local ethics committee. The Department of Pediatrics is a tertiary-level regional referral center and the Department of Obstetrics conducts 2500 deliveries every year. All study neonates underwent screening for IVH using cranial ultrasound examination by a General Electric E8 ultrasound machine (GE Medical Systems, Milwaukee, WI). According to the clinical protocol of the neonatal intensive care unit (NICU), cranial ultrasound was performed within 48 hours of admission to the NICU, and at the end of the first week of life and twice a week until discharge from the NICU. These ultrasound examinations were supervised and reported by a pediatric radiologist, and images were separately reviewed by a blinded pediatric neurologist. IVH was classified into 4 grades as described by Papile[9]: grade I, hemorrhage restricted to the germinal matrix; grade II, IVH without ventricular dilatation; grade III, IVH with ventricular dilatation; and grade IV, parenchymal hemorrhage.

Exclusion criteria for the study comprise the following: infants born without pPROM, uncertain gestational age, severely malformed fetuses, death within a few hours of birth, and incomplete neonatal data. Maternal details were collected, such as age, number of pregnancies, mode of delivery, amniotic fluid index (AFI), chorioamnionitis, time from rupture of membranes to delivery, preeclampsia, diabetes, and antenatal corticosteroids or antibiotics.

Neonatal variables collected were as follows: gestational age, birth weight, gender, Apgar score after 1 and 5 minutes, fetal distress, asphyxia resuscitation, umbilical cord blood white cell count and C-reactive protein (CRP) levels, and early-onset sepsis.

The pPROM was diagnosed when membrane rupture occurred before the onset of spontaneous labor by visualization of amniotic fluid loss. Time from rupture of membranes to delivery was categorized into 4 time periods: 12 hours or less, more than 12 hours to 24 hours or less, more than 24 hours to 48 hours or less, and more than 48 hours. Prolonged rupture of membranes was defined as rupture of membranes at least 24 hours before delivery. Gestational age was estimated by menstrual history and ultrasound examinations performed before 14 weeks of gestation. Histological chorioamnionitis represented pathological findings on placental tissue that included inflammation of the placental membranes and chorionic plate with polymorphonuclear leukocyte infiltration. Clinical chorioamnionitis was diagnosed in the presence of maternal temperature higher than 38°C, white blood cell count of 15,000 cells/mm^3 or higher, or CRP level higher than 8 mg/L. White blood cell count and CRP levels were routinely performed in all pregnancies. Amniotic fluid volume was estimated by ultrasound examination. AFI was determined by the summation of the vertical diameter of the largest pocket in each of the 4 quadrants. Pre-eclampsia was diagnosed when a pregnant woman developed high blood pressure (2 separate readings taken at least 6 hours apart of 140/90 mm Hg or higher) and proteinuria. Gestational diabetes mellitus was defined as plasma glucose at 130 mg/dL or greater following 75 g oral glucose tolerance test. Antenatal steroids included 2 doses of dexamethasone, which was administered parenterally to induce lung maturation. Maternal antibiotics included maternal treatment with antibiotics during labor. Fetal distress was defined as abnormal cardiotocography and/or meconium-stained amniotic fluid. Neonatal sepsis was defined as positive blood and/or urine culture in the presence of clinical manifestations suggestive of infection. Suspected neonatal sepsis was diagnosed in the absence of positive culture when two or more of the following criteria were present: (1) white blood cell count lower than 5000 cells/μL, (2) polymorphonuclear leukocyte count less than 1800 cells/μL, (3) I:T ratio (ratio of immature to total neutrophils) higher than .2, (4) CRP level of 10 mg/L or higher, and (5) platelet count lower than 80,000 cells/μL.

Statistical analysis was performed using SPSS (version 16) software (SPSS Inc., Chicago, IL). The χ^2 test and Fisher's exact test were performed to compare categorical variables. Fisher's exact test was used when χ^2 test assumptions were violated. Continuous data were expressed as mean ± standard deviation. Univariate and logistic regression analyses were performed to identify independent risk factors for IVH with pPROM. All reported P values were those of 2-sided tests. P values less than .05 were considered statistically significant.

Results

Figure 1 shows the enrollment of cases and controls. The following infants were excluded from the study among