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Adverse Short-Term Outcomes of Preterm Infants Born to Mothers with Preeclampsia by Doppler Cranial Ultrasound Investigation

Qiu Luo[1], Guixian Chen[2], Mei Tang[3*]

[1]Department of Rehabilitation Medicine, The Affiliated Hospital of Yunnan University, The Second Hospital of Yunnan Province, Kunming, China
[2]Department of Obstetrics and Gynecology, The First People's Hospital of Yunnan Province, The Affiliated Hospital of Kunming University of Science and Technology, Kunming, China
[3]Department of Rehabilitation Medicine, The First People's Hospital of Kunming, Kunming, China
Email: luoqiu-220@163.com, gx.chenkm@outlook.com, *Tangmeikm@126.com

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Abstract

Objective: In preeclampsia, abnormal fetal hemodynamics changes can be detected by Doppler ultrasound and predicted the perinatal outcome. But seldom studies focus on these preterm neonate's hemodynamics changes during 72 hours after birth and the adverse short-term outcomes. The present study is planned to assess the parameters of middle cerebral arteries and associate the short-term outcome at 37 weeks early term age in pregnancies complicated by preeclampsia. **Methods:** A total of 114 preterm neonates were included. The Doppler cranial ultrasound was performed to bilateral middle cerebral arteries within 12 - 24 hours, 36 - 48 hours, 60 - 72 hours after birth for all the eligible study neonates. The parameters of resistive index (RI), resistive index (PI) and middle cerebral velocity (MBFV) were recorded by Doppler cranial ultrasound and 106 infants survived assessed by the Neonatal Behavioral Neurological Assessment (NBNA) at 37 weeks early term-equivalent age. **Results:** There were a total of 106 subjects that finally completed the NBNA examination at 37 weeks of early term-equivalent age. In the surviving infants, there were a total of 26 infants with abnormal NBNA scores, among them, 12 infants' mothers were diagnosed with preeclampsia, accounting for up to 46.1%. In these preterm neonates, the lower velocity of bilateral middle cerebral arteries was observed in abnormal infants ($p < 0.05$) and the lowest velocity was observed in these abnormal babies with preeclampsia ($p < 0.05$). **Conclusion:** Velocity of middle cerebral artery is significantly abnormal in preeclampsia. The slower velocity in the 72 hours after birth, the higher associated with adverse perinatal short-term outcome.

*Corresponding author.

Keywords

Preeclampsia, Preterm Neonates, Doppler Cranial Ultrasound

1. Introduction

Preeclampsia (PE) is a major disease of pregnancy and is defined as the presence of maternal hypertension (>140/90 mmHg systolic/diastolic blood pressure) and proteinuria > 300 mg/24h) or a urine dipstick protein of 1+ during the second or third trimester of gestation and can present as late as 4 - 6 weeks postpartum [1] [2] [3]. It is a pregnancy-specific clinical disorder of widespread vascular endothelial malfunction and vasospasm and multisystem involvement. PE is a common unique to humans pregnancy and a global estimate of 3% to 5% of pregnancies and 15% with mild preeclampsia in China are complicated by PE with associated maternofetal morbidity and mortality [4] [5]. Although the etiology of preeclampsia is not clear, the placental insufficiency has been considered as a central figure in the etiology of PE, because a complex process of ischemia-reperfusion in the placenta reveals numerous placental infarcts and sclerotic narrowing of arterioles, meanwhile, the cytotoxic factors were released into the maternal circulation. There is a two-stage hypothesis model to explain the placenta ischemia-reperfusion, in stage one, the incomplete spiral artery was remodeled in the uterus. Then, antiangiogenic factors were released from the ischemic placenta into the maternal circulation which could cause the extensive endothelial damage (stage two) [1] [3] [5]. If the normal placenta artery remodeling process is impaired, then could lead to the repeated ischemia-reperfusion episodes and increase in oxidative stress damage in placenta, finally, this results in the systematic vascular endothelial dysfunction including exaggerated inflammatory response and cardiovascular complications. Until now, there is no cure for PE, thus it often requires termination of pregnancy, which could carry the inherent risks of impaired fetal growth and preterm birth [1] [2] [3] [6] [7].

Infants born preterm due to preeclampsia face a series of challenges in various areas of development problems and comorbidities disease [5]. The major short-term adverse effects of PE are intrauterine growth restriction, thrombocytopenia, neutropenia, and early and late-onset sepsis. Most important complications of prematurity include long-term neurodevelopmental problems, such as cerebral palsy, which would be at significantly increase risk 20-fold of being diagnosed with cerebral palsy [4], motor and cognitive impairment, visual and auditory deficits, and behavioral problems [5]. PE continues to have a high impact on the whole health system as it has numerous adverse effects on both mothers and infants.

There is limited literature on accurate prediction of the neurodevelopmental outcome of preterm infants born to PE mothers, thus, this study evaluated the

middle cerebral arteries parameters by cranial Doppler ultrasound at the first 72 hours post birth and early term 37 weeks gestational age neurodevelopmental assessment outcomes of infants born to PE mothers [8]. Furthermore, we try to establish the association of the early cranial hemodynamics parameters of preterm neonates with short-term neurodevelopment outcomes at their early term 37 weeks gestational age.

2. Materials and Methods

This prospective observational study was conducted at a neonatal intensive care unit of a tertiary-care hospital in China. Neonates born at 28 to 32 weeks of gestation were recruited. Neonates were excluded if they had major congenital anomalies, severe respiratory distress syndrome with invasive ventilation therapy, severe anemia (haemoglobin < 12 mg/dl) mean artery pressure less than 30 mmHg were excluded.

Copies of the study information sheet and the consent form were given to the interested parents when their infants were eligible for the study. All the participating parents were asked to complete a questionnaire about the pregnancy and medical history of the family. The parents brought the signed consent form and the completed questionnaire to the study candidate in the first baseline assessment. At the baseline assessment, the medical files of study neonates were reviewed to retrieve results of their physical examination and laboratory tests. Infants were stratified based on the gestational age at the time of delivery and presence or absence of maternal preeclampsia. The Doppler cranial ultrasound was performed to bilateral middle cerebral arteries within 12 - 24 hours, 36 - 48 hours, 60 - 72 hours after birth for all the eligible study neonates. The parameters of resistive index (RI), resistive index (PI) and middle cerebral velocity (MBFV) were recorded by Doppler cranial ultrasound. Before cUS Doppler investigation for each neonate, hand washing and standard cleaning of the transducers with disinfectant were performed to avoid cross-infection in the NICU.

The survived preterm neonates were assessed using the Neonatal Behavioral Neurological Assessment (NBNA) at their 37 weeks early term equivalent age before discharge from Neonates Intensive Care Unit.

The NBNA which is a comprehensive assessment on behavioral and neurological statuses of the infants [9] includes 20 items divided into four components: behavioral ability (6 items), active muscle tone (4 items), passive muscle tone (4 items), primary reflex (3 items) and general condition (3 items). Each item is graded on 3 levels (0, 1, and 2), with a total score of 40 points, the neonate would be considered as abnormal by total score less than 35 [9].

All statistical analyses were performed using SPSS version 24. Descriptive statistics included mean values and standard deviation for normally distributed continuous variables, median and interquartile range for skewed continuous variables, and frequencies and percentages for categorical variables. A value of $p < 0.05$ was considered statistically significant. Comparison between two groups

was done with independent sample T-test for normally distributed variables or Mann-Whitney U test for non-normally distributed data. Intra-group Doppler ultrasound parameters differences were tested using one-way repeated ANOVA for normally distributed data or Friedman Test for non-normally distributed data.

Study sample size was calculated using a confidence limit (α) of 95% and an absolute precision (D) of 20% with a significance level of 0.05 and the margin of error as 10%. In other words, 114 preterm neonates would be recruited in the present study.

3. Results

In this study, we observed a total of 114 preterm birth, among these neonates, one death (<28 weeks gestational age) within the first three days due to pulmonary hemorrhage, five deaths (28 - 32 weeks gestational age) due to the severe respiratory distress syndrome and two deaths (32 - 37 weeks gestational age) from severe sepsis in the second week after birth. Hence, 106 subjects completed the NBNA examination at 37 weeks of early term-equivalent age (Table 1). In the surviving infants, there were a total of 26 infants with abnormal NBNA scores, among them, 12 infants' mothers were diagnosed with preeclampsia, accounting for up to 46.1% (Table 2). Birth weight was not highly significantly different between the two PE groups and NON-PE group, the age of mother were higher in the PE group than those in the NON-PE group, also cesarean section had highly significant difference between two groups, all of neonates by cesarean in PE group.

There was no significant difference in the bilateral RI, PI value across the first 72 hours after birth in both PE and NON-PE group. A significant difference was found in the bilateral MBFV of NON-PE group across the three days ($p < 0.05$)

Table 1. Demographic and clinical variables in preterm neonates born to mothers with and without preeclampsia.

	All Neonates	Non-PE	PE	p*
Number of neonates	114	96	18	
Age of mother, years	31 (17 - 40)	31 (17 - 38)	33 (27 - 40)	0.042
Gestational age, weeks	31.2 (25.1 - 36.5)	31.2 (25.1 - 36.5)	31.5 (28.3 - 36.2)	0.215
Birth weight, grams	1540 (750 - 3020)	1560 (750 - 3020)	1485 (760 - 2285)	0.163
Vaginal delivery	51 (44.7%)	51 (100%)	0	
Cesarean	63 (60.3%)	45 (71.4%)	18 (28.6%)	<0.001

Table 2. NBNA assessment scores in surviving preterm neonates to mothers with and without preeclampsia.

	All Neonates	Non-PE	PE
Number of infants	106	88 (83%)	18 (17%)
Normal NBNA	80	74 (92.5%)	6 (7.5%)
Abnormal NBNA	26	14 (53.8%)	12 (46.1%)

*-tested using Mann-Whitney U test.

with the velocity of blood flow increasing gradually from day 1 to day 3 (Table 3).

There was a significant difference in velocity of middle cerebral arteries across three days measurements between preterm infants with normal NBNA and abnormal NBNA scores ($p < 0.05$), it was obviously decreased velocity in the abnormal groups (Table 4).

It was significant difference in the velocity of middle cerebral arteries in both PE and NON-PE group with abnormal NBNA scores, in the PE group, these abnormal neonates had lower velocity of bilateral middle cerebral arteries in the first 72 hours after birth (Table 5).

4. Discussion

Although the detrimental short-term and long-term effects of PE on both mother and infant have not been clarified. Fetal ultrasound and Doppler ultrasonography are considered as a noninvasive and clinically useful method for monitoring high-risk pregnancies and detecting the perinatal abnormal. In the recent study, these studies focus on the association of the parameters of middle cerebral artery and umbilical artery in predicting perinatal outcome in fetus complicated by PE with or without intrauterine growth restriction. Several similar studies have shown that the ratios of Middle cerebral artery/umbilical artery PI and RI had the maximum specificity but poor specific for predicting small-for-gestational-age and adverse perinatal outcome [6] [10]. However, one of meta-analysis was done by Morris *et al.* indicated that there was a low predictive accuracy of middle cerebral artery Doppler fetus ultrasound for predicting adverse perinatal outcome due to various limitations of studies [10].

Thus, the accurate prediction of the neurodevelopmental outcome is still under research. In this study, we explore the association of the parameters of bilateral middle cerebral arteries with the short-term outcome in the critical first 72 hours after birth and provide the timely intervention information.

There are two major brain injuries for preterm infants: severe intraventricular hemorrhage and periventricular leukomalacia, both of them are strongly associated with neurodevelopmental impairment. The pathophysiology of injury involves the premature infant's fragile immature cerebral vascular structures, any fluctuations in cerebral blood flow in the highly vascularized germinal matrix would increase the risk of the hemorrhage and immature autoregulatory

Table 3. Hemodynamic parameters in surviving preterm neonates to mothers with and without preeclampsia.

Hemodynamics parameters	PE	NON-PE
RI Left mean (min - max)		
Day 1	0.76 (0.56 - 1.29)	0.75 (0.57 - 1.85)
Day 2	0.73 (0.66 - 1.06)	0.77 (0.56 - 1.10)
Day 3	0.75 (0.60 - 1.19)	0.71 (0.54 - 1.20)
p*	0.57	0.66
PI left mean (min - max)		
Day 1	1.41 (0.85 - 1.90)	1.40 (0.82 - 1.70)
Day 2	1.23 (0.81 - 2.01)	1.29 (0.76 - 1.90)
Day 3	1.36 (0.97 - 1.90)	1.41 (0.78 - 1.75)
p*	0.55	0.77
MBFV Left mean (min - max)		
Day 1	22.7 (19.0 - 25.7)	26.2 (20.9 - 37.3)
Day 2	22.4 (19.0 - 28.0)	26.6 (19.2 - 38.0)
Day 3	23.1 (18.7 - 31.0)	27.7 (19.7 - 39.6)
p*	0.89	< 0.001
RI right mean (min - max)		
Day 1	0.73 (0.54 - 1.72)	0.75 (0.54 - 1.87)
Day 2	0.74 (0.51 - 1.70)	0.74 (0.53 - 1.00)
Day 3	0.77 (0.54 - 1.10)	0.76 (0.55 - 1.65)
p*	0.76	0.18
PI right mean (min - max)		
Day 1	1.28 (0.95 - 1.95)	1.41 (0.82 - 2.08)
Day 2	1.16 (0.71 - 1.90)	1.29 (0.76 - 2.16)
Day 3	1.27 (0.81 - 2.08)	1.42 (0.76 - 1.98)
p*	0.06	0.53
MBFV right mean (min - max)		
Day 1	22.4 (18.5 - 26.9)	25.2 (20.10 - 39.9)
Day 2	23.0 (17.6 - 28.8)	26.9 (19.50 - 38.9)
Day 3	22.1 (19.10 - 28.70)	27.8 (22.0 - 39.7)
p*	0.69	<0.001

Day 1 - 12 to 24 hours after birth; Day 2 - 36 - 48 hours after birth; Day 3 - 60 - 72 hours after birth. *-testing using Friedman Test. MBFV Left-velocity of left middle cerebral artery; MBFV Right-velocity of right middle cerebral artery; PI Left-pulsatility index of left side; PI Right-pulsatility index of right side; RI Left-resistive index of left side; RI Right-resistive index of right side.

Table 4. MBFV velocity in surviving preterm infants with normal or abnormal NBNA scores.

	Normal NBNA	Abnormal NBNA	p*
Number of neonates	80	26	
MBFV left day 1	26.3 (20.9 - 27.5)	23.6 (19.0- 27.3)	0.002
MBFV right day 1	25.3 (20.1 - 29.9)	22.6 (18.5 - 27.7)	0.002
MBFV left day 2	27.5 (19.2 - 28.8)	23.0 (19.0 - 28.3)	0.001
MBFV right day 2	27.6 (20.3 - 28.9)	23.9 (17.6 - 27.2)	<0.001
MBFV left day 3	27.9 (19.7 - 39.6)	23.5 (18.7 - 33.3)	<0.001
MBFV right day 3	28.3 (22.0 - 39.7)	24.5 (19.1 - 32.6)	<0.001

Day 1 - 12 to 24 hours after birth; Day 2 - 36 - 48 hours after birth; Day 3 - 60 - 72 hours after birth. *-tested using Mann-Whitney U test.

Table 5. MBFV in surviving preterm neonates with abnormal NBNA scores.

	Non-PE	PE	p*
Number of neonates	14	12	
MBFV left day 1	24.6 (21.5 - 27.3)	21.5 (19.0 - 22.5)	0.023
MBFV right day 1	24.4 (20.3 - 27.7)	22.0 (18.5 - 25.3)	0.004
MBFV left day 2	26.1 (20.4 - 28.3)	22.4 (19.0 - 27.5)	0.016
MBFV right day 2	25.7 (21.5 - 27.2)	23.0 (17.6 - 26.4)	0.047
MBFV left day 3	26.5 (21.7 - 33.3)	20.9 (18.7 - 27.6)	<0.001
MBFV right day 3	27.3 (22.0 - 32.6)	21.8 (19.1 - 28.7)	<0.001

Day 1 - 12 to 24 hours after birth; Day 2 - 36 - 48 hours after birth; Day 3 - 60 - 72 hours after birth. *-tested using Mann-Whitney U test.

system, with rapid changes in perfusion causing rupture of the germinal matrix vessels, or triggering repeated ischemia-reperfusion oxidative stress, leading to white matter injury which is the secondary injury from the persistently low blood pressure and low blood flow in the brain [11]. The pathophysiology of periventricular leukomalacia is a multifactorial and complex process, which is the result of hypoxia, ischemia and inflammation on the progenitor oligodendrocyte cells during trimester gestation [11] [12].

In this study, we observed the obvious decrease in velocity of middle cerebral arteries of infants with abnormal NBNA scores compared with other normal infants. Among these abnormal infants, whose mothers had preeclamptic, they had much lower velocity of bilateral middle cerebral arteries.

Due to pathology of PE, it is characterized with placental vascular lesions, and the main manifestations of fetus present the underlying chronic hypoxia and increase the fetal growth restriction. The previous studies reported that the levels of erythropoietin in cord blood of fetus with their mother suffered preeclampsia

were increased at birth or 48 hours before birth, which suggested chronic and acute hypoxia in these neonates. We know that erythropoietin which is a glycoprotein hormone and it can't cross the placenta, so the umbilical cord blood erythropoietin is of fetal origin, meanwhile, hypoxia stimulates the production of erythropoietin in the fetal liver.

Elevated umbilical cord erythropoietin levels are evidence of chronic fetal hypoxia, as this result, the compromised oxygen and glucose supply to the brain cells leads to cellular energy failure during critical development period [13]. From the beginning of the third trimester to the end of the third trimester, oligodendrocytes cells are formed in the ventricular zone which allows messages to travel down the length of the axon so that neurons can quickly communicate with each other, and these cells are vulnerable to oxidative stress, thus it means myelination deficient is inevitable due to preterm birth [14].

To our knowledge, this is the first study to observe the short-term outcomes in preterm neonates with or without mother preeclampsia. The main strengths of this study investigated the middle cerebral blood RI, PI and velocity dynamic changes at the first 72 hours after birth in the preterm birth, which provide the evidence that underlying factors for cerebral ischemia-reperfusion damage due to slower velocity of middle cerebral arteries in these neonates with their mother preeclampsia. And also due to low sample size in PE groups, data bias may occur. As our study limitation, in this study, we did not compare the Doppler data of these fetuses and miss the further long-term follow up for these abnormal infants and maybe they have confounder effects in final results.

5. Conclusion

Slower velocity of middle cerebral arteries in the first 72 hours after birth is associated with the adverse short-term outcome in preterm infants with mother preeclampsia.

Conflicts of Interest

The authors declare no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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