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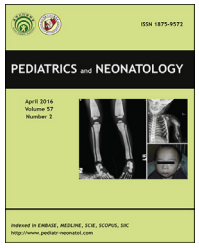

ORIGINAL ARTICLE

A Clinical Study of the N-Terminal pro-Brain Natriuretic Peptide in Myocardial Injury after Neonatal Asphyxia

Rui Zhu [a,*], **Zhenhong Nie** [b]

[a] *Department of Pediatrics, Zhongnan Hospital of Wuhan University, Hubei 430071, China*
[b] *Department of Epidemiology, School of Public Health, Wuhan University, Hubei 430071, China*

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NT-proBNP;
perinatal care

Background: We aimed to study the changes of serum N-terminal pro-brain natriuretic to peptide (NT-proBNP) levels after asphyxia-induced myocardial injury in children and explore the relationship between serum NT-proBNP levels and neonatal asphyxia.
Methods: One hundred and six cases of neonatal asphyxia were randomly selected for the study, including 46 severe cases with myocardial injury and 60 mild cases with no cardiac injury. Sixty-three healthy newborns were selected as the control group. The serum NT-proBNP level was detected using electrochemiluminescence. Creatine kinase MB (CK-MB) and serum sodium and calcium were measured simultaneously.
Results: The serum NT-proBNP level in the myocardial injury group was significantly higher than that of the noncardiac injury and control groups ($p < 0.01$). Asphyxia serum NT-proBNP and cardiac enzymes were significantly correlated. The median value of neonatal NT-proBNP was 1491 pg/mL at postnatal Day 3 (P3) and 1077 pg/mL at postnatal Day 14 (P14). The cutoff value for children with myocardial injury was 3612.5 pg/mL; the area under the receiver operating characteristic curve was 0.80 ($p < 0.001$), with a sensitivity of 83.3%, a specificity of 80.5%, a positive predictive value of 82.8%, and a negative predictive value of 79.4%. After treatment, the serum NT-proBNP level in children with myocardial damage showed a significant decrease.
Conclusion: The serum NT-proBNP level can reflect myocardial injury in neonates with asphyxia and can guide its diagnosis.

* Corresponding author. 169 Donghu Rd., Wuchang District, Wuhan, Hubei 430071, China
E-mail address: ruizhu.wuhan@gmail.com (R. Zhu).

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1. Introduction

Neonatal asphyxia is a common pediatric disease with an incidence of 5—10% in China.[1] Asphyxia causes hypoxia and leads to multiple organ damage, of which heart damage is the most common. Reports show that the occurrence of myocardial damage in neonatal asphyxia was 28—65%[2] or even up to 73%.[3] However, the diagnosis of hypoxic—ischemic myocardial damage has been difficult because of the lack of sensitive laboratory tests for early diagnosis and the absence of standard diagnostic criteria.

Creatine kinase MB (CK-MB), which exists mainly in the cytoplasm of myocardial cells, is currently accepted as an indicator and has high sensitivity and specificity for the diagnosis of myocardial injury.[4] The serum CK-MB level was found to be closely related to the time after myocardial injury; a normal CK-MB level in the first detection does not completely eliminate the possibility of myocardial injury. CK-MB is also present in the bones and brain in small amounts.[5—7] As a result, we aimed to search for an additional laboratory marker for an early diagnosis of myocardial injury.

Brain natriuretic peptide, or B-type natriuretic peptide (BNP), is a heart peptide hormone. When the tension of a blood vessel increases or its volume is overloaded, preproBNP mRNA is rapidly transcribed in the myocardial cells of the ventricles. PreproBNP is then synthesized and processed to produce a signaling peptide and proBNP. The proBNP is then catalyzed to generate N-terminal (NT-proBNP) and BNP, which are released into the blood.

BNP/NT-proBNP has attracted clinical attention as a marker of cardiac function. In recent years, studies in adults have demonstrated that BNP/NT-proBNP is an indicator of left ventricular dysfunction.[8,9] In heart failure, plasma BNP/NT-proBNP levels increase dramatically according to heart failure severity.[10—12] In addition, the BNP/NT-proBNP levels are the strongest independent prognostic indicator for death or cardiovascular incidents in patients with heart failure after discharge.[13,14] In the study of myocardial infarction, an increase in the BNP/NT-proBNP level appears to be correlated with the timing and extent of myocardial infarction.[15] Therefore, the BNP/NT-proBNP level is useful for the detection of chronic ventricular dysfunction in adults and congestive heart failure in patients with breathing difficulty; the BNP/NT-proBNP level allows for the diagnosis of subclinical asymptomatic patients with left ventricular abnormalities.

However, there are relatively few studies regarding BNP/NT-proBNP in the newborn. NT-proBNP does not pass the blood-placenta barrier; thus, any changes in the baby's body are autonomous. Myocardial ischemia and energy metabolism dysfunction lead to irreversible damage and even necrosis. Furthermore, during recovery, blood reperfusion can cause further damage to myocardial cells.

Myocardial injury often occurs simultaneously with elevated ventricular tension and a compensatory increase in cardiac output. Particularly, in the event of heart failure, the ventricle is stretched by atrial and ventricular dilatation. At the same time, pulmonary vasodilation stimulates pulmonary and cardiac nerve receptors, regulating the release of BNP. The increase in the vascular BNP/NT-proBNP concentration leads to an increase of the ventricular volume. The elevated blood vessel pressure further induces the synthesis and secretion of BNP.[16,17] Goetze et al[18] showed that myocardial hypoxia affects ventricular BNP gene expression and increases the plasma BNP/NT-proBNP concentration, suggesting that the elevated plasma BNP/NT-proBNP levels in the acute phase of myocardial injury in children are correlated with acute phase-localized myocardial ischemic injury.

2. Methods

2.1. General information

According to the visit order, every other case was selected from patients who were admitted to our hospital from December 2012 to December 2013 in accordance with the hospital's neonatal asphyxia standards. A total of 106 cases of neonates <3 days old were selected. We obtained informed consent from the parents or legal guardians of the patients, and this study was approved by the Zhongnan Hospital of Wuhan University Ethics Committee.

According to the Apgar scoring method,[19] we performed 1-minute and 5-minute scores for neonatal asphyxia. When the 5-minute score was <7, we scored the patient every 5 minutes until 20 minutes had passed. Patients with a 1-minute Apgar score of 0—3 were categorized as having severe asphyxia, and patients with a score of 4—7 were categorized as having mild asphyxia according to the clinical presentations of myocardial damage in neonatal asphyxia[20]: (1) history of asphyxia and perinatal hypoxia; (2) clinical manifestations: i) low, blunt heart sound and tachycardia; ii) poor circulation, demonstrated by a pale complexion, finger cyanosis, or capillary refill time over 3 seconds; iii) heart failure; iv) severe arrhythmias; and v) cardiac arrest; (3) electrocardiogram (ECG) ST-T changes that last for > 2—3 days; and (4) an increase in serum CK-MB or troponin T. The diagnosis of myocardial injury must satisfy the following: (1) history of asphyxia; (2) low, blunt heart sound and poor circulation; (3) ECG abnormalities; and (4) enzyme abnormalities, as listed above in detail.

In the 106 asphyxia cases, 46 met the diagnostic criteria of myocardial injury.[21] The control group of neonates was admitted in the same period; these neonates did not have asphyxia or neonatal cardiovascular disease. Instead, they had a mild upper respiratory tract infection, omphalitis, or mild diarrhea. Neonates with water and electrolyte balance disorders and kidney dysfunction were excluded from the control group. Gestational age, birth weight, sex, or mode of delivery was not significantly different among the three groups. See Table 1 for the demographic data of all of the cases selected in our study and Table 2 for the clinical manifestations of the patients.

2.2. Methods

We first established a neonatal datasheet that included age, sex, admission time, mode of delivery, birth weight, gestational age, history of fetal distress, and Apgar score. Then, routine ECG and chest X-ray examinations were