European Review for Medical and Pharmacological Sciences 2014; 18: 2596-2598

NT-proBNP plays an important role in the effect of ibuprofen on preterm infants with patent ductus arteriosus

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Abstract. – OBJECTIVE: The aim of this study was to clarify the role of N-terminal pro-brain natriuretic peptide, (NT-proBNP) in ibuprofen on preterm infants with patent ductus arteriosus (PDA).

PATIENTS AND METHODS: Preterm infants with PDA were enrolled in the present study. Patients were randomized into two groups: ibuprofen group received oral ibuprofen 10 mg/kg, followed by 5 mg/kg after 24 and 48 h, and the placebo group received the same volume of 5% glucose. PDA and NT-proBNP were detected during 24 hours, 3 and 7 days of age.

RESULTS: The results indicated that babies who received oral ibuprofen had higher PDA closure at 7 days after treatment ($p < 0.05$). Significantly decrease of NT-proBNP was found in ibuprofen group than the placebo group at 3 and 7 days (all $p < 0.05$).

CONCLUSIONS: Collectively, the favorable effects of ibuprofen on PDA in premature infants maybe mediated in part by the reduction of NT-proBNP level.

Key Words:
N-terminal pro-brain natriuretic peptide (NT-proBNP), Ibuprofen, Patent ductus arteriosus (PDA).

Introduction

Patent ductus arteriosus (PDA) is a congenital disorder in the heart wherein a neonate's ductus arteriosus fails to close after birth, which is associated with mortality and morbidity in premature infants. Early symptoms of PDA are uncommon, but in the first year of life include increased work of breathing and poor weight gain, and the PDA may lead to congestive heart failure if left uncorrected in time. It is well know that intravenous indomethacin is regarded as the standard mode of therapy and is effective in closing the PDA. However, serious concerns still linger about its frequently associated adverse reaction on the cerebral, renal and mesenteric circulation[1]. Ibuprofen (IBU) is a nonsteroidal anti-inflammatory drug (NSAID), acting via cyclooxygenase (COX) inhibition centrally and peripherally[2]. Recent years, ibuprofen is approved for the indication of PDA closure in preterm infants. Moreover, ibuprofen has been proved to be effective in closing PDA without reducing cerebral blood flow or affecting intestinal or renal hemodynamics[3], although it has been associated with a greater risk of chronic lung disease and conflicted about displaces bilirubin at therapeutic doses more than indomethacin[4]. Moreover, limited data exist regarding the possible mechanisms of ibuprofen on PDA in preterm infants.

N-terminal pro- brain natriuretic peptide (NT-proBNP) is an easily measured biomarker released by cardiac myocytes in response to increased ventricular wall stress[5]. Ventricles of heart are the main site of NT-proBNP synthesis and release in response to volume loading, pressure loading, and ventricular stress. NT-pro-BNP circulates at considerable concentrations in human plasma, is stable at room temperature, can easily be detected, and is quantifed on immunoassay[6]. The use of NT-proBNP in evaluating the presence of PDA status of preterm infants is gaining interest in clinic, and recent studies have further demonstrated that the potential of NT-proBNP to guide an indomethacin therapeutic strategy for these patients[7]. However, whether there is a role for NT-proBNP determinations in evaluating the responsiveness to ibuprofen in premature neonates with PDA is unknown. Here, we design a study to investigate the role of NT-proBNP in ibuprofen on preterm infants with PDA.

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Patients and Methods

Patients

Between July 2011 and December 2011, a total of 72 preterm infants with PDA who met the following criteria were enrolled in this study: mean birth weight is 1468.64 ± 447.62 g, mean gestational age is 30.24 ±1.49 weeks. Exclusion criteria were major congenital anomalies, malformation, pulmonary hypertension (> 50 mmHg), and bleeding tendency (Platelet count < 50×10^9 /L).

Study Design

After obtaining informed parental consent, patients were randomly placed into two groups. The first group of ibuprofen (n= 35) received oral ibuprofen (Shanghai Johnson & Johnson Pharmaceuticals, Ltd., China) 10 mg/kg, followed by 5 mg/kg after 24 and 48 h. The second group of placebo (Placebo group, n= 37) received the same volume of 5% glucose. In all infants, color Doppler echocardiography (Philips IE33, Royal Dutch Philips Electronics Ltd.) were performed during 1 day, 3 days and 7 days, by a senior pediatric attending physician who was unaware of the infants' treatment schedule. Blood sample was collected from an indwelling catheter and obtained at the same time as performing echocardiography, and the serum level of NT-proBNP was measured using ELISA kits according to manufacturer's instructions (Shanghai Yueyan Biological Technology Co, Ltd, China). The study was approved by the hospital Ethics Committee.

Statistical Analysis

Values are expressed as mean ± standard deviation. The significance of comparisons between mean values was evaluated by Student's *t*-test. A value of $p < 0.05$ was considered statistically significant.

Results

Compared with the glucose-treated newborns (placebo group), babies who received oral ibuprofen had higher PDA closure at 7 day after treatment (97.14% *vs.* 78.38%, $p < 0.05$). Of note, significant decreases of NT-proBNP was found in ibuprofen administration group than placebo group at 3 and 7 days after treatment, respectively (3 days, 13.27 ± 8.29 *vs.* 19.41 ± 10.69; 7 days, 9.98 ± 4.14 *vs.* 13.85 ± 7.19, ng/L, all $p < 0.05$). The results indicated that the favorable effects of ibuprofen were likely mediated in part by the reduction of NT-proBNP level in preterm infants.

Discussion

In a large network of neonatal intensive care units, the frequency of PDA in infants weighing 501 to 1500 g was 31 percent. Substantial left-to-right shunting through the ductus may increase the risk of necrotizing enterocolitis, intraventricular hemorrhage, bronchopulmonary dysplasia, and death. Indomethacin is the conventional pharmacologic treatment for promoting closure of a patent ductus in premature infants. However, concern remains regarding the safety of indomethacin, which affects renal, gastrointestinal, and cerebral perfusion and may lead to complications such as transient or permanent renal dysfunction. Ibuprofen, a cyclo-oxygenase inhibitor drug, has been used for ductal closure in animals. Increasing number of preliminary experimental and clinical studies had shown that ibuprofen is effective in closing PDA[8]. However, the mechanisms are still poor understand. NT-proBNP has been widely used as a diagnostic biomarker of cardiac dysfunction in adult patients. In recent years, the usefulness of NT-proBNP in pediatric patients, especially in neonates with PDA, has gained attention. For example, NT-proBNP levels strongly correlated with the ductal size in premature neonates[9].

Conclusions

The data in the present study for the first time suggested that oral ibuprofen not only increase PDA closure at 7 days treatment in preterm infants, but also inhibit NT-proBNP level at 3, 7 days treatment, respectively. The results indicated that NT-proBNP might play a vital role in the treatment of ibuprofen on premature neonates with PDA.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Edwards AD, Wyatt JS, Richardson C, Potter A, Cope M, Delpy DT, Reynolds EO. Effects of indomethacin on cerebral hemodynamics in very preterm infants. Lancet 1990; 335: 1491-1495.
2) Chavarria-Bolaños D, Perez-Urizar J, Grandfils C, Pozos-Guillén A. Peripheral Synergism between Tramadol and Ibuprofen in the Formalin Test. Drug Dev Res 2014; 75: 224-230.
3) Van Overmeire B, Smets K, Lecoutere D, Van de Broek H, Weyler J, Degroote K, Langhendries JP. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. N Engl J Med 2000; 343: 674-681.
4) Demirel G, Erdeve O, Dilmen U. Pharmacologic management of patent ductus arteriosus: oral versus intravenous medications. Curr Clin Pharmacol 2012; 7: 263-270.
5) Zhou FJ, Zhou CY, Tian YJ, Xiao AJ, Li PL, Wang YH, Jia JW. Diagnostic value of analysis of H-FABP, NT-proBNP, and cTnI in heart function in children with congenital heart disease and pneumonia. Eur Rev Med Pharmacol Sci 2014; 18: 1513-1516.
6) Hirono K, Sekine M, Shiba N, Hayashi S, Nakaoka H, Ibuki K, Saito K, Watanabe K, Ozawa S, Higuma T, Yoshimura N, Kitajima I, Ichida F. N-terminal probrain natriuretic peptide as predictor of reoperation in children with surgically corrected tetralogy of Fallot. Circ J 2014; 78: 693-700.
7) Apitz C, Sieverding L, Latus H, Uebing A, Schoof S, Hofbeck M. Right ventricular dysfunction and B-type natriuretic peptide in asymptomatic patients after repair for tetralogy of Fallot. Pediatr Cardiol 2009; 30: 898-904.
8) Pezzati M, Vangi V, Biagiotti R, Bertini G, Cianciulli D, Rubaltelli FF. Effects of indomethacin and ibuprofen on mesenteric and renal blood flow in preterm infants with patent ductus arteriosus. J Pediatr 1999; 135: 733-738.
9) Martinovici D, Vanden ES, Unger P, Najem B, Gulbis B, Maréchal Y. Early NT-proBNP is able to predict spontaneous closure of patent ductus arteriosus in preterm neonates, but not the need of its treatment. Pediatr Cardiol 2011; 32: 953-957.