Pulmonary Arterial Hypertension after Ibuprofen Treatment for Patent Ductus Arteriosus in Very Low Birth Weight Infants

Sae Yun Kim, MD[1,2,*], Seung Han Shin, MD[1,*], Han-Suk Kim, MD, PhD[1], Young Hwa Jung, MD[1], Ee-Kyung Kim, MD, PhD[1], and Jung-Hwan Choi, MD, PhD[1]

Objective To describe the clinical course and risk factors for pulmonary arterial hypertension (PAH) after ibuprofen treatment to close patent ductus arteriosus.

Study design All neonates weighing < 1500 g at birth who received ibuprofen to close patent ductus arteriosus and were admitted to Seoul National University Children's Hospital's neonatal intensive care unit in 2010-2014 were eligible for this study. The study population was divided into the PAH and non-PAH groups, and medical records were retrospectively reviewed.

Results Of the 144 eligible infants, 10 developed PAH (6.9%). Relative to the non-PAH group, the PAH group exhibited greater respiratory severity and more frequent severe bronchopulmonary dysplasia or death before 36 weeks postmenstrual age. Multivariable analysis demonstrated that lower gestational age, birth weight in less than the third percentile for age, maternal hypertension of pregnancy, and oligohydramnios were risk factors for developing PAH after ibuprofen treatment.

Conclusion A high incidence of PAH after ibuprofen treatment was observed in the study population. Furthermore, younger gestational age and several prenatal conditions were identified as risk factors for developing PAH after ibuprofen treatment. Additional large cohort studies are necessary to confirm our results. *(J Pediatr 2016;179:49-53).*

In fetal life, the patent ductus arteriosus (PDA) is essential for survival, diverting blood away from the pulmonary circulation toward the systemic circulation. However, a persistent PDA after birth can be associated with left-to-right shunting of blood, resulting in adverse effects such as congestive heart failure, intraventricular hemorrhage, necrotizing enterocolitis (NEC), and death, especially in preterm infants.[1] Although controversy exists regarding when to treat PDA in premature babies, 70% of infants delivered before 28 weeks of gestation experience either medical or surgical closure of PDA.[2]

Ibuprofen is a nonselective cyclooxygenase (COX) inhibitor that reduces prostaglandin-mediated vasodilation.[3] However, the nonselective mechanism of COX inhibition produces unwanted side effects, including renal function alterations and NEC. A recent meta-analysis of 33 studies demonstrated that ibuprofen is as effective as indomethacin for closing PDA and reduces the risk of NEC and renal insufficiency.[4] However, a study by Gournay et al[5] on ibuprofen prophylaxis in preterm infants was terminated because three infants developed serious pulmonary arterial hypertension (PAH). Amendolia et al[6] also reported that 2 infants developed PAH after receiving therapeutic ibuprofen for PDA closure. Thus far, the potential association between ibuprofen and PAH has received little attention, and some studies have reported no instances of this complication.[7] This study aimed to determine how often PAH develops in preterm infants who receive ibuprofen to close PDA, and to investigate the risk factors for this complication.

Methods

This retrospective cohort study was conducted in the neonatal intensive care unit of Seoul National University Children's Hospital between January 2010 and December 2014. All neonates who weighed < 1500 g at birth and received ibuprofen to close symptomatic PDA were eligible for the study. During the study period, ibuprofen was used only for symptomatic treatment and

BPD	Bronchopulmonary dysplasia
COX	Cyclooxygenase
iNO	Inhaled nitric oxide
IV	Intravenous
NEC	Necrotizing enterocolitis
PAH	Pulmonary arterial hypertension
PDA	Patent ductus arteriosus
THAM	Trishydroxyaminomethane

From the [1]Department of Pediatrics, Seoul National University College of Medicine, Seoul, Republic of Korea; and [2]Department of Pediatrics, Kangwon National University Hospital, Chuncheon, Republic of Korea

*Contributed equally.

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not for prophylaxis. Two preparations of intravenous (IV) ibuprofen (Pedea, ibuprofen trishydroxyaminomethane [THAM; Orphane Europe SARL, Paris, France]; NeoProfen, ibuprofen lysine [AAIPharma Services, Charleston, South Carolina]), and 1 preparation of oral ibuprofen (Carol, ibuprofen [Ildong Pharmaceutical Company, Seoul, Korea]) were used during the study period. The same dosing strategy was used for each preparation: an initial dose of 10 mg/kg followed by 5 mg/kg at 24 and 48 hours. This study was approved by the Seoul National University Institutional Review Board.

An echocardiogram was routinely performed within 72 hours after birth or if the infant showed any symptoms or signs indicative of PDA, such as hypotension, oliguria, pulmonary edema, or hemorrhage. Infants with hemodynamically significant PDA on the echocardiogram were treated with ibuprofen unless they had contraindications, such as active bleeding, oliguria, low platelet count (<60 000/mm^3), or NEC.[3] A follow-up echocardiogram was performed within 24 hours after the final ibuprofen dose.

Exclusion criteria were persistent pulmonary hypertension of the newborn or pulmonary vasodilator therapy that included inhaled nitric oxide (iNO) for any reason before the administration of ibuprofen; major congenital anomalies, including congenital heart anomalies other than PDA, an atrial septal defect, or a single small ventricular septal defect; chromosomal abnormality; hydrops fetalis; death within the first 24 hours after birth; and a lack of echocardiogram data. Demographic data and neonatal morbidity and mortality were reviewed. Maternal data on histologic chorioamnionitis, oligohydramnios, antenatal steroid treatment, and hypertensive disorders of pregnancy were extracted from medical records.

The echocardiographic diagnosis of PAH was based on the following criteria: (1) tricuspid valve regurgitation velocity ≥3 m/s in the absence of pulmonary stenosis, (2) flat or left-deviated interventricular septal configuration, and (3) right-to-left shunt or right-to-left dominant bidirectional shunt flow through the PDA. If PAH occurred within 24 hours after the last dose of ibuprofen, it was considered to be associated with the medication. The study population was divided into the PAH and non-PAH groups according to posttreatment echocardiographic findings. Fenton growth charts were used to classify infants as less than the third percentile of weight for age at birth.[8] The respiratory severity score was defined as the product of the mean airway pressure and the fraction of inspired oxygen,[9] and respiratory severity worsening was defined as (1) an respiratory severity score increase of ≥30% after ibuprofen treatment in previously intubated infants or (2) the need for invasive mechanical ventilation after ibuprofen treatment in infants who did not require it before treatment. The criteria for subsequent intubation were partial P_aCO_2 > 60 mm Hg, a need for fraction of inspired oxygen of >0.4 to maintain peripheral oxygen saturation >90%, or respiratory distress with apnea. The National Institute of Child Health Workshop criteria for bronchopulmonary dysplasia (BPD) were used.[10] Hypertensive disorders of pregnancy was defined by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy.[11]

Statistical Analyses

Statistical analysis was performed using SPSS version 21 (IBM Corp, Armonk, New York). Continuous variables are presented as medians and ranges, and dichotomous variables are presented as frequencies. The differences between infants with and without PAH after ibuprofen treatment were assessed using the Mann–Whitney *U* test for continuous variables and Fisher exact test for categorical variables. Factors with $P < .05$ in the univariate analysis were included in the multiple logistic regression analysis to identify associations with PAH. To exclude possible confounding risk factors, adjusted proportions were calculated for neonatal outcomes. All tests were 2 tailed, and $P < .05$ was considered significant.

Results

Very low birth weight infants (n = 528) were screened; 12 infants were excluded because they lacked available echocardiograms, and 16 infants died within the first 24 hours after birth. Infants with persistent pulmonary hypertension of the newborn, severe hypoxemia requiring iNO immediately after birth, complex congenital heart anomalies, or other major congenital anomalies were also excluded. Two infants were excluded due to severe hydrops fetalis (**Figure**; available at www.jpeds.com). There were no infants with PAH before treatment in the study population. Among the 416 remaining infants, 217 infants had a PDA diagnosis confirmed by color Doppler echocardiogram more than 24 hours after birth.

In South Korea, indomethacin has not been available commercially since March 2010; consequently, ibuprofen has been the primary choice for closing PDA in premature infants, except for a 6-month period (September 2011 to February 2012) when a temporary supply of indomethacin was available. Twenty-one infants who were treated during that period were excluded from the analysis. Thirty-six infants underwent primary surgery for PDA, and 16 infants were not symptomatic or could not be treated because of poor general condition.

Among the 144 infants treated with ibuprofen, 40 infants received oral ibuprofen, 100 infants received IV ibuprofen THAM, and 4 infants received IV ibuprofen lysine. PAH subsequently developed in 10 patients (6.9%), including 2 patients, 7 patients, and 1 patient who had received oral ibuprofen, IV ibuprofen THAM, and IV ibuprofen lysine, respectively.

Adjusted proportions of neonatal outcomes were calculated by controlling for covariates such as gestational age, birth weight at less than the third percentile for age, maternal hypertensive disorders of pregnancy, and maternal oligohydramnios (**Table I**). Respiratory severity worsened in 8 of the 10 infants in the PAH group and in 8 of the 134 infants in the non-PAH group (80.0% vs 6.0%; $P = .007$). Severe BPD or death at 36 weeks postmenstrual age was more prevalent in the PAH group than in the non-PAH group (90.0% vs 15.7%; $P = .023$). The incidence of NEC, retinopathy of prematurity, periventricular leukomalacia, and mortality was higher in the PAH group than in the non-PAH group, but the differences were not significant. The overall

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