의학석사 학위논문

Pulmonary hypertension after ibuprofen treatment for patent ductus arteriosus in very low birth weight infants

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The Department of Medicine

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Pulmonary hypertension after ibuprofen treatment for patent ductus arteriosus in very low birth weight infants

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SAE YUN KIM

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Approved by Thesis Committee:

Professor Chung-Il Noh Chairman

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Abstract

Pulmonary hypertension after ibuprofen treatment for patent ductus arteriosus in very low birth weight infants

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Background: Patent ductus arteriosus (PDA), affecting approximately 70% of preterm infants, associated with substantial infant mortality and morbidity. Ibuprofen has been recommended as well as indomethacin to close PDAs but cardiopulmonary effects such as pulmonary hypertension could happen which is rare but potentially fatal complication. This study aimed to describe the clinical courses of and risk factors for pulmonary hypertension after ibuprofen treatment to close PDA.

Method: All neonates weighing <1,500 g at birth who received ibuprofen to close PDA 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 PH

and non-PH groups, and medical records were retrospectively reviewed. PH was diagnosed by echocardiogram, more than one of followings were documented; 1) Interventricular septum flattening, 2) tricuspid regurgitation jet velocity was more than 3 meter per second. 3) right to left or bidirectional shunt through PDA. Logistic regression analysis was done for the univariate assessment of the risk factors for PH after ibuprofen treatment.

Results: Of the 144 eligible infants, 10 developed PH (6.9%). Relative to the non-PH group, the PH group exhibited greater respiratory severity aggravation (P=0.07), with severe bronchopulmonary dysplasia (BPD) or death prior to 36 weeks postmenstrual age occurring more frequently (P=0.023).

Gestational age is younger in infants of PH group than infants of non-PH group (P=0.006). Birth weight < 3rd percentile for gestational age (P<0.001), maternal hypertensive disorders (P<0.001) and oligohydramnios (P=0.003) were independent risk factors for PH. Multivariable OR for PH were 0.644 [95%CI 0.41-0.98, P=0.043] for younger gestational age(day) infant, 1.71 x10^{5} [95%CI 1.65-1.76 x10^{10}, P=0.041], for infants with birth weight < 3rd percentile for gestational age, 1.32 x10^{3} [95%CI 3.86-4.51 x10^{5}, P=0.016], for infants with maternal hypertension during pregnancy, 47.98 [95%CI 1.10-2.10 x10^{3}, P=0.045] for infants with oligohydramnios in utero. Multivariable

analysis demonstrated that lower gestational age (GA), birth weight <3rd percentile for gestational age, maternal hypertension of pregnancy and oligohydramnios were risk factors for developing PH after ibuprofen treatment.

Conclusion: A high incidence of PH after ibuprofen treatment was observed in the study population. Furthermore, lower GA and several prenatal conditions were identified as risk factors for developing PH after ibuprofen treatment. Because of the fatal complications of ibuprofen such as PH, neonatologist should be very careful in choosing a treatment method for PDA. Additional large cohort studies are necessary to confirm our results.

Keywords: ibuprofen; adverse effect; premature infant

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List of Abbreviations

COX	Cyclooxygenase
FiO_2	Fraction of inspired oxygen
iNO	Inhaled nitric oxide
NEC	Necrotizing enterocolitis
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PH	Pulmonary hypertension
PDA	Patent ductus arteriosus
PPHN	Persistent pulmonary hypertension of the newborn
RSS	Respiratory severity score
THAM	Trishydroxyaminomethane
VLBW	Very low birth weight
HFOV	High-frequency oscillatory ventilation

1. Introduction

In fetal life, the patent ductus arteriosus (PDA) is essential for survival, diverting blood away from the pulmonary circulation towards 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 whether or when to treat PDA in premature babies, 70 percent 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 hypertension (PH). Amendolia et al.(6) also reported that 2 infants developed PH after receiving therapeutic ibuprofen for PDA closure. Thus far, the association between ibuprofen and PH has received little attention, and some studies have reported no instances of this complication (7). This study aimed to determine how

often PH develops in preterm infants who receive ibuprofen to close PDA, and to investigate the risk factors for this complication.

2. Materials and Methods

2.1 Study design and study population

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 <1,500 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, 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 one 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 h.

An echocardiogram was routinely performed within 72 h 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 h after the final ibuprofen dose in infants whose PDA was treated medically.

Exclusion criteria were persistent pulmonary hypertension of the newborn (PPHN); 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 histological chorioamnionitis, oligohydramnios, antenatal steroid treatment and hypertensive disorders of pregnancy were extracted from medical records.

2.2 Definitions

The echocardiographic diagnosis of PH 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 PH 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 PH and non-PH groups according to post-treatment echocardiographic findings. Fenton growth charts were used to classify infants as $<3^{rd}$ percentile of weight for gestational age at birth (8). The respiratory severity score (RSS) was defined as the product of the mean airway pressure and the fraction of inspired oxygen (F_iO_2) (9), and respiratory severity aggravation was defined as follows: 1) an RSS increase ≥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 pressure of carbon dioxide in arterial blood (P_aCO_2) >60 mmHg, a need for F_iO_2 >0.4 to maintain percutaneous oxygen saturation >90%, or respiratory distress with apnea. The National Institute of Child Health Workshop criteria for 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).

This study was approved by the Seoul National University Institutional Review Board.

2.3 Statistical analyses

Statistical analysis was performed using SPSS version 21 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as medians and ranges, and dichotomous variables are presented as frequencies. The differences between infants with and without PH after ibuprofen treatment were assessed using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. Factors with $P<0.05$ in the univariate analysis were included in the multiple logistic regression analysis to identify associations with PH. To exclude possible confounding risk factors, adjusted proportions were calculated for neonatal outcomes. All tests were two tailed, and $P<0.05$ was considered significant.

3. Results

3.1 PH development after ibuprofen treatment

Five hundred twenty-eight very low birth weight (VLBW) infants were screened. Twelve infants were excluded because they lacked available echocardiograms, and 16 infants died within the first 24 hours after birth. Infants with PPHN, 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 1). There were no infants with PH 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 commercially available 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 ibuprofen-treated infants, 40 infants received oral ibuprofen, 100 infants received IV ibuprofen trishydroxyaminomethane (THAM), and 4 infants received IV ibuprofen lysine. PH subsequently

developed in 10 patients (6.9%), including two patients, seven patients, and one patient who had received oral ibuprofen, IV ibuprofen THAM, and IV ibuprofen lysine, respectively.

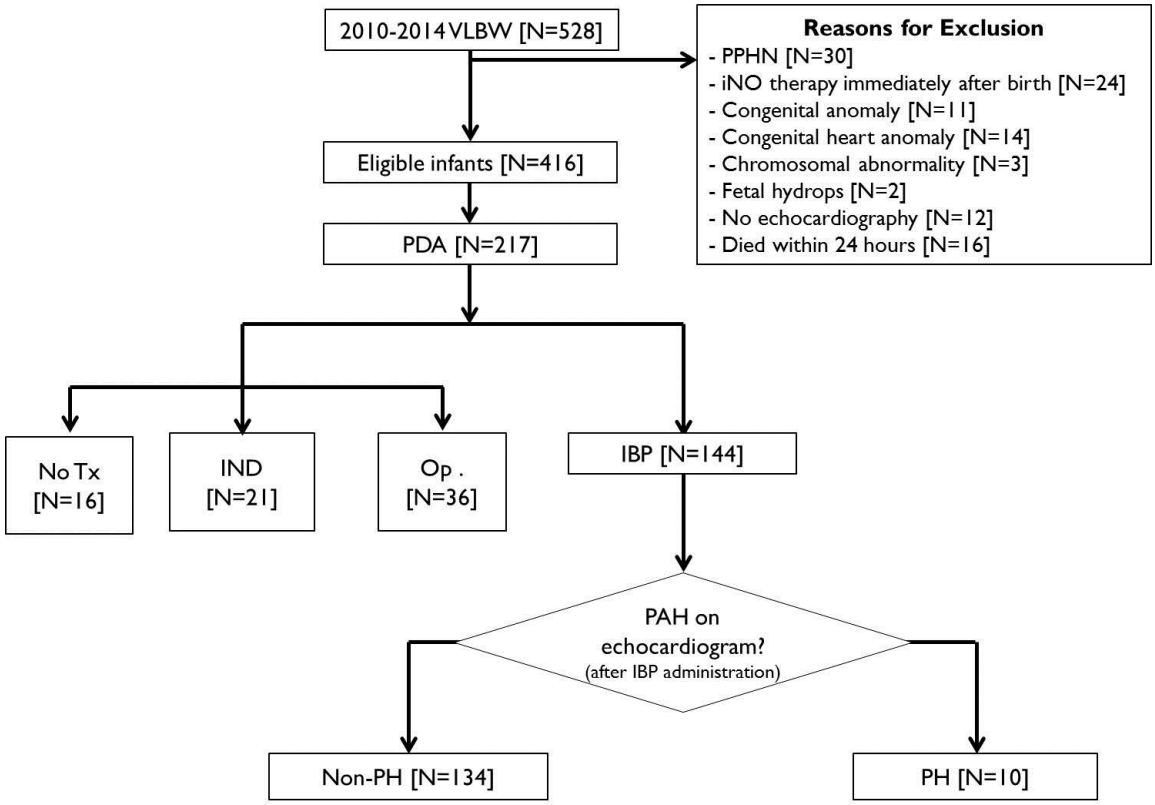

Figure 1. Flow diagram of the study design used to select the 144 infants enrolled in this study who received ibuprofen to treat PDA.
Abbreviations: VLBW, very low birth weight; PPHN, persistent pulmonary hypertension of newborn; No Tx, no treatment; IND, indomethacin; Op, PDA ligation operation; IBP, ibuprofen

Table 1. Demographics of the study population

	PH (n=10)	Non-PH (n=134)	*P*-value
Gestational age (weeks)	25^{+5} [23^{+3}, 28^{+4}]	27^{+5} [23^{+4}, 35^{+2}]	0.006
Birth weight (g)	555[370,950]	955 [500, 1490]	<0.001
1-minute Apgar score, median	2 [1,5]	4 [0, 8]	0.010
5-minute Apgar score, median	5 [2,7]	7 [0, 9]	0.009
Male sex	5 (50.0%)	64 (47.8%)	1.000
Birth weight <3rd percentile for gestational age	5 (50.0%)	6 (4.5%)	<0.001
Maternal hypertensive disorders of pregnancy	8 (80.0%)	19 (14.2%)	<0.001
Histological chorioamnionitis	4 (40.0%)	67 (51.5%)	0.529
Maternal oligohydramnios	6 (60.0%)	21 (15.7%)	0.003
Administration of antenatal steroids	10 (100.0%)	106 (79.1%)	0.210
RDS	9 (90.0%)	84 (62.7%)	0.098
Diameter of PDA/birth weight (mm/kg)	3.45 [2.42, 5.13]	2.54 [0.75, 6.71]	0.010
PND (ibuprofen administration)	3 [1, 12]	3 [1, 28]	0.233
PMA (ibuprofen administration, weeks)	26^{+3} [23^{+4}, 29^{+2}]	28^{+3} [23^{+5}, 36^{+0}]	<0.001

Mann–Whitney *U* test or Fisher's exact test.
Abbreviations: RDS, respiratory distress syndrome of newborn; PND, postnatal day; PMA, postmenstrual age;
Data are presented as median [minimum, maximum] or as number (percentage).

3.2 Neonatal outcomes

Adjusted proportions of neonatal outcomes were calculated by controlling for covariates such as gestational age, birth weight <3rd percentile for gestational age, maternal hypertensive disorders of pregnancy and maternal oligohydramnios (Table 1). Respiratory severity worsened in 8 of the 10 infants in the PH group and in 8 of the 134 infants in the non-PH group (80.0% vs. 6.0%; *P*=0.007). Severe BPD or death at 36 weeks postmenstrual age was more prevalent in the PH group than in the non-PH group (90.0% vs. 15.7%; *P*=0.023). The incidence of NEC, retinopathy of prematurity, periventricular leukomalacia and mortality was higher in the PH group than in the non-PH group, but the differences were not significant (Table 2). The overall mortality rate of VLBW infants during the study period was 13.8% (73/528).

Table 2. Neonatal outcomes of the study population

	PH (n=10)	Non-PH (n=134)	*P*-value
Aggravation of respiratory severity	8 (80.0%)	8 (6.0%)	0.007
Further treatment for PDA	5 (50.0%)	54 (40.3%)	0.257
NEC (≥IIa) or higher	3 (30.0%)	13 (9.7%)	0.381
ROP (requiring laser photocoagulation)	6 (60.0%)	27 (20.1%)	0.369
Severe BPD or death	9 (90.0%)	21 (15.7%)	0.023
PVL (or death before PMA 36 weeks)	2 (20.0%)	5 (3.7%)	0.889
Mortality	2 (20.0%)	2 (1.5%)	0.762

Adjusted proportions were calculated after adjusting for gestational age, birth weight <3rd percentile for gestational age, maternal hypertensive disorders of pregnancy and maternal oligohydramnios.
Abbreviations: NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia; PVL, periventricular leukomalacia
Data are presented as median [minimum, maximum] or as number (percentage).

In the PH group, 8 infants were treated with iNO. Among them, two infants required iNO until death, and the remaining six infants required iNO for an average of 10 days (Table 3). Two infants who died (P05 and P09) experienced intrauterine growth restriction. Infant P05 developed PH after ibuprofen treatment on postnatal day 4 and died on postnatal day 22, despite high-frequency oscillatory ventilation (HFOV) and subsequent iNO treatment. Ibuprofen was administered to patient P09 on the third day of life; twelve hours after the first dose, he became hypotensive and hypoxemic and required ventilatory support with HFOV (F_iO_2, 1.0; mean airway pressure, 12–16 cm H_2O). On day 4, severe PH was documented by echocardiogram; this infant rapidly deteriorated and died without evidence of sepsis or NEC.

Table 3. Duration of PH after ibuprofen treatment

	GA at birth, BW	IBP day [PND]	PH treatment	Improvement of PH on EchoCG [PND]	Mortality
P01	GA 25^{+6}, 370 g	1	(-)	16	Alive
P02	GA 25^{+3}, 950 g	6	iNO: from PND 9 to 26	21	Alive
P03	GA 24^{+5}, 710 g	1	iNO: from PND 2 to 8	3	Alive
P04	GA 23^{+3}, 570 g	2	iNO: from PND 8 to 20	14	Alive
P05	GA 25^{+1}, 400 g	2	iNO: from PND 7 to death; iloprost: from PND 8 to death	NA	Died on PND 22
P06	GA 28^{+3}, 390 g	7	iNO: from PND 8 to 15	Developed BPD-related PH§	Alive
P07	GA 26^{+5}, 670 g	3	iNO: from PND 4 to 7	19	Alive
P08	GA 26^{+6}, 490 g	3	iNO: from PND 8 to 17	Developed BPD-related PH§	Alive
P09	GA 28^{+4}, 540 g	3	iNO: from PND 4 to death	NA	Died on PND 4
P10	GA 25^{+1}, 590 g	12	(-)	22	Alive

§, diagnosed on the basis of echocardiograms demonstrating elevated right ventricle (RV) pressure beyond 2 months of age (Neonatology. 2012;101(1):40-6).

Abbreviations: GA, gestational age; BW, birth weight; IBP, ibuprofen; PND, postnatal day; PH, pulmonary hypertension; echoCG, echocardiogram; iNO, inhaled nitric oxide; NA, not available

3.3 Risk factors for PH

The gestational ages of the infants in the PH group (median, 25^{+5}; range, 23^{+3}-28^{+4} weeks) were younger than those of infants in the non-PH group (median, 27^{+5}; range, 23^{+4}-35^{+2} weeks; P=0.006). Infants in the PH group had a lower birth weight (555 g vs. 955 g; P<0.001) and a higher rate of birth weight <3rd percentile (50.0% vs. 4.5%; P<0.001) than infants in the non-PH group. PDA diameter over birth weight was larger in the PH group than in the non-PH group prior to treatment (3.45 vs. 2.54 mm/kg; P=0.010). The median postnatal age at ibuprofen administration did not differ between the groups; however, postmenstrual age at ibuprofen administration was younger for the PH group than for the non-PH group (26^{+3} vs. 28^{+3} weeks; P<0.001). Maternal hypertensive disorders of pregnancy were more prevalent in the PH group than in the non-PH group (80.0% vs. 14.2%; P<0.001). Six mothers of infants in the PH group and 21 mothers of infants in the non-PH group had oligohydramnios based on antenatal ultrasonography (60.0% vs. 15.7%; P=0.003). After controlling for potential confounders using multivariable logistic regression, a younger gestational age, birth weight <3rd percentile for gestational age, maternal hypertensive disorders of pregnancy and oligohydramnios were significant risk factors for developing PH after ibuprofen treatment (Table 4).

Table 4. Risk factors for the development of PH in each group, as determined by multivariable logistic regression analysis

	Odds ratio	95% CI	*P*-value
Gestational age (day)	0.64	0.41-0.98	0.043
Birth weight (g)	1.01	0.99-1.03	0.247
Birth weight <3rd percentile for gestational age	1.71 x10^{5}	1.65-1.76 x10^{10}	0.041
5-minute Apgar score, median	0.78	0.32-1.89	0.580
Diameter of PDA/birth weight (mm/kg)	0.70	0.20-2.47	0.570
PMA (ibuprofen administration, days)	1.08	0.83-1.40	0.570
Maternal hypertensive disorders of pregnancy	1.32 x10^{3}	3.86-4.51 x10^{5}	0.016
Maternal oligohydramnios	47.98	1.10-2.10 x10^{3}	0.045

Adjusted for gestational age, birth weight, birth weight <3rd percentile for gestational age, 5-minute Apgar score, diameter of PDA/birth weight, PMA at ibuprofen administration, maternal hypertensive disorders of pregnancy and oligohydramnios.
Abbreviations: PDA, patent ductus arteriosus; PMA, postmenstrual age

4. Discussion

4.1 Incidence and neonatal outcomes of PH development after ibuprofen treatment

We have documented that PH is a potential cardiopulmonary adverse effect after ibuprofen treatment for PDA in VLBW infants. A high incidence of PH after ibuprofen treatment (6.9%) was observed in the study population, and subsequent severe BPD or death was more prevalent in the PH group than in the non-PH group.

Currently, the association between PH and ibuprofen treatment has not been established. Although a recent Cochrane review reported no significant risk for PH in ibuprofen-treated infants with PDA, the results should be interpreted cautiously (4). Only one study in the review showed no difference in PH development between IV ibuprofen lysine and placebo (2/68 vs. 1/68), but it did not document any echocardiographic findings when defining PH (12). Furthermore, the study population for which PH after ibuprofen was reported and ibuprofen and indomethacin were compared was small (1/16 vs. 0/19) (13). In another study, the incidence of PH after ibuprofen treatment was not clearly provided (14). A large-scale randomized controlled trial, which was not included in the Cochrane review and showed no differences in the incidence of major complications, did not describe how PH or its incidence were defined.[7] Meanwhile, the study by Gournay et al. of prophylactic ibuprofen THAM was prematurely terminated because of the unexpected

adverse events of mortality or PH (15). In that study, severe PH developed in 3 of the 131 enrolled patients, and the incidence of severe hypoxemia and the requirement for iNO or HFOV tended to be higher in the ibuprofen group, but the authors did not identify PH in all cases of hypoxemia. An echocardiogram with a high index of suspicion is crucial for identifying PH in premature infants with severe hypoxia.

4.2 Risk factors for developing PH after ibuprofen treatment

PH in preterm infants after ibuprofen treatment was first reported in 2002 (5); the authors postulated that the early administration of ibuprofen (<6 hours) could prevent the normal fall in pulmonary vascular resistance. In the present study, the median age at ibuprofen treatment was three days of life, and younger gestational age at birth, birth weight <3rd percentile for gestational age, maternal hypertensive disorders of pregnancy and maternal oligohydramnios were independent risk factors for the development of PH after ibuprofen treatment.

Younger gestational age at birth can result in both anatomical and functional immaturity of lungs, particularly in terms of pulmonary endothelial cell function (16). In fact, the study population of Gournay et al. was of a younger gestational age than in studies that did not observe ibuprofen-associated PH (5). Small-for-gestational age infants are also at risk of impaired lung development (17), as shown by Peacock et al, who reported strong relationships between adverse respiratory outcomes and birth weight Z-scores (18). Furthermore, we previously demonstrated that maternal

oligohydramnios is a specific risk factor for PH in preterm infants with BPD (19). Lung fluid pressure is essential for fetal lung development, as illustrated by the pulmonary hypoplasia observed in infants with oligohydramnios (20). The inhibitory effects of oligohydramnios on lung development might influence PH development and disturb the normal progression of neonatal pulmonary vascular resistance.

Interestingly, maternal hypertensive disorders of pregnancy were an independent risk factor for developing PH after ibuprofen treatment. Infants who were exposed to maternal hypertension in pregnancy have evidence of endothelial dysfunction in the feto-placental circulation (21,22). Experimental in vitro data and human studies suggest that an imbalance in angiogenic/anti-angiogenic factors causes endothelial cell dysfunction and is associated with preeclampsia (23,24). Future studies on the correlation between maternal hypertensive disorders of pregnancy and fetal lung development will be of interest.

In contrast, PH has not been reported as an adverse effect of indomethacin, the other non-selective COX inhibitor used for PDA treatment or prophylaxis. This difference is not well understood, but the pharmacodynamics of these two drugs might differ. Although a report suggested that the two COX inhibitors have different pharmacologic effects on kidney development (24), their effects on lung vascular regulation and development remain unclear and require further study.

Besides, PH was diagnosed on the basis of echocardiogram, in present study. However, it is difficult to distinguish between pulmonary arterial hypertension

and pulmonary venous hypertension by this limited echocardiographic data. But, since the mechanism is very different, more detailed echocardiographic exam should be needed in the further study. Although our single-center study was retrospective with a limited sample size, the considerably high incidence of PH after ibuprofen treatment in preterm infants might have a clinical impact because PH is a critical and serious respiratory complication. Additional large cohort studies are necessary to confirm our results and to ascertain the pathophysiology of PH development after ibuprofen treatment.

5. References

1. Noori S, McCoy M, Friedlich P, Bright B, Gottipati V, Seri I, et al. Failure of ductus arteriosus closure is associated with increased mortality in preterm infants. Pediatrics 2009;123:e138-e44.
2. Clyman RI. Ibuprofen and patent ductus arteriosus. N Engl J Med 2000;343:728-30.
3. Heuchan AM, Clyman RI. Managing the patent ductus arteriosus: current treatment options. Arch Dis Child Fetal Neonatal Ed 2014;99:F431-6.
4. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. The Cochrane Library 2015.
5. Gournay V, Savagner C, Thiriez G, Kuster A, Roze J. Pulmonary hypertension after ibuprofen prophylaxis in very preterm infants. Lancet 2002;359:1486-8.
6. Amendolia B, Lynn M, Bhat V, Ritz SB, Aghai ZH. Severe pulmonary hypertension with therapeutic l-lysine ibuprofen in 2 preterm neonates. Pediatrics 2012;129:e1360-e3.
7. Van Overmeire B, Allegaert K, Casaer A, Debauche C, Decaluwe W, Jespers A, et al. Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2004;364:1945-9.

8. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:59.
9. Ballard RA, Truog WE, Cnaan A, Martin RJ, Ballard PL, Merrill JD, et al. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. N Engl J Med 2006;355:343-53.
10. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163:1723-9.
11. National High Blood Pressure Education Program. Report of the National High Blood Pressure Education Program Working Group on high blood pressure in pregnancy. Am J Obstet Gynecol 2000;183:s1-s22.
12. Aranda JV, Clyman R, Cox B, Van Overmeire B, Wozniak P, Sosenko I, et al. A randomized, double-blind, placebo-controlled trial on intravenous ibuprofen L-lysine for the early closure of nonsymptomatic patent ductus arteriosus within 72 hours of birth in extremely low-birth-weight infants. Am J Perinatol 2009;26:235-45.
13. Adamska E, Helwich E, Rutkowska M, Zacharska E, Piotrowska A. [Comparison of the efficacy of ibuprofen and indomethacin in the treatment of patent ductus arteriosus in prematurely born infants]. Medycyna wieku rozwojowego 2004;9:335-54.
14. Yadav S, Agarwal S, Maria A, Dudeja A, Dubey NK, Anand P, et al. Comparison of oral ibuprofen with oral indomethacin for PDA closure in Indian preterm neonates: a randomized controlled trial. Pediatr Cardiol 2014;35:824-30.

15. Gournay V, Roze J, Kuster A, Daoud P, Cambonie G, Hascoet J, et al. Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial. Lancet 2004;364:1939-44.

16. Rackley CR, Stripp BR. Building and maintaining the epithelium of the lung. J Clin Invest 2012;122:2724.

17. Regev RH, Lusky A, Dolfin T, Litmanovitz I, Arnon S, Reichman B, et al. Excess mortality and morbidity among small-for-gestational-age premature infants: a population-based study. J Pediatr 2003;143:186-91.

18. Peacock JL, Lo JW, D'Costa W, Calvert S, Marlow N, Greenough A. Respiratory morbidity at follow-up of small-for-gestational-age infants born very prematurely. Pediatr Res 2012;73:457-63.

19. Kim D-H, Kim H-S, Choi CW, Kim E-K, Kim B-I, Choi J-H. Risk factors for pulmonary artery hypertension in preterm infants with moderate or severe bronchopulmonary dysplasia. Neonatology 2012;101:40-6.

20. Nicolini U, Fisk NM, Rodeck CH, Talbert DG, Wigglesworth JS. Low amniotic pressure in oligohydramnios—is this the cause of pulmonary hypoplasia? Am J Obstet Gynecol 1989;161:1098-101.

21. Jayet P-Y, Rimoldi SF, Stuber T, Salmòn CS, Hutter D, Rexhaj E, et al. Pulmonary and systemic vascular dysfunction in young offspring of mothers with preeclampsia. Circulation 2010;122:488-94.

22. Lazdam M, de la Horra A, Pitcher A, Mannie Z, Diesch J, Trevitt C, et

al. Elevated blood pressure in offspring born premature to hypertensive pregnancy: is endothelial dysfunction the underlying vascular mechanism? Hypertension 2010;56:159-65.

23. Silasi M, Cohen B, Karumanchi SA, Rana S. Abnormal placentation, angiogenic factors, and the pathogenesis of preeclampsia. Obstet Gynecol Clin North Am 2010;37:239-53.

24. Bueters RR, Klaasen A, Maicas N, Florquin S, van den Heuvel LP, Schreuder MF. Impact of early postnatal NSAID treatment on nephrogenesis in Wistar rats. Birth Defects Res B Dev Reprod Toxicol 2015;104:218-26.

국 문 초 록

서론: 동맥관 개존증은 미숙아의 약 70%에서 이환되는 질환으로 상당한 합병증이 이환되며 높은 사망률을 보인다. 이부프로펜은 인도메타신과 함께 동맥관 개존증의 치료제로 사용되고 있으나 폐고혈압과 같은 매우 드물지만 치명적인 합병증이 발생할 수 있다. 본 연구는 동맥관 개존증 치료를 위한 이부프로펜 투약 후 발생하는 폐고혈압의 임상 경과 및 발생에 관계된 위험인자를 기술하고자 한다.

방법: 2010년부터 2014년 사이에 서울대학교 어린이병원 신생아 중환자실에 입원하였던 출생체중 1,500 g 미만의 극소 저체중 출생아 가운데 동맥관 개존증을 치료하기 위해 이부프로펜이 투약된 신생아의 의무기록을 후향적으로 분석 하였다. 대상 환아들은 폐고혈압 군과 비 폐고혈압군으로 나뉘었다. 폐고혈압은 심장 초음파 검사를 통하여 진단하였으며 다음 중 하나이상의 소견을 확인할 수 있을 때 진단하였다; 1) 심실 사이 중격 평탄화가 관찰되는 경우 2)삼천판막 폐쇄 부전에서 관찰되는 제트 속도(jet velocity) 가 3m/s 이상인 경우 3)동맥관을 통하여 우좌 단락 혹은 양측성 단락이 관찰되는 경우.

결과: 총 144명 대상 환아를 분석하였으며 그 중 10명에서 폐고혈압이 발생하였다(6.9%). 폐고혈압 군에 속한 미숙아들의 임신 주수가 더 어렸고(P=0.006), 출생 체중이 더 가벼웠다(P<0.001). 나

이에 따른 체중이 3백분위가 되지 않는 경량아, 산모의 고혈압성 질환, 산모의 양수과소증은 폐고혈압 발생의 독립적인 위험인자임을 확인할 수있었다. 폐고혈압 군은 호흡 곤란 정도가 더 악화되었으며 (80.0% vs 6.0%, P=0.007), 중증 기관지 폐 이형성증의 발생 빈도가 높았다(90.0% vs 15.7%, P=0.023). 다변량 분석을 통하여 확인한 승산비는 나이에 따른 체중이 3백분위가 되지 않는 경량아에서 1.71 x10^5 [95%CI 1.65−1.76 x10^{10}, P=0.041], 산모의 고혈압성 질환에서 1.32 x10^3 [95%CI 3.86−4.51 x10^5, P=0.016], 산모의 양수과소증이 동반된 경우에 47.98 [95%CI 1.10−2.10 x10^3, P=0.045] 로 확인되었다.

결론: 본 연구에서 이부프로펜 투약 후 폐고혈압이 발생하는 빈도가 높음을 알 수 있었으며 임신 주수가 어릴수록, 나이에 따른 체중이 3백분위가 되지 않는 경량아인 경우, 산모가 고혈압성 질환이 있거나 양수과소증이 있었던 경우를 이부프로펜 투약 후 발생하는 폐고혈압의 독립적인 위험인자라고 할 수 있다. 치료가 필요한 동맥관 개존증에서 상기의 위험인자가 동반된 경우 치료 방법의 선택에 세심한 주의가 필요하다.

주요어: 이부프로펜, 부작용, 미숙아

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