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Can Early Diagnosis - Treatment of A Hemodynamically Significant Patent Ductus Arteriosus Reduce the Incidence of Pulmonary Hemorrhage in Extreme Low Birth Weight Infants?

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ABSTRACT

Objective: *To identify pulmonary hemorrhage incidence modification after early diagnosis-treatment of an hsPDA in ELBW infants.*

Study design: *Data from extreme preterm infants treated by Ibuprofen were retrospectively and prospectively reviewed. X^2 test and Fisher's exact test were used for categorical analyses. t-test and Kruskl-Wallis test were used for continuous analyses. Multivariate analyses with logistic regression models were used to control for differences in observed covariates.*

Results: *Fifty-five ELBW infants were diagnosed with PDA. Significant increase in survival in early ibuprofen group (67.7% vs 91.5%; p = .033) was seen; with a significant reduction in the pulmonary hemorrhage incidence in the 26 – $27^{6/7}$ WGA in EIG (22.7% vs 0%; p = .047). To note that, proven – NEC cases occurred more frequently in the 24 – $25^{6/7}$ WGA in EIG with a significant difference (44.4% vs 0%; p = .041).*

Conclusion: *Early treatment of hemodynamically significant patent ductus arteriosus is associated with an increase in survival in ELBW infants with less pulmonary hemorrhage, especially in the 26 – $27^{6/7}$ WGA. In another hand, developing proven-NEC increased if 24 – $25^{6/7}$ WGA were treated earlier by Ibuprofen for their PDA. Future prospective, multi-centric, large-scale randomized trials should be conducted to determine the best strategies for PDA management, especially in ELBW infants.*

Keywords

Extreme low birth weight infant, Patent ductus arteriosus, Pulmonary hemorrhage, Ibuprofen.

Abbreviation

hsPDA: Hemodynamically significant Patent Ductus Arteriosus; ELBW: Extreme low birth weight; PGE_2: Prostaglandin E_2; WGA: Weeks Gestational Age; NO: Nitric Oxide; BPD: Bronchopulmonary dysplasia; HFOV: High frequency oscillatory ventilation; RDS: Respiratory distress syndrome; CLD: Chronic lung disease; SIP: Spontaneous Intestinal Perforation.

Introduction

Spontaneous closure of the ductus arteriosus tends to occur in most infants born > 28 WGA (73%), and those with birth weight > 1000 g (94%) [1]. However, its rates among ELBW infants are still unknown, and late treatment is associated with lower success rate. Therefore, no consensus for PDA treatment in this category of patients is agreed and the optimal timing, dosage and drug use are still yet to be identified.

PDA can be easily detected by echocardiography. The most important parameter to define hsPDA remains Transductal

diameter ≥ 1.5 mm, but its sole measure is insufficient and other indices are needed:
Left atrium: Aortic root ratio ≥ 1.4
PDA maximal flow velocity < 2 $m.s^{-1}$
Left pulmonary artery flow pattern and mean velocity ≥ 0.2 $m. s^{-1}$ [2]

Clinical signs of hsPDA typically appear during the first two to three days after birth in premature infants; but they may develop earlier in infants treated with exogenous surfactant for RDS [3].

PDA shunting direction determines its pathophysiological effects. In case of persistent pulmonary hypertension, right-to-left shunting is present and hypoxemia occurs. In another hand, in case of low pulmonary vascular resistance, left-to-right shunt occurs resulting in cardiac overload, diastolic steal and pulmonary complications (e.g., pulmonary hemorrhage) [4].

First description of pulmonary hemorrhage in neonates goes back to 1855 [5]. It remains a life-threatening condition, especially in ELBW infants. Its incidence is 1 to 12 per 1000 live births, and much more in ELBW infants. Its clinical presentation varies from a mild, self-limited disorder to massive life-threatening complications [6].

The exact pathophysiology of pulmonary hemorrhage remains unknown, but the most accepted theory is that after birth, there is a decrease in pulmonary vascular resistance; and in the presence of left-to-right shunting hsPDA, pulmonary overcirculation occurs. The increased filtration in the pulmonary microvasculature leads to hemorrhagic edema fluid and pulmonary hemorrhage [6,7].

Therefore, the purpose of this study was to evaluate if early-diagnosis and Ibuprofen-based treatment of hsPDA decreased the incidence of pulmonary hemorrhage in ELBW infants.

Methods

This is a single center study done in Centre Hospitalier Intercommunal André-Grégoire, Montreuil – France, a level-III hospital with approximately 4200 deliveries and 80 ELBW infants per year.

This study has had the approval of the Ethics Committee of the hospital and was divided into 2 cohorts.

The 1st one – LIG (Late Ibuprofen Group): Retrospective, ELBW born between $24^{0/7}$ and $27^{6/7}$ weeks of gestational age and admitted to the NICU from September 1st, 2015 through August 30, 2016.

The 2nd cohort – EIG (Late Ibuprofen Group): Prospective, ELBW born between $24^{0/7}$ and $27^{6/7}$ weeks of gestational age and admitted to the NICU from September 1st, 2016 through May 31, 2017.

Infants were excluded if they were born < 24 weeks and/or birth weight < 500 grams. Were also excluded all deaths within the 1st day of birth, born with major congenital anomalies, severe asphyxia or with incomplete data.

All infants and their mothers' data was collected by chart review that contained gestational age (Date of last menstrual period and by an ultrasonic exam done between 10 to 15 weeks of gestation), birth weight, small-for-gestational age (Birth weight below the 10th percentile of the French standards using AUDIPOG), gender, delivery method, Apgar 1st and 5th minutes, ethnicity, antenatal steroids, preeclampsia, HELLP syndrome, chorioamnionitis and maternal educational level. Number of exogenous surfactant doses administered (Curosurf®, Poractant alfa, Chiesi SA, UK)

All ELBW infants were resuscitated upon birth by a pediatric team according to the latest ILCOR recommendations (wrapped with plastic bags under radiant warmer and using a T-piece resuscitator for respiratory support with a PEEP 5 cm H_2O and/or PIP 20 cm H_2O provided through a face mask within 1 minute of life). Intubation was provided at the discretion of the attending physician in the delivery room. Oxygen supplementation was given and adjusted according to the target saturation on a pulse oximeter (Masimo SET®). Upon their transfer to the NICU, ELBW infants were installed in an enclosed neonatal intensive care incubator (GE Giraffe Omnibed®) using a servo-controlled temperature and 85% humidity. They were put on nasal continuous positive airway pressure (nCPAP) or on a ventilator. Respiratory severity was evaluated by a physician on duty and if clinical profile and radiological findings were in favor of a neonatal RDS, curative exogenous surfactant Curosurf® (200 mg/kg) was given intratracheally within 2 hours following birth; subsequent doses were given if needed. Parenteral nutrition was given according to the unit protocol. Total fluid intake was initiated at 80 mL/kg/d, with daily increments of 20 mL/kg/d to a total of 160 mL/kg/d at the 1st week of life.

Pulmonary hemorrhage was defined by a clinical deterioration and worsening respiratory status, accompanied focal ground-glass opacities or complete "white out" on chest x-ray and a drop in hematocrit if present. They were intubated if not and put on HFOV modes (SLE 5000 ventilators).

The short-term outcomes of the infants were recorded for in-hospital mortality, advanced IVH (Grades III-IV according to Dr. Papile and Levene's classification criterias), periventricular leukomalacia, BPD (Any oxygen requirement at 36 weeks' postmenstrual age), confirmed NEC (Stage II_A or greater as by modified Bell's classification), spontaneous intestinal perforation, transitory renal dysfunction (Serum creatinine ≥ 132.6 µmol/L, urine output < 1 mL/kg/hour).

Starting on 1st September 2016, an early echocardiography was performed (between H_{12} and H_{24} of life) using Philips CX_{50} portable with S12-4 sector array transducer [12 MHz] (2-D, M-mode, Color, Pulsed and Continuous-wave Doppler). Before that date, echocardiography was only performed if hsPDA was clinically sympotmatic. Ibuprofen Pedea® (Orphan Europe, France) was given with a loading dose of 10 mg/kg intravenously followed by two intravenous doses of 5 mg/kg each every 24h. During the

72 hours of ibuprofen treatment, the infants were given Nil Per Os (NPO) with exclusive parenteral nutrition given via central catheter. Initial total fluid intake started at 80 mL/kg/d with no volume restriction and increments of 20 mL/kg/d to a total volume of 160 mL/kg/d at day 4 of life. Withholding the treatment in case of a gastrointestinal bleeding *and/or* transitory renal dysfunction. Transfer of ELBW infants for surgical ligation in case of two full medical treatment courses failure (IV Ibuprofen for 3 days followed by IV Paracetamol for 5 days).

The data were analyzed using SPSS for Mac version 20.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistical analyses were used to describe mothers and infants characteristics. The categorical variables were compared between the 2 groups using Chi-squared test or Fisher exact tests, and continuous ones by using *t*-test or Kruskl Wallis test by ranks. Multivariate regression models were used to control for differences in observed covariates. *p value* < .05 was considered to be statistically significant.

Results

From the total eligible ninety-two ELBW infants, fifty-five ELBW infants were diagnosed with PDA as shown in Figure 1.

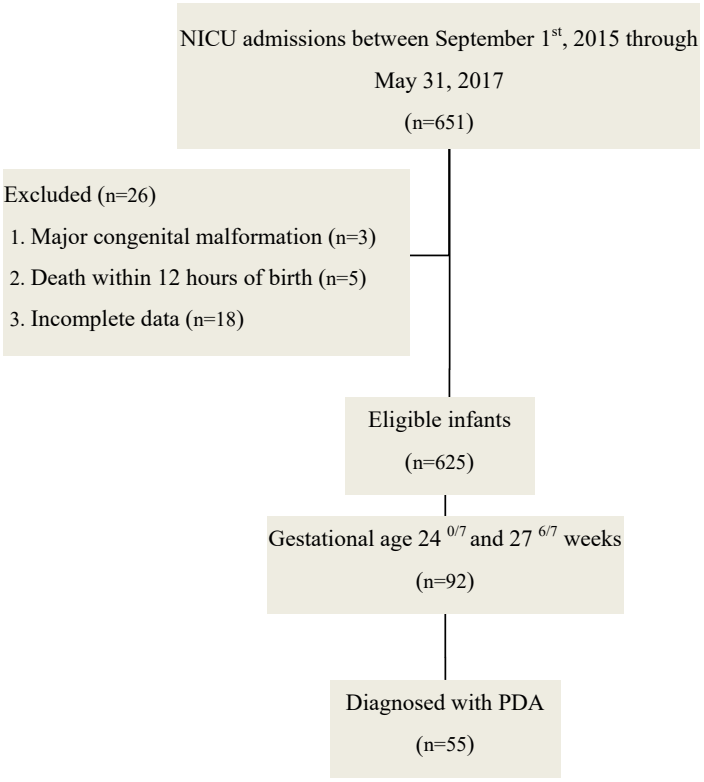

Figure 1: Diagram for study cohort.

Infants and theirs mothers demographic characteristics are shown respectively in *Table 1* and *Table 2* with no significant differences between the 2 cohorts in the distribution of mean gestational age (26.28 WGA ± 1.09 *vs* 26.32 WGA ± 0.99); mean birth weight (797g ±114 *vs* 808g ±117), male gender (38.7% *vs* 37.5%; *p* = .979), Apgar scores and antenatal steroids (64.8% *vs* 91.6%; *p* = .157).

Table 1: Demographic parameters of ELBW preterm infants.

	Early Ibuprofen Group (n=24)	Late Ibuprofen Group (n=31)	*p value*
Weeks of gestation (mean) (± SD)	26.32 (± .99)	26.28 (± 1.09)	.886
Birth weight mean (grams) (± SD)	808 (± 117)	797 (± 114)	.702
Male gender (%)	9 (37.5)	10 (32.3)	.979
Postnatal steroids (%)	7 (29.2)	9 (29.03)	.542
Cesarean section delivery (%)	10 (41.6)	23 (74.19)	**.015***
Apgar score - median 1st minute 5th minute	0 5 8	0 5 8	0 - -
≥3 criterias on the echocardiography (%) Surfactant administration (%)	11 (45.8)	11 (35.5)	.437
≤ 24 hours	12 (50)	23 (74.19)	.091
> 24 hours	7 (29.16)	13 (41.9)	.328

Table 2: Demographic parameters of ELBW preterm infants' mothers.

	Early Ibuprofen Group (n=24)	Late Ibuprofen Group (n=31)	p value
Antenatal steroids (%)	22 (91.6)	24 (77.4)	.157
Race/Ethnicity (%)			
Caucasian	7 (29.16)	11 (35.48)	.342
African	7 (29.16)	16 (51.61)	.147
Others	10 (41.66)	4 (12.9)	.086
Preeclampsia (%)	9 (37.5)	12 (38.7)	.927
HELLP syndrome (%)	1 (4.2)	3 (9.7)	.624
Magnesium Sulfate given (%)	7 (29.16)	4 (12.9)	.180
Multiple gestations (%)	7 (29.16)	9 (29)	.991
Chorioamnionitis / Preterm labor (%)	17 (70.8)	15 (48.38)	.094
Maternal educational level (%)			
Secondary	5 (20.8)	6 (19.3)	.845
Tertiary	5 (20.8)	8 (25.8)	.924
College	14 (58.3)	17 (54.8)	.792

Also, no significant changes in the incidence of preeclampsia (*p* = .927), HELLP syndrome (*p* = .624), preterm labor (*p* = .094), nor maternal education level were seen between the 2 cohorts, except for cesarean section deliveries that decreased significantly in the EIG (*p* = .015).

A significant reduction in the mortality rate in ELBW infants (32.2% *vs* 8.3%; *p* = .033) was seen in EIG but in another hand an increase in confirmed NEC cases in the same cohort (20.8% *vs* 3.2%; *p* = .038) as shown in Table 3 and Figure 2.

No significant difference in the incidence of respiratory distress syndrome, BPD, IVH, transitory renal dysfunction, sepsis nor pulmonary or intestinal hemorrhages between the 2 groups as shown in Table 3.

To have a better idea about the results, we divided the ELBW infants in two different subgroups.

Table 3: Study groups' outcomes.

	Early Ibuprofen Group (n=24)	Late Ibuprofen Group (n=31)	*p* value
Mortality (%)	2 (8.33)	10 (32.25)	.033*
IVH – Grade 3 or 4 (%)	2 (8.33)	1 (3.22)	.575
BPD (%)	10 (41.66)	10 (32.25)	.575
Pulmonary hemorrhage (%)	1 (4.16)	7 (22.58)	.058
Confirmed NEC (%)	5 (20.8)	1 (3.2)	**.038***
Spontaneous intestinal perforation (%)	3 (12.5)	0	.077
Transitory renal dysfunction (%)			
Oliguria	3 (12.5)	4 (12.9)	.645
Creatinin level ≥ 132.6 µmol.L^{-1}	2 (8.3)	1 (3.22)	.403
Cerebral palsy (%)	1 (4.16)	0	.436
Epilepsy (%)	2 (8.3)	0	.186
Periventricular leukomalacia (%)	1 (4.16)	0	.436

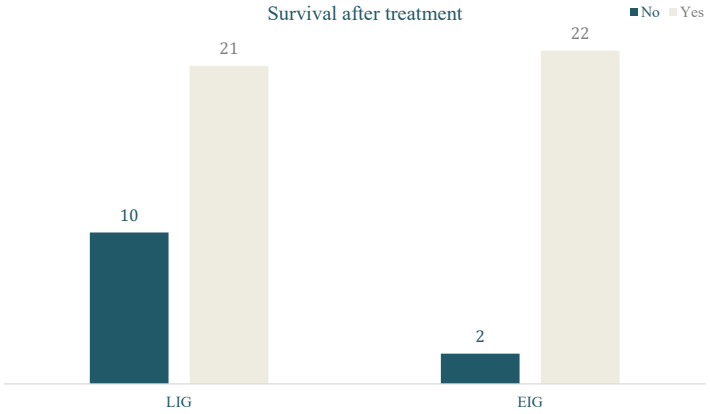

Figure 2: Survival rate before and after implementation of early ibuprofen treatment protocol

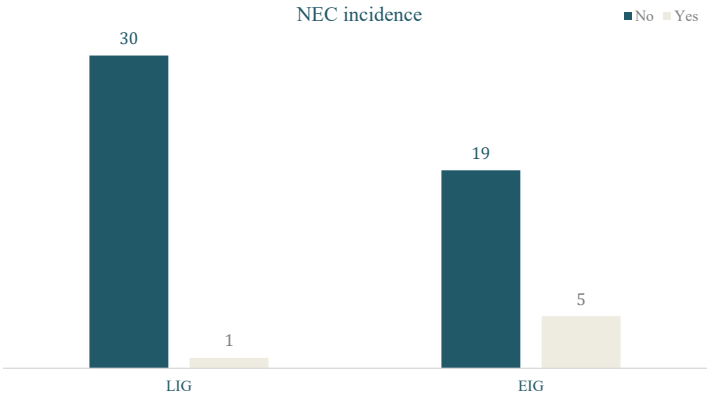

Figure 3: NEC incidence before and after implementation of early ibuprofen treatment protocol.

The 1st one including all 24 – 25$^{6/7}$ WGA and the 2nd one including 26 – 27$^{6/7}$ WGA. Table 4 and Table 5 showed no significant differences in the baseline characteristics between the 2 subgroups.

Table 4: Baseline ELBW preterm infants' characteristics of the two study subgroups.

	24 – 25^{6} weeks			26 – 27^{6} weeks		
	Early Ibuprofen Group	Late Ibuprofen Group	*p* value	Early Ibuprofen Group	Late Ibuprofen Group	*p* value
Weeks of gestation (Mean)	25.07	24.93	.431	26.84	26.88	.352
Male (%)	2 (28.6)	4 (44.4)	.633	7 (41.2)	6 (27.3)	.361
Postnatal steroids (%)	1 (14.2)	4 (44.4)	.308	6 (35.2)	5 (22.7)	.482
Cesarean section delivery (%)	2 (28.6)	7 (77.8)	.072	8 (47.1)	16 (72.7)	.101
≥ 3 cardiac US criterias (%)	4 (57.1)	5 (55.6)	.671	7 (41.2)	6 (27.3)	.361
Surfactant given (%)						
≤ 24h	3 (42.9)	9 (100)	**019***	9 (52.9)	14 (63.6)	.501
> 24h	2 (28.6)	6 (66.7)	.315	5 (29.4)	7 (31.8)	.872

Table 5: Study subgroups' baseline maternal ELBW preterm infants' characteristics.

	24 – 25^{6} weeks			26 – 27^{6} weeks		
	Early Ibuprofen Group	Late Ibuprofen Group	*p* value	Early Ibuprofen Group	Late Ibuprofen Group	*p* value
Antenatal steroids (%)	7 (100)	5 (55.5)	.088	15 (88.2)	19 (86.4)	.862
Race/ Ethnicity (%)			.111			.129
Caucasian	2 (28.6)	1 (11.1)		5 (29.4)	10 (45.5)	
African	1 (14.2)	6 (66.7)		6 (35.3)	10 (45.5)	
Others	4 (57.2)	2 (22.2)		6 (35.3)	2 (9.0)	
Preeclampsia (%)	1 (14.3)	1 (11.1)	.700	8 (47.1)	11 (50)	.556
HELLP syndrome	0	0	-	1 (5.9)	3 (13.6)	.618
Magnesium sulfate (%)	2 (28.6)	0	.175	5 (29.4)	4 (18.2)	.465
Multiple gestations (%)	0	4 (44.4)	.088	7 (41.2)	5 (22.7)	.216
Chorioamnionitis/ preterm labor	6 (85.7)	5 (55.5)	.308	11 (64.7)	10 (45.5)	.232
Maternal educational level			.423			.892
Secondary (%)	2 (28.5)	3 (33.3)		3 (17.6)	3 (13.6)	
Tertiary (%)	1 (14.3)	2 (22.2)		4 (23.5)	6 (27.2)	
College (%)	4 (57.1)	4 (44.4)		10 (58.8)	13 (59.1)	

We found that proven – NEC cases occurred more frequently in the 24 – 25$^{6/7}$ WGA in EIG with a significant difference (44.4% vs 0%; p = .041) as shown in Table 6. Also, we found a significant reduction in the pulmonary hemorrhage incidence in the 26 – 27$^{6/7}$ WGA infants in EIG (22.7% vs 0%; p = .047) as shown in Table 6.

Discussion

In this study, we found that ELBW preterm infants when treated earlier (within 72 hours of life) for their hsPDA by intravenous ibuprofen for 3 consecutive days were more likely to survive (p = .033) with a significant reduction in the incidence of pulmonary hemorrhage in the 26 – 27$^{6/7}$ WGA subgroup of patients (p = .047).

Early treatment of hsPDA can lead to its closure and stopping "*Ductal steal*" reducing the excessive pulmonary flow [8]. By this mechanism, we supposed the survival rate is increased significantly and the reduction of pulmonary hemorrhage in ELBW infants.

Table 6: Different outcomes of the two study subgroups.

	24 – 25⁶ weeks			26 – 27⁶ weeks		
	Early Ibuprofen Group	Late Ibuprofen Group	*p* value	Early Ibuprofen Group	Late Ibuprofen Group	*p* value
Mortality (%)	2 (22.2)	6 (66.7)	.077	0	4 (18.2)	.111
IVH – Grade 3 or 4 (%)	2 (22.2)	1 (11.1)	.527	0	0	NA
BPD (%)	5 (55.6)	3 (33.3)	.343	5 (33.3)	7 (31.8)	.923
Pulmonary hemorrhage (%)	1 (11.1)	2 (22.2)	.527	0	5 (22.7)	**.047***
Confirmed NEC (%)	4 (44.4)	0	.041*	1 (6.7)	1 (4.5)	.653
SIP (%)	2 (22.2)	0	.235	1 (6.7)	0	.405
Transitory renal dysfunction						
Oliguria	2 (22.2)	3 (33.3)	.500	1 (6.7)	1 (4.5)	.653
Creatinine ≥132.6 µmol.L^{-1}	1 (11.1)	0	.500	1 (6.7)	1 (4.5)	.653

Contrary to other studies [9] where early PDA closure was associated with a lower incidence of NEC, our findings showed that the more mature the ELBW infant is (24 – 25$^{6/7}$ WGA), the more the risk to develop proven-NEC (stage IIA or greater) if treated earlier by intravenous ibuprofen.

To note that NEC is a multifactorial illness with a poorly understood pathogenesis. While on Ibuprofen-treatment, the newborns in our institution were NPO for 72 hours. TPN-associated loss of epithelial barrier function is a well-known complication for fasting [10], leading to potential bacterial leakage injuring the intestinal mucosa and causing NEC. Another theory is that Ibuprofen with its COX-inhibitor effects can cause disturbances in gut perfusion leading to ischemia that may play an important role in NEC.

Recent reports suggest that the early (day 0 to day 3 of life) use of prophylactic COX-inhibitors as an independent risk factor for spontaneous intestinal perforation in very premature infants [11]. In our study, 3 cases of spontaneous intestinal perforation in EIG were noted compared to 0 case in LIG, but these findings were not statistically significant. Knowing the potential complications of Ibuprofen treatment, including renal failure, intestinal bleeding and perforation, pulmonary hypertension, it is important to use a predetermined treatment protocol and to identify which infants are more likely to benefit from the treatment.

Our results should be interpreted with caution due to the limitations of a small, single-center observational study. Despite these limitations, we believe that ELBW preterm infants are more likely to survive after early Ibuprofen treatment with a significant reduction of pulmonary hemorrhage.

In conclusion, ELBW preterm infants treated within 72 hours of life by ibuprofen for hsPDA were more likely to survive with less pulmonary hemorrhage, but at risk to develop more proven-NEC.

Large, randomized, multi-centric, prospective studies may help confirm our findings and determine the optimal treatment strategy.

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