Association of patent ductus arteriosus size with clinical features and short-term outcomes in preterm infants less than 34 weeks

Chandrakala Bada Shekharappa[1], Edison Albert Balakrishnan Elizabeth[2], Bharathi Balachander[3]

From [1]Professor and Head, [3]Assistant Professor, Department of Neonatology, [2]Post-graduate, Department of Pediatrics, St. John's Medical College Hospital, Bengaluru, India

Correspondence to: Dr. Bharathi Balachander, Department of Neonatology, St. John's Medical College Hospital, Bengaluru - 560 034, Karnataka, India. E-mail: bharathibalachander@gmail.com

Received -14 January 2020 Initial Review - 28 January 2020 Accepted - 09 March 2020

ABSTRACT

Background: Preterm patent ductus arteriosus (PDA) is a challenging situation faced by the neonatologists every day. The devastating consequences of a hemodynamically significant PDA (hsPDA) compared to the harms of medical therapy, make treatment decisions challenging. The diagnosis of an hsPDA is not uniform and multiple classifications are available to assess its severity. **Aim:** The present study was aimed to analyze whether the size of PDA, based on echocardiography, had any association with clinical features and neonatal outcomes. **Materials and Methods:** This retrospective study was done in a Level 3 newborn intensive care unit (NICU) from January 2016 to December 2017. Preterm (≤34 weeks) infants with hsPDA formed the study group. Data were collected from the NICU database. hsPDA was classified based on the size into small, moderate, and large and analysis was done. Data for each infant until discharge were collected in pre-designed pro forma from medical records. **Results:** A total of 1064 preterm infants were admitted during the study period and 94 had hsPDA. The mean gestational ages were 31.8±4.2, 29.6±3.3, and 31.9±4.2 weeks for mild, moderate, and severe PDA, respectively. Among the clinical parameters, it was found that shock, metabolic acidosis ($p<0.01$), and thrombocytopenia were significantly associated with larger PDA size ($p=0.02$). Infants with a larger PDA size had a higher risk of bronchopulmonary dysplasia (BPD) and ventilation days ($p=0.03$). Logistic regression was done to analyze independent factors associated with shock, BPD, and PDA severity. **Conclusion:** Large PDA is associated with an increased risk of higher ventilation days and BPD.

Key words: *Bronchopulmonary dysplasia, Ductus arteriosus, Prematurity*

Prematurity is one of the largest contributors to neonatal mortality worldwide [1]. One of the prominent complications in a preterm infant is the presence of a hemodynamically significant patent ductus arteriosus (hsPDA). It can have devastating consequences in preterm infants such as pulmonary hemorrhage, necrotizing enterocolitis, and intraventricular hemorrhage [2]. However, it is not established as to the extent of these complications being attributed to the presence of PDA. It is found that there is 30% chance of spontaneous closure of PDA in infants <28 weeks and 70% in infants >28 weeks. However, the presence of an hsPDA is found to have reduced celiac artery flow and cerebral oxygen extraction [3,4]. The diagnosis of hsPDA requires echocardiographic screening and treatment. The clinical features alone are poor predictors of hsPDA and relying on them leads to delay in diagnosis [5].

The first line of therapy is non-selective cyclooxygenase (COX) inhibitors such as ibuprofen, indomethacin, or paracetamol in most neonatal units. However, COX inhibitors have potential adverse effects on the renal system and GIT [6]. Recently, the poor neurodevelopmental outcome has been reported in infants undergoing medical closure of PDA [7]. Studies have shown that hsPDA could be an innocent bystander with spontaneous closure rates [8]. Thus, the diagnosis and treatment of hsPDA in preterm is a challenging situation. Treatment of PDA based only on echocardiographic evaluation without clinical manifestation has led to the overtreatment and exposure to the complications associated with the medications. Hence, we aimed to analyze if the severity of PDA (based on size) had any correlation with clinical features and neonatal outcomes.

MATERIALS AND METHODS

This was a retrospective study conducted in the Level 3 newborn intensive care unit (NICU) during January 2016–December 2017. The Institutional Ethics Committee approval was obtained before the initiation of the study. The preterm infants (≤34 weeks) who were diagnosed to have PDA based on the echocardiography were included in the study. Term babies with PDA, infants with a right to left shunt, congenital malformations, and babies whose charts were not available for analysis were excluded from the study.

Sample size calculated was based on the study by Sehgal and McNamara [9] considering the proportion of preterm infants

with PDA as 64% with 20% relative precision and alpha error as 5%. All infants with symptoms or signs of hsPDA underwent echocardiographic screening for PDA. PDA was classified, based on echocardiography [9], as small with PDA size <1.5 mm, left atrium (LA) and aortic valve (Ao) ratio <1.4:1, moderate with PDA size >1.5–3 mm, and LA: Ao >1.4:1 and large PDA size >3 mm with LA: Ao >1.6:1.

hsPDA was considered, when size was >1.4 mm/kg or LA:Ao >1.4:1. The data were collected from the NICU database and from their medical records. The clinical features, echocardiographic, and laboratory parameters were recorded in a data collection pro forma. The parameters included detailed maternal history, neonatal morbidities, demographic details, and clinical and laboratory details. The clinical parameters recorded were tachycardia (>160/min), tachypnea (>60/min) or apnea, peripheral bounding pulses, systemic hypotension with hyperdynamic precordium, increased need for respiratory support, feeding intolerance, or oliguria (urine output <1 ml/kg/h).

PDA was treated with oral ibuprofen (10 mg/kg once daily on day 1 followed by 5 mg/kg/day for 2 days) as the first line. If ibuprofen was contraindicated, then oral paracetamol was started. If the infant had contraindication to oral feeding, then IV paracetamol was used.

The laboratory parameters that were analyzed included the presence of metabolic acidosis (HCO_3< 15), creatinine for acute kidney injury, bilirubin for the presence of cholestasis, and platelet count for thrombocytopenia (<50,000). Data were analyzed using the SPSS software. Data were presented as mean and standard deviation for continuous variables and analyzed using *t*-test or Mann–Whitney U-test. Data were represented as percentage and distribution of frequency for categorical variables. Chi-square or Fisher's exact test was used. p≤0.05 was considered statistically significant.

RESULTS

A total of 1064 preterm infants were admitted during the study period. There were 94 infants with hsPDA. The total number of infants studied was 88. The baseline characteristics of the study population are outlined in Table 1.

Among the clinical parameters, it was found that shock (p=0.005), acidosis (p=0.015), and thrombocytopenia (p=0.029) were significantly associated with larger PDA size (Table 2). Tachypnea, tachycardia, presence of hyperdynamic precordium, and systolic murmur were not significantly different between the three groups.

Infants with a larger PDA size had a higher risk of bronchopulmonary dysplasia (BPD) and ventilation days (Table 3).

On the application of logistic regression, none of the clinical features individually had a strong relation to PDA. However, the combination of wide pulse pressure, shock, acidosis, and thrombocytopenia was weakly predictive of a large PDA (p=0.025) by regression analysis. Surfactant administration (p=0.006) and culture-positive sepsis (p=0.004) had a strong association with BPD rather than the size of PDA alone.

DISCUSSION

The PDA in preterm has been an ongoing enigma with regard to its implications and its treatment. The definition of hsPDA has been unclear and varied classifications have been proposed. Although most of the definitions for classification are based on the size of the PDA, a detailed staging has recently been proposed by McNamara and Sehgal, which includes both clinical and echocardiographic parameters [10].

In the present study, we found a significant association between the presence of shock, acidosis, and the size of PDA. There

Table 1: Baseline characteristics of the study population

Parameter (Mean±SD) or number	Small PDA (15)	Moderate PDA (56)	Large PDA (17)	*P*-value
Birth weight (g)	1490±736	1187.7±521.8	1683.1±722.4	0.017
Gestational age (weeks)	31.8± 2.2	29.6±3.3	31.9±2.1	0,025
Age at presentation	2.8±0.98	3.5±5.1	3.5±4.0	0.877
Extremely low birth weight	3	22	5	0.402
Male infants	6	26	9	0.661
Maternal Preeclampsia	6	17	7	0.597
Gestational diabetes mellitus	1	6	2	0.855
Antepartum hemorrhage	0	6	0	0.192
Intrauterine growth restriction	0	3	0	0.495
Antenatal steroids	7	23	4	0.306
Lower segment cesarean section	10	25	4	0.70
Required resuscitation	5	8	4	0.146
Received surfactant	5	29	6	0.298
Culture-positive sepsis	3	13	5	0.583
Death and discharge against medical advice	3	10	5	0.768

PDA: Patent ductus arteriosus

Table 2: Clinical, laboratory, and echocardiographic characteristics of hsPDA before treatment

Parameter	Small PDA	Moderate PDA	Large PDA	*P*-value
PDA size (mm) (Mean±SD)	1.8±0.4	2.5±0.3	3.9±1.1	<0.01
LA:Ao	1.4±0.3	2.5±0.3	3.9±1.1	<0.0001
Hyperdynamic precordium	4	33	6	0.19
Systolic murmur	9	38	12	0.705
Shock	4	8	9	0.005
Acidosis	5	12	10	0.015
Wide pulse pressure	6	38	13	0.016
Bounding pulses	8	39	8	0.66
AKI	14	55	16	0.304
Thrombocytopenia	14	55	17	0.029

PDA: Patent ductus arteriosus, LA: Left atrium, AO: Aortic valve, AKI: Acute kidney injury, hsPDA: Hemodynamically significant patent ductus arteriosus

Table 3: Treatment course and complications of hsPDA

Events	Small PDA	Moderate PDA	Large PDA	*P*-value
Treated with ibuprofen	4	32	7	0.102
Treated with paracetamol	4	24	10	0.309
Required rescue therapy	0	3	0	0.485
Total number of PDA not closed	1	4	1	0.909
PDAs requiring surgery	0	4	0	0.633
Mortality	1	5	3	0.770
Number of days on ventilator	3.3±1.7	12.32±11.8	8.4±6.06	0.032
Bronchopulmonary dysplasia	0	11	0	0.039
Necrotizing enterocolitis	0	4	3	0.143
Jaundice requiring phototherapy	7	40	7	0.112
Cholestasis	0	2	2	0.128
Intraventricular hemorrhage	2	15	4	0.61
AKI (all stages)	3	24	7	0.3

PDA: Patent ductus arteriosus, AKI: Acute kidney injury, hsPDA: Hemodynamically significant patent ductus arteriosus

is also an emphasis on clinical correlation with the neonate's condition [11]. The phenomenon of ductal steal which is described in the pathophysiology of PDA can compromise the left ventricular output and lead to shock. The left ventricular output and celiac flow are better markers of ductal steal than size alone [12,13]. Among other clinical parameters, we found that wide pulse pressures correlated significantly with the size of the PDA. Han *et al*. found that wide pulse pressure alone was not a useful indicator. They found low systolic and diastolic blood pressure to be better markers of hsPDA which was in accordance with our study [14].

In our study, the severity of PDA was associated with the presence of thrombocytopenia. This was in accordance with the study done by Echtler *et al*. They observed that platelets were recruited to the ductal lumen for its closure. Induced platelet dysfunction was found to impair ductal closure [15]. Simon *et al*. observed that thrombocytopenia in the first few days was associated with hsPDA [16].

In our study, 53% of infants with mild PDA were treated with medical treatment. However, all infants with moderate-severe PDA were given a trial of medical treatment. Clyman and Liebowitz found that 40–70% of PDA underwent spontaneous closure without any medical treatment at the end of the 1st week. However, the fallacy of this trial was that infants in the non-treatment group were crossed over to the treatment group and were analyzed [17].

We found that there was higher occurrence of BPD in infants with moderate-to-severe PDA. There were also higher ventilation days. However, the actual reason was unclear whether the PDA itself or the treatment of PDA contributed to BPD. On regression analysis, culture-positive sepsis and surfactant administration were associated with BPD rather than PDA alone. Schena *et al*. and Mirza *et al*. found that the persistence of PDA for a longer duration was most likely associated with BPD [18,19]. The interaction between PDA and BPD was found to be complex by Chock *et al*. [20].

The complex multifactorial nature of BPD was observed by Rojas *et al*., Marshall *et al*., and Oh *et al*. and they found gestation, low birth weight, sepsis, ventilation, liberal fluids, and PDA to be associated with BPD [21-23]. The presence of combination shock, acidosis, thrombocytopenia, and wide pulse pressure does predict the presence of a large PDA with a weak correlation coefficient of 0.2. This, however, necessitates an echocardiographic correlation before confirmation. The study had a few limitations. It was a retrospective analysis and samples were unequally distributed across the three groups.

CONCLUSION

Larger PDA size is associated with shock, thrombocytopenia, acidosis, BPD, and increased ventilator days. In a preterm infant, the presence of these factors warrants a high index of suspicion for an underlying hsPDA.

REFERENCES

1. Lawn JE, Cousens S, Zupan J, Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: When? Where? Why? Lancet 2005;365:891-900.
2. Prescott S, Keim-Malpass J. Patent ductus arteriosus in the preterm infant: Diagnostic and treatment options. Adv Neonatal Care 2017;17:10-8.
3. Shimada S, Kasai T, Hoshi A, Murata A, Chida S. Cardiocirculatory effects of patent ductus arteriosus in extremely low-birth-weight infants with respiratory distress syndrome. Pediatr Int 2003;45:255-62.
4. Arman D, Sancak S, Gürsoy T, Topcuoğlu S, Karatekin G, Ovalı F. The association between NIRS and Doppler ultrasonography in preterm infants with patent ductus arteriosus. J Matern Fetal Neonatal Med 2020;33:1245-52.
5. Skelton R, Evans N, Smythe J. A blinded comparison of clinical and echocardiographic evaluation of the preterm infant for patent ductus arteriosus. J Paediatr Child Health 1994;30:406-11.

6. Heymann MA, Rudolph AM, Silverman NH. Closure of the ductus arteriosus in premature infants by inhibition of prostaglandin synthesis. N Engl J Med 1976;295:530-3.
7. Janz-Robinson EM, Badawi N, Walker K, Bajuk B, Abdel-Latif ME, Neonatal Intensive Care Units Network. Neurodevelopmental outcomes of premature infants treated for patent ductus arteriosus: A population-based cohort study. J Pediatr 2015;167:1025-32000.
8. Slaughter JL, Reagan PB, Newman TB, Klebanoff MA. Comparative effectiveness of nonsteroidal anti-inflammatory drug treatment vs no treatment for patent ductus arteriosus in preterm infants. JAMA Pediatr 2017;171:e164354.
9. Sehgal A, McNamara PJ. Does echocardiography facilitate determination of hemodynamic significance attributable to the ductus arteriosus? Eur J Pediatr 2009;168:907-14.
10. McNamara PJ, Sehgal A. Towards rational management of the patent ductus arteriosus: The need for disease staging. Arch Dis Child Fetal Neonatal Ed 2007;92:F424-7.
11. Condò M, Evans N, Bellù R, Kluckow M. Echocardiographic assessment of ductal significance: Retrospective comparison of two methods. Arch Dis Child Fetal Neonatal Ed 2012;97:F35-8.
12. El-Khuffash A, Higgins M, Walsh K, Molloy EJ. Quantitative assessment of the degree of ductal steal using celiac artery blood flow to left ventricular output ratio in preterm infants. Neonatology 2008;93:206-12.
13. Sehgal A, Tran H, Carse E. Doppler manifestations of ductal steal: Role in decision making. Eur J Pediatr 2011;170:795-8.
14. Han UJ, Cho HJ, Cho YK, Choi YY, Ma JS. Change in blood pressure and pulse pressure in preterm infants after treatment of patent ductus arteriosus with indomethacin. Korean Circ J 2011;41:203-8.
15. Echtler K, Stark K, Lorenz M, Kerstan S, Walch A, Jennen L, *et al*. Platelets contribute to postnatal occlusion of the ductus arteriosus. Nat Med 2010;16:75-82.
16. Simon SR, van Zogchel L, Bas-Suárez MP, Cavallaro G, Clyman RI, Villamor E. Platelet counts and patent ductus arteriosus in preterm infants: A systematic review and meta-analysis. Neonatology 2015;108:143-51.
17. Clyman RI, Liebowitz M. Treatment and nontreatment of the patent ductus arteriosus: Identifying their roles in neonatal morbidity. J Pediatr 2017;189:13-7.
18. Schena F, Francescato G, Cappelleri A, Picciolli I, Mayer A, Mosca F, *et al*. association between hemodynamically significant patent ductus arteriosus and bronchopulmonary dysplasia. J Pediatr 2015;166:1488-92.
19. Mirza H, Garcia J, McKinley G, Hubbard L, Sensing W, Schneider J, *et al*. Duration of significant patent ductus arteriosus and bronchopulmonary dysplasia in extremely preterm infants. J Perinatol 2019;39:1648-55.
20. Chock VY, Punn R, Oza A, Benitz WE, Van Meurs KP, Whittemore AS, *et al*. Predictors of bronchopulmonary dysplasia or death in premature infants with a patent ductus arteriosus. Pediatr Res 2014;75:570-5.
21. Rojas MA, Gonzalez A, Bancalari E, Claure N, Poole C, Silva-Neto G. Changing trends in the epidemiology and pathogenesis of neonatal chronic lung disease. J Pediatr 1995;126:605-10.
22. Marshall DD, Kotelchuck M, Young TE, Bose CL, Kruyer L, O'Shea TM. Risk factors for chronic lung disease in the surfactant era: A North Carolina population-based study of very low birth weight infants. North Carolina neonatologists association. Pediatrics 1999;104:1345-50.
23. Oh W, Poindexter BB, Perritt R, Lemons JA, Bauer CR, Ehrenkranz RA, *et al*. Association between fluid intake and weight loss during the first ten days of life and risk of bronchopulmonary dysplasia in extremely low birth weight infants. J Pediatr 2005;147:786-90.

Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Shekharappa CB, Elizabeth EAB, Balachander B. Association of patent ductus arteriosus size with clinical features and short-term outcomes in preterm infants less than 34 weeks. Indian J Child Health. 2020; 7(3):105-108.

Doi: 10.32677/IJCH.2020.v07.i03.003