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Risk factors for patent ductus arteriosus in preterm neonates

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Abstract

Background The reported prevalences of patent ductus arteriosus (PDA) in preterm neonates vary, and are currently unknown in Palembang. Birth weight, gestational age, asphyxia, history of antenatal steroid use, hyaline membrane disease (HMD), race and ethnicity, are potential risk factors for PDA.

Objective To determine the prevalence of PDA and its risk factors in preterm neonates at Mohammad Hoesin Hospital, Palembang.

Methods This cross-sectional study was conducted from October 2011 to April 2012. Echocardiographic examinations were performed on 242 preterm neonates aged 15 hours to 7 days. Data was taken from medical records and interviews, and analyzed by Chi square and logistic regression analyses.

Results Patent ductus arteriosus was found in 142 (58.7%) preterm neonates with a prevalence ratio of 1.43. Neonates with birthweight ≤2,000 grams tended to have 1.9 (95% CI 1.17 to 3.32) times higher risk for PDA (P=0.01). Neonates ≤30 weeks gestation were also at 1.9 times higher risk for PDA (P=0.16). Probabilities for PDA occurrence in neonates with asphyxia, without antenatal corticosteroids and HMD were 1.6 (95% CI 1.13 to 3.36) times, 1.3 (95%CI 0.73 to 2.50) times and 2.2 (95%CI 1.29 to 3.72) times higher risk for PDA, respectively (P=0.22, 0.41, and 0.005, respectively).

Conclusion Birth weight and HMD are statistically significant risk factors of PDA, but the more significant one is HMD.

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Keywords: *patent ductus arteriosus, preterm neonates, risk factors*

The prevalence of patent ductus arteriosus (PDA) varies among regions. Becker *et al.* and Botto *et al.* reported that PDA comprised 7.5% and 10.6% of all congenital heart defects in Saudi Arabia and Atlanta, Georgia, USA, respectively.[1,2] The *National Birth Defects Prevention Network* in 2005 reported that US prevalence of PDA varied from 8.08 to 99.85 per 10,000 live births.[3] The PDA incidence in Texas, USA from 1999 to 2002 was 4.3 per 10,000 live births.[4] The prevalence of PDA in preterm neonates has not been reported in Indonesia, nor in Palembang.

Factors that lead to the opening of ductus arteriosus (DA) in the first days of life are not fully understood. Several potential risk factors for the onset of PDA are low birth weight, low gestational age, asphyxia, no history of antenatal steroids, respiratory distress (RD), race and certain ethnicities.[5-8] However, the most prominent risk factor remains unclear. The aim of this study was to determine the prevalence and risk factors of PDA in preterm neonates aged 15

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hours to 7 days who were admitted at Mohammad Hoesin Hospital.

Methods

This cross-sectional study was conducted at the Neonatal Ward, Neonatal Intensive Care and Rooming In Nursery at Mohammad Hoesin Hospital between October 2011 to April 2012. Subjects were neonates with <37 weeks gestational age, aged 15 hours to 7 days, and collected using a consecutive sampling method. Written informed consent was obtained from parents. Inclusion criteria were no other congenital abnormalities and no history of prostaglandin inhibitor therapy. Diagnosis was based on echocardiographic examination.

Data was recorded on research forms and analyzed by *SPSS version 16*. The PDA prevalence was calculated based on the proportion of disease, and dichotomic variables were analyzed by Chi square and logistic regression analyses with significance level of P <0.05. This protocol was approved by the Bioethics Humaniora Unit, Sriwijaya University Medical School.

Results

There were 242 neonates recruited in this study, whose gestational age ranged from 25 to 36 weeks, with a mean of 33 (SD 2.3) weeks. Birth weights ranged from 500 to 2,900 grams, with mean of 1,956 (SD 452) grams. Subjects' ages at the time of echocardiographic examination ranged from 16 to 151 hours with a mean of 37 (SD 25.8) hours. Subjects' characteristics are shown in **Table 1**.

Patent ductus arteriosus was observed in 142 (58.7%) neonates with a prevalence ratio of 1.43. Majority of PDA size was moderate (82.4%). Some of PDA neonates (33.7%) also had other intracardiac abnormalities as can be seen in **Table 1**.

The neonate with the lowest birth weight (500 grams) did not have PDA, but the neonate with the highest birth weight (2,900 grams) had PDA. Most neonates with birth weights of 2,000 grams (15 subjects, 10.6%), had PDA, whereas infants without PDA mostly had birth weights of 2,200 grams (14 neonates, 14%). Gestational age ranged from 25 weeks in 1 neonate (0.4%) to 36 weeks in 61 (25.2%) neonates. The lowest gestational age neonate with PDA was 27 weeks. The prevalences of risk factors for PDA in our subjects are shown in **Table 2**.

Table 1. Subjects' characteristics (n=242)

Characteristics	n	%
Gender		
Male	133	55
Female	109	45
Birth place		
Mohammad Hoesin Hospital	157	64.9
Others	85	35.1
Birth weight		
≤1,500 g	49	20.2
1,501-2,499 g	159	65.7
≥2,500 g	34	14
Gestational age		
≤30 weeks	29	12
31-34 weeks	107	44.2
35-36 weeks	106	43.8
Delivery types		
Uncomplicated vaginal	155	64
Caesarian section	76	31.4
Forceps extraction	7	2.9
Partial extraction	4	1.7
Ductus arteriosus defect size		
Small	16	11.3
Moderate	117	82.4
Large	9	6.3
Other intracardiac abnormalities		
Tricuspid regurgitation	32	22.5
Atrial septal defect	7	4.9
Ventricular septal defect	5	3.5
Patent foramen ovale	2	1.4
Atrioventricular septal defect	1	0.7
Mitral regurgitation	1	0.7

One hundred fifty-seven subjects were born in Mohammad Hoesin Hospital and 51 (32.4%) of them had asphyxia. Neonates with severe asphyxia had a 6.7 times higher risk for PDA, whereas neonates with mild-moderate asphyxia had a 1.3 times higher risk. There were 112 (46.3%) neonates with HMD and 68.8% of these had PDA. Pneumonia increased the risk of PDA 3.5 times, while HMD and transient tachypneu of newborn (TTN) increased the risk of PDA 2- and 1.3 times , respectively.

We performed an adjustment of risk factors with P>0.25 using bivariate analysis (**Table 3**). History of antenatal steroid use was excluded since P>0.25, and asphyxia was excluded since the information of asphyxia was only available in 157 neonates.

Table 2. Prevalences of risk factors for PDA

Risk factors		With PDA n (%)	No PDA n (%)	Total
Birth weight	≤1,500 g	35 (71.4)	14 (28.6)	49
	1,501-2,499 g	89 (56)	70 (44)	159
	≥2,500 g	18	16	34
Gestational age	≤30 weeks	21	8	29
	31-34 weeks	64 (59.8)	43 (40.2)	107
	35-36 weeks	57 (53.8)	49 (46.2)	106
Asphyxia	Severe	7	1	8
	Mild-moderate	25 (58)	18 (42)	43
	Non-asphyxia	54 (50.9)	52 (49.1)	106
Antenatal steroid use	No	114 (60.3)	75 (39.7)	189
	Yes	28 (52.8)	25 (47.2)	53
Respiratory distress	BP	32 (78)	9 (22)	41
	HMD	29 (67.4)	14 (32.6)	43
	TTN	16	12	28
	Non-RD	65 (50)	65 (50)	130

BP=bronchopneumonia, HMD=hyaline membrane disease, TTN=transient tachypneu of newborn, Non-RD=non respiratory distress.
Note: the data of asphyxia was only available in neonates born in Hoesin Hospital (157 neonates).

Table 3. Logistic regression test on risk factors for PDA

Risk Factors	Unadjusted			Adjusted		
	OR	95% CI	P* value	OR	95% CI	P** value
HMD	2.2	(1.29 to 3.72)	0.005	1.8	(1.07 to 3.28)	0.02
Birth weight	1.9	(1.17 to 2.78)	0.01	1.6	(0.92 to 2.79)	0.09
Gestational age	1.9	(0.84 to 4.70)	0.16			
Asphyxia	1.6	(0.81 to 3.21)	0.22			
Antenatal steroid use+	1.3	(0.73 to 2.50)	0.41			

* Chi square test; ** logistic regression test, +History of antenatal steroid use was excluded since P>0.25.

Discussion

There were 142 (58.7%) preterm neonates with PDA in our study, similar to a previous multicentre study which reports the prevalence of PDA in preterm neonates was 50%. However, a study at Cipto Mangunkusumo Hospital, Jakarta found the prevalence of preterm neonates with PDA to be 32%.[10] A study in Chicago, USA found the prevalence was 16%,[11] and the *Extremely Preterm Neonates Study in Sweden* (EXPRESS) discovered that 61% of extremely low birth weight neonates had PDA.[12]

Most of our subjects were delivered by uncomplicated spontaneous vaginal (155 neonates, 64%). A study reported that the most common mode of delivery for neonates in their study was similarly uncomplicated spontaneous vaginal in 50.7% neonates.[10] Age of subjects at the time of echocardiographic examination ranged from 16 to 151 hours with a mean of 37 (SD 25.8) hours. According to Park, the closure of DA is functionally within 10 to15 hours after birth.[7] Similarly an in vivo experiment on mice found that physiological DA closure occurred in the first 3 hours and would be completed within 10 to 12 hours. [13]

We found that 71.4% of neonates with birth weight ≤1,500 grams had PDA. In contrast, a cohort study reported the PDA prevalence in very low birth weight neonates to be 28% in Canada.[14] However, another study discovered that 10/18 neonates with birth weight <1,500 grams had PDA.[10] Furthermore, subjects with birth weight ≤2,000 grams had a 1.9 times risk of PDA. A study reported PDA prevalence in neonates'with birth weight <1,750 grams to be 45%, which increased to 80% for those with birth weight <1,200 grams.[6] Pees *et al*. summarized that over the last 30 years, there was a negative correlation between PDA prevalence and neonates' birth weight.[15] Similar reports were issued by Xiao-Yu *et al*.[16]

Of those with gestational age ≤ 30 weeks, 72.4% had PDA with an OR of 1.9 (95%CI 0.84 to 4.70). Similarly, a study reported that PDA prevalence in neonates with gestational age <28 weeks was 60%,[18] while another study discovered that 10/18 neonates with gestational age ≤31 weeks had PDA.[10] In contrast, Leonhardt *et al*. reported that the PDA prevalence in neonates with gestational age ≤32 weeks was 19%.[17] In addition, Dani *et al*. reported that 50% of neonates with 23 to 27 weeks gestation had PDA.[19] Pees *et al*. stated that the PDA prevalence was 72% in neonates less than 28 weeks gestation who underwent Doppler echocardiography at 24 to 72 hours of life (unpublished data).[15] Furthermore, Xiao-Yu *et al*. reported that PDA prevalence was negatively correlated to gestational age.[16]

The severity of asphyxia was positively correlated to the onset of PDA. We discovered that neonates with asphyxia tended to have PDA 1.6 (95%CI 0.81 to 3.21) times more than neonates without asphyxia. Furthermore, neonates with severe and mild-moderate asphyxia had a 6.7 (95%CI: 0.80 to 56.70) times and 1.3 (95%CI: 0.65 to 2.73) times higher risk for PDA, respectively. Similarly, Xiao-Yu *et al*. stated that a lower Apgar score was related to higher PDA onset.[16] Deselina *et al*. reported that 7/11 neonates with asphyxia had PDA,[10] while Masyur reported that 6/22 neonates with asphyxia had PDA.[20]

Of subjects whose mothers did not get antenatal corticosteroids, 60.3% had PDA with OR 1.3 (95%CI 0.73 to 2.50). A study reported that 8/23 preterm neonates at 28 to 31 weeks gestation whose mothers received antenatal steroids had PDA.[10] However, another study said that antenatal corticosteroids at 22 to 23 weeks of gestation was useless for preventing PDA.[21] In contrast, a meta-analysis found that antenatal corticosteroid trials prevented PDA in preterm neonates.[22]

A neonate with respiratory disease (RD) had 2.2 times risk for PDA (95%CI: 0.58 to 3.03), including bronchopneumonia (3.5 times) as the one with the highest probability of risk, the most common RD risk factor followed by hyaline membrane disease/HMD (2 times) and transient tachypneu of the newborn/TTN (1.3 times). Pneumonia increased the risk of PDA 3.5 times while HMD and TTN increased the risk of PDA 2- and 1.3 times, respectively.

A study reported that 6/10 HMD neonates had PDA,[10] while another study reported that 65% of HMD neonates <30 weeks gestation had PDA.[23] Kachel *et al* reported that in Birmingham, Alabama about $^1/_3$ of all neonates with HMD simultaneously had PDA, and the occurence of HMD increased the chance for PDA 7-fold. This increased risk for PDA with HMD in premature neonates was thought to be due to more frequent events of hypoxia and apneic spells, the need for artificial ventilation, shear stress of lung tissue, release of arachidonic acid and prostacyclin,as well as PGE release along with apneic spells.[24] In our study, logistic regression test revealed that RD and birth weight ≤2,000 grams were the only significant risk factors for PDA.

This study has several limitations including the uneven distribution of gestational age and birth weight among respondents. Also, 36.8% of subjects were born outside Mohammad Hoesin Hospital, had complications from other diseases and were without initial Apgar scores. As such, these issues might have led to bias and could not be analyzed. Furthermore, other risk factors such as race/ethnicity, sepsis, genetics, fluid therapy, blood transfusion, type or duration of ventilator, or exposure to drugs, and maternal illness during pregnancy, were not investigated.

In conclusion, birth weight and HMD are statistically significant PDA risk factors. Other risk factors such as gestational age, asphyxia, and antenatal steroid use are correlated to PDA, but not statistically significant. The lower the gestational age and birth weight, the higher the prevalence of PDA. Echocardiographic examination is a standard screening test for PDA. In remote areas where echocardiography is generally unavailable, preterm neonates with risk factors should be considered for PDA evaluation at a tertiary center.

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