SHORT COMMUNICATION

Outcomes of preterm neonates with patent ductus arteriosus: A retrospective review from a tertiary care hospital

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Abstract

The management of patent ductus arteriosus (PDA) in preterm neonates remains controversial. A retrospective review was conducted to determine the outcomes in preterm neonates with PDA. Data of neonates admitted to the Aga Khan University Hospital from January 2012 to December 2016 were retrieved from patient records. Of the 208 neonates included in the study, 143 (68.7%) received no treatment, while 65 (31.2%) underwent pharmacotherapy and/or surgical ligation for PDA closure. PDA closure was spontaneous in 109 (52.4%) neonates. The mean ±SD gestational age (GA) of neonates with spontaneous ductal closure was greater as compared to those who required some form of treatment [33±3.3 vs 29.7±3.1weeks, p=0.001]. Apnoea (OR:4.47; 95% CI:1.21-16.44), sepsis (OR:3.81; 95% CI:1.33-10.87), pulmonary haemorrhage (OR:4.88; 95% CI:1.24-19.19), and lower APGAR (OR:0.69; 95% CI:0.54-0.90) were associated with higher odds of mortality in our cohort. Our findings demonstrate that PDA resolves spontaneously in most preterm neonates and provide evidence that conservative treatment is not associated with mortality.

Keywords: Conservative treatment; ligation; mortality; patent ductus arteriosus; premature.

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Introduction

Patent ductus arteriosus (PDA) is one of the most common complications in preterm neonates.[1] Without closure, the persistent left-to-right shunt can increase the risk of severe morbidities such as intraventricular haemorrhage (IVH), bronchopulmonary dysplasia (BPD), and necrotising enterocolitis (NEC) in these neonates.[2] PDA can be treated by conservative management, pharmacotherapy (Ibuprofen, Indomethacin, and Acetaminophen), and surgical ligation. However, clinical practice remains inconsistent due to the uncertainty of the effectiveness and the complications caused by the current methods of PDA management.[3]

Studies have reported that most PDAs close spontaneously by the time the child is discharged from the hospital.[4] Moreover, recent evidence suggests that conservative management of PDA does not increase morbidity or mortality and may be more beneficial than active treatment.[5,6] This is primarily due to several adverse effects associated with pharmacotherapy and ligation.[7,8] The traditional approach of early and aggressive treatment has shifted towards watchful waiting with close follow-ups in several high-income countries.[5] However, scarce data about PDA management approaches and their outcomes from low- and middle-income countries prevent formulation of evidence-based protocols specific to low-resource settings. Therefore, we aimed to assess the short-term outcomes of interventional and non-interventional approaches to PDA management in preterm neonates (<37 weeks' gestation) and determine the predictors of mortality in this cohort.

Methods and Results

Data of all preterm neonates born from 24+0 to 36+6 weeks' gestation and admitted to the level 3 neonatal intensive care unit (NICU) of the Aga Khan University Hospital, Karachi from January 2012 to December 2016 were collected retrospectively. Data was retrieved from the online central laboratory system and patients' files. Outcomes included spontaneous ductal closure before discharge from hospital (average length of stay for preterm neonates is 15 days), frequency of NEC (modified Bell stage ≥II), IVH, BPD, retinopathy of prematurity (ROP), sepsis, pulmonary haemorrhage, and death before discharge. Neonates with severe congenital anomalies and heart defects requiring PGE1 infusion to keep the ductus patent were excluded from the study.

The initial diagnosis of PDA was based on clinical signs such as presence of a systolic murmur, wide pulse pressure, bounding peripheral pulses, tachycardia, hyperdynamic precordium, apnoea, and feeding difficulties as per the unit protocol. All patients with suspected PDA based on bed-side clinical findings subsequently underwent a routine confirmation by echocardiography. Although there is no universal definition of a haemodynamically significant PDA

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Table-1: Demographic and clinical characteristics of preterm neonates with PDA.

	Total (n = 208)	Died (n = 25)	Alive (n = 183)	P-value
Birth weight (g)				
VLBW (<1500)	101 (48.6)	20 (19.8)	81 (80.2)	0.001
Others (≥1500)	107 (51.4)	5 (4.7)	102 (95.3)	
Gestational age (weeks)				
<28	49 (23.6)	10 (20.4)	39 (79.6)	0.015
29-32	72 (34.6)	11 (15.3)	61 (84.7)	
>32	87 (41.8)	4 (4.6)	83 (95.4)	
Delivery				
Inborn	164 (78.8)	20 (12.2)	144 (87.8)	0.99
Sex				
Male	111 (53.4)	14 (12.6)	97 (87.4)	0.833
Gestational diabetes	54 (25.7)	4 (7.4)	50 (92.6)	0.331
Pregnancy induced hypertension	55 (26.4)	6 (10.9)	49 (89.1)	0.768
Antenatal steroids	116 (55.8)	15 (12.9)	101 (87.1)	0.675
Mode of delivery				
ELSCS	45 (21.6)	2 (4.4)	43 (95.6)	0.195
EMLSCS	130 (62.5)	19 (14.6)	111 (85.4)	
SVD	33 (15.9)	4 (12.1)	29 (87.9)	
Abnormal antenatal Doppler	41 (19.7)	7 (17.1)	34 (82.9)	0.420
APGAR score (minutes)				
1	6.66 (± 1.82)	5.23 (± 2.16)	6.85 (± 1.69)	<0.001
5	8.03 (± 1.56)	6.68 (± 2.26)	8.20 (± 1.34)	<0.001
Time on ventilator (days)	7.42 (± 8.75)	9.64 (± 8.66)	7.11 (± 8.75)	0.177
Surfactant therapy	111 (52.9)	21 (19.1)	89 (80.9)	0.001
Apnoea	23 (11.1)	6 (26.1)	17 (73.9)	0.040
HSPDA	17 (8.2)	1 (5.9)	16 (94.1)	0.418
Morbidities				
Sepsis	53 (25.2)	17 (32.1)	36 (67.9)	<0.001
IVH	31 (14.8)	6 (19.4)	25 (80.6)	0.224
BPD	12 (5.7)	1 (8.3)	11 (91.7)	0.999
NEC	14 (6.7)	4 (28.6)	10 (71.4)	0.071
ROP	15 (7.1)	0 (0)	15 (100)	0.225
Pulmonary haemorrhage	14 (6.7)	6 (42.9)	8 (57.1)	0.002
Postnatal steroids	5 (2.4)	1 (20)	4 (80)	0.473
Feeding issues	22 (10.6)	6 (27.3)	16 (72.7)	0.020
Left atrium to aortic root ratio				
≥ 1.4	73 (35.1)	5 (6.8)	68 (93.1)	0.118
<1.4	135 (64.9)	20 (14.8)	115 (85.2)	
PDA size (mm)				
≤1.5	81 (38.9)	5 (6.2)	76 (93.8)	0.127
>1.5	127 (61.0)	20 (15.7)	107 (84.2)	
Management approach				
No treatment	143 (68.7)	19 (13.3)	124 (86.7)	0.694
Treatment	65 (31.2)	6 (9.2)	59 (90.8)	

*Results presented as n (%) and mean ± SD unless stated otherwise.

[BPH: bronchopulmonary dysplasia; EMLSCS: elective lower segment caesarean section; ELSCS: emergency lower segment caesarean section; HSPDA: haemodynamically significant patent ductus arteriosus; IVH: intraventricular haemorrhage; NEC: necrotising enterocolitis; ROP: retinopathy of prematurity; SVD: spontaneous vaginal delivery; VLBW: very low birth weight].

(HSPDA) in literature,[9] for this study, we defined HSPDA as a defect >1.5mm, with a wide pulse pressure, grade II-III systolic murmur, and a left atrium to aortic root ratio (LA : Ao) of 1:4 or more.

Management of PDA was classified into two categories: "no treatment" and "treatment". The no treatment approach aimed to stabilise the neonate through ventilation optimisation, fluid restriction, and loop diuretics. The treatment approach aimed to achieve ductal closure through pharmacotherapy and/or surgical ligation. The pharmacotherapy approach included administration of intravenous Indomethacin, oral

Table-2: Factors associated with mortality in preterm neonates with PDA.

	Univariate analysis			Multivariable analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Birth weight (g)						
VLBW (<1500)	5.04	1.81, 14	0.002	3.16	0.87, 11.42	0.079
Others (≥1500)	Ref.			Ref.		
Gestational age (weeks)						
<28	5.32	1.57, 18.03	0.007			
29-32	3.74	1.14, 12.31	0.030			
>32	Ref.					
Apgar score (minutes)						
1*	0.66	0.53, 0.83	<0.001	0.69	0.54, 0.90	0.007
5	0.63	0.49, 0.8	<0.001			
Time on ventilator (days)	1.03	0.99, 1.07	0.181			
Surfactant	5.54	1.83, 16.79	0.002			
Apnoea	3.08	1.08, 8.77	0.035	4.47	1.21, 16.44	0.024
Complications						
Sepsis	8.68	3.47, 21.69	<0.001	3.81	1.33, 10.87	0.012
IVH	1.99	0.73, 5.48	0.179			
NEC	3.3	0.95, 11.44	0.060			
Pulmonary haemorrhage	6.91	2.17, 22.03	0.001	4.88	1.24, 19.19	0.023
Left atrium to aortic root ratio						
≥ 1.4	0.423	0.15, 1.17	0.100			
<1.4	Ref.					

[IVH: intraventricular haemorrhage, NEC: necrotising enterocolitis, VLBW: very low birth weight].

Ibuprofen, or intravenous Acetaminophen. All neonates were initially managed according to the "no treatment" approach. Neonates who failed to improve and remained symptomatic (were ventilator-dependent, apnoeic, unable to tolerate reduced oxygen support, or had feeding intolerance) subsequently received pharmacologic management. Surgical ligation was considered for neonates who were unresponsive to pharmacologic therapy and deteriorated (exhibited pulmonary oedema, extubation failure, feeding difficulties, failure to thrive, aspirations, or needed persistent oxygen therapy). The decision to initiate pharmacologic or surgical management was subject to the clinical practices of the treating neonatologist and paediatric cardiologist.

Approximately, 620 preterm neonates are admitted to the Aga Khan University Hospital annually. As the prevalence of PDA in preterm neonates is 57.2%,[10] and this study reviewed data over five years, the population size was taken as 1,770. Taking the frequency of spontaneous PDA closure by the seventh day of life as 78%,[4] 95% confidence level, and 6% precision, the sample size was estimated to be 167 neonates.

Data were analysed using SPSS v15.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were reported as mean±SD and median ± IQR for continuous variables and frequencies with percentages for categorical variables. Chi-square test of independence was performed to evaluate the association of morbidity with the treatment approach. Unpaired t-test was used to determine the association of gestational age (GA) with spontaneous closure of PDA. Multivariable logistic regression was carried out to identify the factors associated with mortality. Univariate analyses were first conducted to identify variables significant at $p<0.2$. Variables with $p<0.10$ were retained in the multivariable model. Model fitness was assessed via Hosmer-Lemeshow test. The results were reported as odds ratios and 95% CI.

This study was approved by the ethical review committee of the Aga Khan University (ERC:4971-Ped-ERC-17).

During the study period, 208 preterm neonates were diagnosed with PDA. The mean GA and birth weight of the cohort was 31.4±3.61 weeks and 1.59±0.67 kg, respectively. The median length of stay was 11(IQR 15.75) days. Neonatal characteristics are presented in Table-1.

The most observed clinical signs were murmur in 133 (63.9%) neonates and wide pulse pressure in 89 (42.8%), followed by bounding pulses in 25 (12%), tachycardia 24 (11.5%), apnoea in 23 (11.1%), feeding intolerance in 22 (10.6%), and hyperdynamic precordium in 20 (9.6%). Cardiomegaly on chest x-ray was seen in 8 (3.8%) neonates.

Echocardiographic data showed that 127 (61%) neonates had a defect larger than 1.5mm, 193 (92.8%) had a left-to-right shunt, 54 (26%) had left ventricular enlargement, and 73 (35.1%) had LA : Ao $\geq$1:4. According to the study criteria, only 17 (8.2%) neonates had an HSPDA.

A majority, i.e. 143 (68.7%) neonates received no treatment for PDA closure. This approach failed in 65 (31.2%) neonates who subsequently received pharmacologic treatment, which was successful in closing the PDA in 56 (26.9%) neonates. Ibuprofen was the most administered drug (n=47, 72.3%), followed by Acetaminophen in 11 (16.9%), and Indomethacin in 7 (10.8%). Nine (4.3%) neonates underwent surgical ligation which was performed at an average age of three weeks.

PDA spontaneously closed in 109 (52.4%) neonates by the time of discharge or death. The mean GA of neonates who underwent spontaneous closure was 33±3.3 weeks compared to 29.7 (±3.1) weeks in neonates without spontaneous closure (p<0.001).

The morbidities observed in the cohort included sepsis, IVH, ROP, NEC, BPD, and pulmonary haemorrhage. Sepsis was observed in 30 (21%) neonates in the no treatment group, compared to 23 (35.4%) in the treatment group (p=0.027). IVH was seen in 15 (10.5%) neonates who did not receive treatment and in 12 (24.6%) who did (p=0.008). BPD was diagnosed in four (2.8%) neonates who were not treated and in 8(12.3%) who were treated (p=0.010). None of the other morbidities were associated with the treatment approach.

In all, 25 (12%) neonates from this cohort died. Neonates with a lower APGAR score at 1 minute (OR: 0.69; 95%CI: 0.54-0.90), apnoea (OR: 4.47; 95%CI: 1.21-16.44), sepsis (OR: 3.81; 95%CI: 1.33-10.87), and pulmonary haemorrhage (OR: 4.88; 95% CI: 1.24, 19.19) had higher odds of mortality (Table-2).

Conclusion

PDA closed spontaneously in over half of the cohort before discharge. Gestational age was significantly associated with spontaneous closure. Although all neonates were initially managed with the no-treatment approach, approximately one-third of the cohort eventually received some form of treatment for ductal closure. A statistically significant difference in neonatal morbidities (sepsis, IVH, and BPD) was observed between the treatment and no-treatment groups. Mortality was not associated with the treatment approach. Our findings corroborate recent studies that favour conservative management for PDA and have shown a lack of association of treatment approach with mortality. Prospective studies are recommended with evidence-based local unit PDA management guidelines to evaluate various modalities of treatment and outcomes.

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