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Prevalence, outcomes and management of haemodynamically significant patent ductus arteriosus in very-low-birthweight neonates: A retrospective cohort study in a resource-limited setting

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Background. Haemodynamically significant patent ductus arteriosus (hsPDA) remains a significant challenge in neonatal care, particularly in very-low-birthweight (VLBW) infants. Data on its prevalence, outcomes, and management in resource-limited settings, such as the Free State Province of South Africa, remain limited.

Objective. To determine the prevalence, outcome and management approach of hsPDA in VLBW infants at two tertiary hospitals.

Methods. This retrospective cohort study reviewed records from 2020 to 2022 at Universitas Academic Hospital and Pelonomi Tertiary Hospital. The study included all VLBW (≤ 1 500 g) neonates diagnosed with hsPDA by echocardiogram. Data collected included management (no treatment, conservative, medical or surgical) and short-term outcomes (death, length of stay, and complications).

Results. Of 1 523 VLBW neonates, 161 (10.6%) received an hsPDA diagnosis. The median interquartile range (IQR) gestational age was 29 (27 - 30) weeks (range 23 - 34 weeks). Conservative management was most common (50.3%), followed by medical management (32.9%) and no treatment (29.2%). Definite necrotising enterocolitis (14.4%) and moderate-to-severe bronchopulmonary dysplasia (13.0%) were the most observed complications. Overall mortality was 30.4% (n=49). The median (IQR) length of stay was 38 days (14 - 60 days). The 'no treatment' group showed a statistically significant shorter length of stay (p<0.001).

Conclusion. HsPDA prevalence at our centres was 10.6%. The high mortality rate, particularly in the extremely low-birthweight (ELBW) subgroup, requires attention. Conservative management was the preferred approach. Treatment modalities may not significantly reduce the length of stay in VLBW infants with hsPDA.

Keywords: haemodynamically significant patent ductus arteriosus; very low birthweight; neonatal morbidity and mortality; conservative management; resource-limited setting; Free State.

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For a foetus, patent ductus arteriosus (PDA) is essential, but when it persists in a newborn, it might result in haemodynamic compromise. The ductus arteriosus directs oxygenated blood away from the lungs *in utero* towards the systemic circulation in the foetus.[1] This form of circulation between the pulmonary and systemic circulation operates in parallel. After birth, there is a need for the pulmonary and systemic circulation to function in series by the closure of three ducts, one of which is the ductus arteriosus. However, persistent patency of the ductus arteriosus may cause haemodynamic compromise secondary to pulmonary over-circulation and systemic under-perfusion.[2]

While the ductus arteriosus loses its patency within 72 hours of life, half to two-thirds of extremely low-birthweight (ELBW) (<1 000 g) neonates have been shown to develop persistent patency of their PDA.[3] ELBW is defined as neonates born weighing ≤1 000 g at ≤25 weeks' gestational age.[3] The incidence of PDA is higher in preterm infants born at 24 weeks compared with those with gestational age at 25 weeks or more.[4] In approximately 13% of infants born at 24 weeks' gestation, the ductus closes by day 7 post-delivery.[5] Poor outcomes (haemodynamic and respiratory complications) of hsPDA depend on the degree of left-to-right shunt of the PDA. This 'ductal steal' phenomenon has been described in PDA as characterised by the shunting of blood to the pulmonary artery from the aorta.[4] This results in the excessive blood flow to the lungs, resulting in pulmonary congestion, pulmonary oedema and, consequently, respiratory failure. Reduced blood flow in the systemic circulation results in compromised perfusion of vital organs, such as the brain, kidney and bowel. Eventual complications include bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), pulmonary haemorrhage and acute kidney injury (AKI).[6]

A consensus on the definition and management of haemodynamically significant PDA (hsPDA) remains elusive.[7,8] While the occurrence of hsPDA in very-low-birthweight (VLBW; ≤1 500 g) neonates has been reported,[9] there is a paucity of data regarding the prevalence of hsPDA in low- and middle-income countries (LMICs). Diagnosing hsPDA is based on physical examination and clinical findings of the neonate. However, the gold standard for diagnosis is echocardiography.[3,10] Indomethacin, ibuprofen, and paracetamol (alternative) have been used in the medical closure of hsPDA, while surgical ligation or device closure has been used for interventional closure of hsPDA.

For this study, the authors used echocardiographic criteria. These include PDA diameter >1.5 mm, left atrium-aortic root ratio (LA/

AO) >1.5, peak instantaneous gradient <8, left atrial dilation and left to right shunting.[7,11] Clinical criteria were noted, but they were not utilised owing to the presence of numerous confounders. Newer and more objective diagnostic methods, such as near-infrared spectroscopy, have been prescribed but are not currently available at our centre.[12]

Owing to the aforementioned complications, timely management within the first few days is critical. The question of who, when, what to treat with, and how to treat remains a huge dilemma among healthcare providers. Some believe that neonates who are at-risk can receive pre-symptomatic treatment upon the confirmation of a persistent duct between day 1 and day 5 of neonatal life. This has been shown to reduce PDA symptoms and the duration of supplemental oxygen requirement significantly.[13] Others hold that only symptomatic PDA should be treated.[3]

The present study aims to determine the prevalence of hsPDA in preterm infants and report on their outcomes, management approach, and proportion of follow-up echocardiogram of hsPDA conducted in very-low-birthweight infants.

Methods

Study design, setting and study population

This was a retrospective cohort study of hsPDA of neonates weighing less than 1 500 g admitted to Pelonomi Tertiary Hospital and Universitas Academic Hospital. These are two urban referral centres in Bloemfontein, central South Africa (SA). According to departmental statistics, the delivery rate at Pelonomi Tertiary Hospital and Universitas Academic Hospital was 98% and 68% respectively, in the year 2023.

The study was done between January 2020 and December 2022. Both hospitals admit ~500 VLBW neonates every year. The departmental protocol does not allow ventilation of neonates less than 900 g. Limited care is provided for these neonates. Echocardiography services are offered to our department by trained technicians in the Department of Cardiology twice a week. As per protocol, infants weighing <1 500 g have a screening echocardiogram, mostly done within the first week of life. Management of patients with hsPDA was determined by the treating physicians, typically the responsible registrar and neonatal consultant, based on the clinical condition and echocardiogram results.

Inclusion criteria

Newborns with very-low birthweight and PDA that were deemed haemodynamically significant on echocardiography were included in the present study.

Exclusion criteria

Neonates with significant birth defects/complex heart defects coexisting with PDA (except atrial septal defect), preterm neonates whose hospital files could not be accessed, as well as preterm neonates who demised or were discharged within the first 3 days of life, were excluded.

Diagnostic criteria

The diagnosis of hsPDA was based on echocardiographic criteria. The following parameters, as reported in the literature, were used to determine haemodynamic significance: ductal diameter >1.5 mm, left atrial/aortic (LA/AO) ratio >1.5, presence of left atrial dilation, peak instantaneous gradient in the PDA < 8 and left-to-right shunting PDA. Clinical criteria were collected but excluded from the primary diagnosis.

Data collection

Eligible neonates were identified using the neonatal statistics database, and echocardiography reports were retrieved from the Department of Cardiology. The Meditech summary and patient paper files were used to complete the REDCap data capture form for the neonates who met the inclusion criteria.

From the records, we extracted clinical data such as the gestational age, weight at birth, respiratory support, treatment modalities, and echocardiographic parameters. Furthermore, short-term outcomes included death, discharge, and associated conditions such as moderate to severe BPD (defined as the need for supplemental oxygen at 36 weeks postmenstrual age), pulmonary haemorrhage, spontaneous intestinal perforation, respiratory distress syndrome (RDS), NEC (Modified Bell staging 2 and 3), AKI (KDIGO stage 2 and 3), and IVH Papile grade 3 and 4. Moderate-to-severe BPD was classified according to NICHD 2001,[14] which states that grade 2 (moderate) BPD is <30% oxygen requirement, and grade 3 (severe) BPD is ≥30% oxygen requirement or requires positive pressure. Subgroup analyses were performed within the cohort.

Statistical analysis

Data analysis was done by the Department of Biostatistics, Faculty of Health Sciences at the University of the Free State. Data were exported to Excel (Microsoft Corp., USA) and statistically analysed using the statistical software program SPSS version 23 (IBM Corp., USA). The Shapiro-Wilk test was used to check for normality of data distribution. Non-normally distributed data were reported as median values with interquartile ranges (IQRs). Frequencies and percentages were utilised to describe categorical variables. The denominator for calculating prevalence was the total number of VLBW neonates within the study period. Treatment was sub-categorised into 'no treatment', 'conservative', 'medical' and 'surgical'. The outcome per treatment group was analysed. Only valid data were reported, i.e. missing variables were excluded from the analysis. To test for associations, the Wilcoxon test was used for numerical data, while Fisher's exact test and Pearson chi-squared tests were used for categorical data.

Ethical considerations

The study was approved by the Human Research Ethics Committee of the University of the Free State (ref. no. UFS-HSD2022/1959/2803) in Bloemfontein, SA. Owing to the retrospective nature of the present study, consent was waived. All data forms were completed anonymously, as the forms were coded and the identity of the codes was only available to the principal researcher.

Results

Baseline characteristics

A total of 1 523 patients were admitted to the neonatal intensive care units (NICUs) with a birthweight less than 1 500 g during the study period. Of these, 421 patients had a PDA diagnosed by echocardiography, and 195 had hsPDA. However, 34 were excluded as 7 patients had significant birth defects/complex heart defects coexisting with PDA, 19 case records were incomplete and 8 preterm neonates died within the first 72 hours. The study therefore included 161 patients.

The period prevalence of hsPDA in neonates weighing less than 1 500 g at both tertiary hospitals in Bloemfontein, SA, was 10.6%, which equates to 106 per 1 000 live births.

Just over half (n=83; 51.6%) of the neonates were females. The median (IQR) gestational age was 29 (27 - 30) weeks (range 24 - 34)

and the median (IQR) birthweight was 1 060 (950 - 1 250) g (range 530 - 1 490). The median (IQR) age of patients at the time of the first echocardiography was 5 (3 - 14) days (range 6 - 53).

Echocardiography findings

The frequency of echocardiography parameters used to determine hsPDA included: (*i*) ductal diameter >1.5 mm (*n*=152, 96.8%), (*ii*) left atrial dilation (*n*=72, 45.6%), (*iii*) left atrial-to-aortic (LA/AO) > 1.5 (*n*=36, 24.0%), and (*iv*) peak instantaneous gradient in the PDA < 8 (*n*=15, 9.4%). All the patients had left-to-right shunting through the PDA. The clinical characteristics are summarised in Table 1.

Almost all the patients required respiratory support (*n*=160; 99.4%), with 89 (55.6%) patients needing nasal continuous positive airway pressure (NCPAP), 65 (40.6%) required invasive intermittent positive-pressure ventilation (IPPV), and 6 (3.8%) needing nasal prongs. Ten of the patients who were invasively ventilated required high frequency oscillation, almost two-thirds of the patients received surfactant (*n*=107; 66.5%) and antenatal steroids (*n*=102; 63.4%).

Treatment patterns

Forty-seven (29.2%) patients received no treatment, 81 (50.3%) received conservative treatment, 53 (32.9%) received medical management and 2 (1.3%) received surgical ligation. Some patients received more than one treatment modality. The most common treatment modality was conservative management, with 33.5% (*n*=54) of patients receiving fluid restriction and 16.8% (*n*=27) receiving diuretics. We also noted that more than half (*n*=87; 54.0%) of the patients received blood transfusion, but the timing of transfusion and indication are not known.

Of the 53 patients who were medically managed, the majority received paracetamol (*n*=47; 88.7%) and 6 (11.3%) received ibuprofen (Table 2). None of the patients received indomethacin. The choice of medication was determined by clinician preference while individualising and considering contraindications. Of the two patients with percutaneous closure of the PDA, one had the PDA closed with a device, while the other was surgically ligated. The following devices are used in our institution: Amplatzer Duct Occluder 1 (ADO1) (Amplatzer, USA); Occlutech duct occluder (Occlutech, Sweden); and Amplatzer Piccolo (Amplatzer, USA).

The median (IQR) length of hospitalisation was 38 (14 - 60) days. The group of patients who had no treatment had a statistically significant shorter length of stay ($p<0.001$).

Outcome

We observed that NEC (Modified Bell staging 2 and 3) was the most common complication in 23 (14.5%) patients, while AKI (KDIGO Stage 2 and 3) was the least commonly encountered complication – it occurred in 2 (1.2%) patients (Table 3). NEC was reported in 6.8% of patients who did not receive blood transfusion compared with 20.9% who received blood transfusion. A statistically significant association was observed between blood transfusion and NEC ($p=0.011$). BPD was observed in 21 (13.0%) patients, and 13 (61.9%) of these patients received medical treatment to close the PDA. Pulmonary haemorrhage was less frequent in the fluid-restricted group compared with the non-fluid-restricted group (9.3% vs 11.2%). The frequency of IVH was found to be lower in the medically managed group (7.7%) compared with non-medically managed patients (11.9%), though this was not statistically significant ($p=0.4$). No patient had spontaneous intestinal perforation. Sepsis occurred in 96 (58.6%) of our patients. However, there was no significant relationship between sepsis and PDA closure rate ($p>0.9$).

Two-thirds (*n*=108; 67.0%) of the study population had a follow-up echocardiogram done, of which 81 (75.0%) were performed before discharge, while 27 (25.0%) were done after discharge. Of the 53 patients who did not have a follow-up echocardiogram, 49 died before the echocardiogram could be repeated, and 4 were lost to follow-up. The closure rate was 59.3%, as 64 of the 108 patients with follow-up echocardiograms had a closed PDA.

Table 1. Clinical characteristics of patients in the study group (*N*=161)

Characteristic	*n* (%)*	Range
Birthweight (g), median (IQR)	1 060 (950 - 1 250)	530 - 1 500
Gestational age (weeks), median (IQR)	29 (27 - 30)	24 - 34
Length of stay (days), median (IQR)	38 (14 - 60)	0 - 752
Female sex	83 (51.6)	
Antenatal steroids	102 (63.4)	
Surfactant administered	107 (66.5)	

IQR = interquartile range.
*Unless otherwise specified.

Table 2. Management modality and LOS of VLBW neonates with hsPDA (n=161)

Characteristic	Specific modality	*n* (%)	LOS (days), median (IQR)
No treatment	Spontaneous closure/early demise	47 (29.2)	26 (8 - 40)
Conservative management	Fluid restriction	54 (33.5)	57 (24 - 83)
	Diuretics	27 (16.8)	41 (26 - 74)
	Fluid restriction and diuretics	12 (7.5)	66 (25 - 89)
Medical management	Ibuprofen	6 (3.7)	66 (37 - 76)
	Paracetamol	47 (29.2)	52 (26 - 79)
Surgical management	Surgical intervention	2 (1.3)	81 (73 - 89)

LOS = length of stay; VLBW = very low birthweight; hsPDA = haemodynamically significant patent ductus arteriosus; IQR = interquartile range.

Table 3. Outcomes and complications of patients with hsPDA (*n*=161), n (%)

	Outcomes			Complications			
Treatment group	Discharge, *n*=112	Death, *n*=49	BPD, *n*=21	PH, *n*=17	NEC, *n*=23	AKI, *n*=2	IVH, *n*=17
No treatment, *n*=47 (29.2)	31 (27.7)	16 (34.0)	0	3 (17.6)	5 (21.7)	0	5 (29.4)
Conservative, n=69 (42.9)	48 (42.9)	21 (42.9)	14 (66.7)	7 (41.2)	11 (47.8)†	2 (100)	7 (41.2)
Medical,* *n*=52 (32.3)	39 (34.8)	13 (26.5)	13 (61.9)	4 (23.5)	7 (30.4)	1 (50.0)	4 (23.5)
Surgical, *n*=2 (1.3)	2 (1.8)	0	1 (4.8)	0	1 (4.3)	0	0
Conservative and medical, *n*=65 (40.4)	44 (39.3)	21 (42.9)	12 (57.1)	7 (41.2)	11 (47.8)	2 (100)	7 (41.2)

hsPDA = haemodynamically significant patent ductus arteriosus; BPD = bronchopulmonary dysplasia; PH = pulmonary haemorrhage; NEC = necrotising enterocolitis (Modified Bell staging 2 and 3); AKI = acute kidney injury; IVH = intraventricular haemorrhage.

*The outcomes and complications were calculated for 52 patients, as one patient had both treatments.

†Result missing for *n*=1 patient.

A total of 112 (69.6%) neonates were discharged, and 49 (30.4%) neonates died. Almost half (*n*=23; 44.2%) of the ELBW patients died compared with 26 (23.9%) VLBW patients. The following echocardiographic parameters were most frequently noted in the patients who died: ductal diameter >1.5 mm (*n*=46; 93.9%); peak instantaneous gradient in the PDA ≥8 (*n*=31; 63.3%); and left atrial dilatation (*n*=22; 44.9%). It was also noted that more patients who died had an LA/AO ratio ≤1.5 (*n*=32; 65.3%) than those with a ratio ≥1.5, which is associated with hsPDA. It should be noted that not all of the patients who died had all the echocardiographic parameters mentioned.

Discussion

The period prevalence of hsPDA in neonates weighing less than 1 500 g was 10.6% at two tertiary hospitals in Bloemfontein, central SA, which was similar to another SA study[9] using echocardiographic parameters that found the prevalence to be 11.9%. The median gestational age was 29 weeks in our cohort. Previous studies have recorded variable prevalences of hsPDA rates, e.g. 33.0% in infants <29 weeks in an American study,[15] 39% in a cohort of infants ≤28 weeks in Australia[16] and 52% in neonates with an average gestational age of 29 weeks in Egypt.[17] A study[18] done in the neonatal ICU of Cairo University (Egypt) reported a prevalence of 37.9%, while the prevalence was as high as 63% in neonates <28 weeks (and weighing <1 000 g) at Kanuni Sultan Suleyman Training and Research Hospital's NICU in Turkey.[19] The variation in prevalence might be because of the different methods of assessing the haemodynamic significance of a patent duct. Soliman *et al.*[18] used clinical, radiological and echocardiographic parameters to assess haemodynamic significance and reported the prevalence of hsPDA to be 37.9%.

We noted that just over half of the patients with hsPDA were female. A recent meta-analysis reported an equal distribution between male and female neonates regarding the incidence of PDA and response to pharmacological treatment.[20]

During antenatal care, 64.3% of the mothers received antenatal steroids. Approximately 99.4% of the neonates received oxygen therapy, of which 66.5% received surfactant for RDS. This highlights the need for improved antenatal care to reduce the burden of morbidity in premature infants. The median age for the first echocardiogram was at 5 days of life, which can be considered late if one wants to consider early echocardiography targeted treatment. However, the evidence that early targeted treatment reduces morbidity and mortality remains unclear.[21]

Conservative management was the most common method used to treat hsPDA at our study centre, which highlights recent evidence where there has been an increasing trend towards conservative management among hsPDA neonates.[22-28] However, the length of stay was statistically significantly reduced in the group that received no treatment compared with other treatment modalities. This was interesting given the fact that these patients did not undergo fluid restriction, and it is known that higher fluid administration in the first two days of life is associated with a prolonged duration of hsPDA and, thus, length of stay.[29] We also noted that all patients who received no treatment for their PDA also did not have BPD. Perhaps the reason the PDA was not treated was due to the absence of respiratory and other complications, which could, in turn, lead to a shortened length of stay. Blood transfusion occurred in over 50% of our cohort. Blood transfusion has a pathophysiological basis as a supportive management measure in hsPDA, as the viscosity of blood may influence the left-to-right shunting of blood.[2]

The mortality rate in our study was 30.4%, which was higher than the mortality rate of 22% found in the study done at another SA centre.[9] This might be attributed to different guidelines regarding limitation of care in ELBW patients. In our study, we noted that a greater proportion of ELBW infants died compared with VLBW patients (44.2% v. 23.9%), most likely owing to limitation of care in patients weighing less than 900 g. A multicentre cohort study in a high-income country showed that medical (oral ibuprofen and paracetamol) and surgical treatment reduced mortality in ELBW neonates.[30]

We found the most common associated morbidities to be NEC and BPD. Neonates with a PDA are more likely to develop NEC if they receive a blood transfusion.[31-34] In our study we found NEC to be three times more likely to develop in patients who received blood transfusion compared with those who did not receive blood transfusion and blood transfusion was significantly associated with hsPDA. The majority (61.9%) of our patients with BPD had received medical treatment for closure of the PDA, suggesting that medical treatment does not decrease the development of BPD (p=0.002). This is in keeping with the findings of the PDA TOLERATE TRIAL,[35] where they found that there was no decrease in BPD

when comparing early medical treatment with a control group. Similarly, the baby OSCAR Trial that focused on ELBW found that early medical treatment did not result in reduced BPD at 36 weeks postmenstrual age. [21]

Lee *et al*.[36] found a higher number of infants in the PDA group compared with the non-PDA group with early sepsis. Visconti *et al*.[37] concluded that late sepsis significantly coexisted with hsPDA, which was consistent with our study, where 58.6% of preterm VLBW babies had confirmed early or late sepsis. This was in agreement with normal physiology, which explains a high frequency of infection in preterm infants that can lead to PDA reopening as circulating prostaglandin levels can reach pharmacological levels.[38]

In our study, the hsPDA closure rate was 59.3%, which was lower than that in high-income countries. The closure rate was independent of the treatment modality. Only 63.4% of our study population had received antenatal steroids, which have not been shown to accelerate ductal closure after the start of PDA treatment.[39] A study in Denmark reported a spontaneous closure rate of 69%.[39] A level 4 Canadian hospital reported a spontaneous closure rate in 91% of their cohort, with a mean gestational age of 26 weeks and follow-up was up to 36 weeks post menstrual age.[40] In the Canadian study, the PDA closure rate before discharge was 76% in infants born before 26 weeks' gestation and 66% in infants ≥26 weeks.[40] In summary, hsPDA closure rates vary with location and management strategy.

Of the two patients who had surgical intervention of their PDA, one had a device closure and the other had surgical ligation. The patient who had surgical ligation was initially planned for device closure, but the procedure was aborted owing to a pulmonary hypertensive crisis during cardiac catheterisation, eventually undergoing ligation at 5 months of chronological age. This patient had complications of left-to-right shunting of the PDA, which included recurrent respiratory tract infection, cardiac failure, failure to thrive and pulmonary hypertension. The other patient had a device closure with Amplatzer device closure. This procedure was done via cardiac catheterisation at one year (chronological age).

Strengths and limitations

The strength of this study lies in the use of more than one echocardiographic criterion to define hsPDA, indicating an objective and reliable cohort. Study limitations included the retrospective nature of the study with no comparative group. The study was based on echocardiograms done at different times during the first week of life. As a result, the duration of hsPDA was not considered. Even though clinical parameters were collected, it was difficult to attribute the clinical signs to hsPDA alone. Lastly, only 108 (67.0%) patients had a follow-up echocardiogram.

Conclusion and recommendations

The prevalence of hsPDA at two tertiary hospitals in central SA was 10.6%. NEC (Modified Bell staging 2 and 3) and BPD were the most commonly associated complications. Conservative management was the most common treatment modality at the study centres. More than half of the study population had follow-up echocardiograms done, with a low closure rate when compared with high-income countries.

Further research is needed in resource-limited settings where access to timely echocardiography is difficult and antenatal care is still a challenge. The approach to managing a VLBW neonate with hsPDA should be individualised. Clinical, diagnostic and echocardiographic criteria should be considered. Standardising conservative management should be considered for hsPDA as treatment may not influence clinically relevant outcomes such as length of stay. The unit should consider strategies to decrease the rate of blood transfusion in patients with hsPDA as over half of our patients who developed NEC received blood transfusion. The timing of blood transfusion in relation to PDA closure should be captured as part of unit statistics.

Future studies should compare findings with the non-hsPDA group. In conclusion, the management of hsPDA in resource-limited settings remains a challenge owing to many factors. If resources permit and serial echocardiography can be done, the relationship between the duration of hsPDA, its impact on outcome and complications should be studied.

Data availability statement. None.

Declaration. None.

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