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Patency of the Ductus Arteriosus in Newborns: Experience in a Special Care Baby Unit

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Summary

Omokhodion SI, Baiyeroju-Agbeja AM, Adegboye VO, Adeyemo A, Lagunju IA. Patency of the Ductus Arteriosus in Newborns: Experience in a Special Care Baby Unit. *Nigerian Journal of Paediatrics* **2001; 29:61.** A prospective cohort study of infants admitted into the Special Care Baby Unit, University College Hospital, Ibadan, has revealed a 24.5 per cent prevalence of patency of the ductus arteriosus (PDA) among 97 infants, who were admitted over a six-month period. The major factor predisposing to PDA was prematurity ($p=0.014$). A higher incidence of PDA (35 per cent) was found among the preterm infants, and of these preterm infants, the very low birth weight (VLBW) infants were found to be more highly susceptible to PDA ($p = 0.028$). The mean birth weight of the preterm infants who developed PDA in the study was 1447g, while that of those preterm infants without PDA was 1835g. There was no relationship between the sex of the infants and the development of PDA. A strong association was however, found between respiratory distress and PDA ($p<0.001$). Nine of the hospital mortalities recorded occurred in the preterm infants and more than half of them (55.5 per cent) had PDA. Thus, prematurity is a risk factor for PDA and the presence of a PDA appears to increase the risk for mortality for such infants. Evidence for PDA should be sought in all premature infants and prompt and aggressive management of those infants who show signs of decompensation from PDA is recommended to reduce mortality from this disease.

Introduction

THE ductus arteriosus originates from the distal portion of one of the paired sixth aortic arch present in the normal foetus,[1] and usually connects the junction of the main and left pulmonary arteries to the descending aorta. It is a normal and an essential component of the foetal circulation. Closure of the ductus arteriosus is one of the cardiovascular changes that occur in the transition from foetal to newborn circulation in the process of adapting to extrauterine life. This usually takes place within 48 hours of birth in most healthy term infants and within 72 hours in most healthy preterm infants,[2] and involves many complex interactive factors.[3-7] One of the prime factors is the establishment of alveolar ventilation. This results in a marked increase in oxygen tension, which exerts a direct constrictory effect on the duct while blunting its sensitivity to the dilatory effects of circulating prostaglandins E series.[6] In addition, a net decrease in prostaglandin E series resulting from elimination of placental and pulmonary sources helps bring about functional closure. A cessation of intraluminal flow leads to ischaemic damage to the duct structure which over a period of four to eight weeks, leads to anatomic closure.[6,7]

A number of factors have been described which predispose to persistent patency of the ductus arteriosus in the newborn.[6-8] These include hypoxaemia and prematurity. In the very immature newborns, hypervolaemia, phototherapy, administration of frusemide, surfactant therapy and sepsis are particularly important.[6-8] Genetic and environmental factors particularly maternal infection with rubella in the first trimester

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of pregnancy are also known to predispose to patency of the ductus arteriosus (PDA).[9-13] PDA as an isolated lesion is estimated to occur in 1 in 2500 to 1 in 5000 live births.[8] As an isolated lesion, it constitutes about 9-12 per cent of all presenting congenital heart lesions.[8] A previous report from this locality was provided over 30 years ago[14] and was not in newborns only. There is therefore, a need for a current and systematic description of the incidence and the factors predisposing to persistent ductus arteriosus in newborns in this environment. The present communication describes our experience of PDA in a Special Care Baby Unit (SCBU).

Subjects and Methods

This prospective study was carried out over a six-month period from January to June 1995. During this period, there were 346 live births in the hospital; of these, 106 (30.6 per cent) were admitted into the SCBU. Seventeen other babies were admitted from outside centres, resulting in a total of 123 admissions into the SCBU during this period. All consecutive admissions to the SCBU were evaluated clinically for the presence of PDA at the age of three days, five days and at one week. Only in infants that had the features as described below, persisting for up to a week, was the diagnosis of PDA made. Other information recorded included antenatal, intrapartum and immediate post-partum antecedents such as risk factors for sepsis, perinatal asphyxia as determined by the one minute Apgar score, presence of respiratory distress, prolonged recurrent apnoea, and outcome within the one-week observation period for each baby. Demographic data including birth weight, gestational age (which was obtained by Ballard's score when the last menstrual period date was in doubt), and sex were also documented on proformas specially prepared for the study.

Diagnosis of PDA

For the purpose of this study, the diagnosis of PDA was made if a systolic murmur, of at least grade 2/6 intensity was heard on auscultation with the diaphragm of a standard neonatal sized stethoscope in the first and second left intercostal spaces at the left sternal border which may radiate down the left sternal border and out over both lung fields, with the simultaneous presence of bounding femoral artery, brachial artery, radial artery and dorsalis pedis artery pulses.[7,8] The presence of a hyperactive precordium[7] was an adjunct to diagnosis when found, as was the finding of cardiac enlargement[8] on chest radiograph when it was obtained as part of the normal management. The presence of any clinical feature suggestive of other congenital anomalies constituted an exclusion criterion. Identification of these signs by at least, two of three independent observers, comprising one of the authors (SIO) and two senior residents, (AA, IAL) was a minimum requirement for the diagnosis of PDA in any of the babies evaluated.

In a pre-test run on accuracy of the diagnosis of PDA using the above clinical criteria on ten babies (five preterm and five term babies), there was complete concordance between SIO and each of the two senior residents participating in the study, and both of whom had had prior training in the clinical recognition of PDA. Four of the babies (three preterm and one term) had PDA and were not included in the overall study. The clinical evaluations were independently carried out.

Based on the defined inclusion and exclusion criteria, 97 of the 123 admissions were recruited into the study. The remaining 26 were excluded from the study for a number of reasons, which included previous administration of indomethacin (six babies) and those that had missed the "third and fifth day of life" clinical evaluation for PDA (20 babies).

Management and Follow-up

Management in the SCBU consisted initially of fluid restriction to three quarters of daily requirement. Those babies with signs of cardiac decompensation, were placed on diuretic therapy (frusemide at 1-2mg/kg body weight/day in acute situations or hydrochlorothiazide at 2-4mg/kg/day in 2-3 divided doses when the acute phase of cardiac failure had subsided), and potassium supplement (at 2 mEq/kg body weight/day). Where heart failure proved refractory to these measures, digoxin was added to the treatment regimen. This was usually initiated with a total digitalizing dose of 0.03-0.04mg/kg body weight. They were placed on antibiotics where sepsis was suspected as well, usually initially comprising cloxacillin (100mg/kg body weight/24hr in four divided doses given intravenously six-hourly) and gentamicin (5mg/kg body weight/24hr in two divided doses given intramuscularly 12-hourly). Modification of antibiotic regimen was made according to the clinical condition of the infant, and the bacteriological report on body fluids, substituting a first or second-generation cephalosporin for cloxacillin as may be required. The same criteria for the diagnosis of PDA were followed throughout.

All babies discharged from the SCBU are normally followed-up for developmental assessment in addition

to being evaluated for possible long-term sequelae from medical indications of admission for at least six months and are thereafter, usually discharged from the neonatology clinic at the chronologic age of two years. All 88 surviving infants were therefore, followed up. The infants identified clinically with PDA were selected specifically for follow-up in the neonatology clinic from the time of their discharge by the same team of observers. They were seen at two-weekly intervals following discharge, for the first six weeks. Thereafter, they were seen at monthly intervals for the next three months and if stable, they were then seen at three-monthly intervals.

Results were entered into an Excel spreadsheet and descriptive analysis was undertaken. Appropriate statistical tests of significance were applied where necessary, including Fisher's exact test and chi squared test to ascertain association between observed variables.

Table I

Characteristics of the Study Subjects

Characteristic	*Preterm (n = 38)*	*Term (n = 59)*	*p*
Mean gestational age (weeks)	32.2 (2.9)	39.5 (1.5)	<0.0001
Mean birthweight (g)	1712 (517)	2946 (543)	<0:0001
Mean Apgar scores*	7.3 (1.4)	8.5 (1.8)	0.003
Sex (male:female)	22:16	38:21	0.667

* 11 preterm and 7 term study subjects had no recorded Apgar scores

Figures in parentheses are standard deviations

Results

Ninety-seven babies were recruited into the study. Of these, 60 (62 percent) were males and 37 (38 per cent) females. While 38 (39 per cent) were preterm, 59 (61 per cent) were term babies. The mean gestational age of the preterm babies was 32.2 weeks while that of the term babies was 39.5 weeks. The preterm babies had a mean birthweight of 1712g and the term, 2946g. While the mean gestational ages and mean birth weights differed significantly between preterm and term babies, (p=0.0001), the sex distribution and Apgar scores did not differ significantly (Table I).

The clinical diagnosis of PDA was made in 14 preterm babies of whom 10 were of very low birth weight (VLBW), three low birth weight (LBW) and one was large for date (LGA). The diagnosis was also made in 12 term infants as shown in Table II; giving a study population PDA incidence in preterm infants of 37 per cent and in term infants of 20 per cent.

Relationship of observed variables with occurrence of PDA

Apgar scores

Of the 38 preterm infants, 31 had Apgar scores recorded, while the Apgar scores were not recorded in the remaining seven. Of these 31, 10 had birth asphyxia (score at one minute <6; mean = 5), and four (40 per cent) of these 10 had PDA. Of the remaining 21 who were not asphyxiated, three (14 per cent) had PDA. All seven of the preterm infants whose Apgar

Table II

The Prevalence of PDA and Correlates among Study Subjects

	Preterm			*Term*		
	PDA		*p*	*PDA*		*p*
	Yes (n=14)	*No (n=24)*		*Yes (n=12)*	*No (n=47)*	
Mean gestational age (wks)	30.5(3.5)	33.0(2.3)	0.014	39.6(1.5)	39.4(1.5)	0.776
Mean birthweight (g)	1447(534)	1835(470)	0.028	2884(321)	2961(588)	0.667
Mean Apgar scores	6.7 (1.5)	7.4 (1.4)	0.257	8.1 (1.6)	8.6 (1.8)	0.526
Sex (male:female)	7:5	15:11	0.752	6:6	32:15	0.315

Standard deviations (SD) are expressed in parentheses

scores were not recorded had been delivered outside the UCH and they all had PDA. In addition, they also showed multiple organ dysfunction either in the form of seizures (2), hyperbilirubinaemia (4), respiratory distress (7), or acute renal failure (2).

Of the 59 term infants recruited into the study, 50 had Apgar scores recorded and eight of them were asphyxiated. Two (25 per cent) of the asphyxiated term babies had PDA, while six (14 per cent) of the remaining 42 term babies who were not asphyxiated had PDA. Four (44 per cent) of the nine term infants in respect of whom Apgar scores were not documented, had PDA. Fisher's exact test however, revealed a poor association between Apgar score and occurrence of PDA in preterm and term infants ($p = 0.257$ and 0.526, respectively; Table II).

Table III

Clinical Events among the Study Subjects

Events	*Preterm n(%)*	*Term n(%)*
Significant antenatal event	18(47.4)	14(23.7)
Birth asphyxia	4(10.5)	14(23.7)
Apnoea	13(34.2)	12(20.3)
Respiratory distress	7(18.4)	11(18.6)
Septicaemia (confirmed)	3(7.9)	2(3.4)
Sepsis (suspected)	31(81.6)	48(81.4)

Sepsis

Septicaemia was confirmed in three preterm infants and two (67 per cent) of these had PDA while two term infants had confirmed septicaemia and both (100 per cent) had PDA (Table III). None of the four preterm and eight term infants who did not have sepsis, had PDA. In all the other infants, sepsis was suspected but not confirmed, and the incidence of PDA among them was as stated above. The Fisher's exact test with correction for the relatively small numbers, applied to test any association between sepsis and occurrence of PDA showed a significant association in

Table IV

Association of other Clinical Events with the Prevalence of PDA among the Study Subjects

	Preterm			*Term*		
	PDA		*p*	*PDA*		*p*
	Yes %	*No* %		*Yes* %	*No* %	
Mode of delivery						
Caesarean	16.7	83.3		14.3	85.7	
Vaginal	34.4	65.6	0.643	21.2	78.8	1.000
Birth asphyxia						
Yes	25.0	75.0		50.0	50.0	
No	32.4	67.6	1.000	11.1	88.9	0.004
Recurrent apnoea						
Yes	30.8	69.2		41.7	58.3	
No	32.0	68.0	1.000	14.9	85.1	0.056
Respiratory distress						
Yes	57.1		42.9	72.7	27.3	
No	25.8	74.2	0.176	8.3	91.7	<0.001
Sepsis						
Confirmed	66.7	33.3		100.0	0.0	
Suspected	32.3		67.7	20.8	79.2	
Nil	0.0	100.0	0.168	0.0	100.0	0.006
Antenatal events						
Yes	61.1		38.9	28.6	71.4	
No	5.0	95.0	<0.001	17.8	82.2	0.453

term infants ($p = 0.006$) but not in preterm infants ($p = 0.168$; Table IV).

Recurrent prolonged apnoea with bradycardia

This was documented in 13 preterm infants, six (46 percent) of whom had PDA and in 11 term infants, five (45 percent) of whom had PDA. Fisher's exact test showed no association between recurrent prolonged apnoea and the occurrence of PDA in preterm and term infants ($p = 1.00$ and 0.056, respectively; Table IV).

Respiratory distress

This was documented in seven preterm infants, five (71 per cent) of whom had PDA. Fisher's exact test showed a strong association between respiratory distress and occurrence of PDA in term infants ($p < 0.001$), but not in preterm infants ($p = 0.176$).

Outcome

There were 13 hospital deaths among the study population, nine of whom were preterm infants and five (56 per cent) of them had PDA. The other four were term infants and none of them had PDA.

Follow-up phase

The follow-up phase had to be 'truncated' at 15 months after the study was commenced because of prolonged industrial dispute during which the hospital was shut. No new case of PDA was found among the surviving 84 infants in whom it had not been previously documented while on the ward. As five of the preterm infants with PDA had died while on the ward, only nine preterm and 12 term infants with previously documented PDA were available for follow-up.

Three of the preterm infants and four of the term infants with PDA were lost to follow-up before their fourth month of follow-up. One of them, a term infant, however, showed up at the age of four months with florid signs of heart failure and failure to thrive, having sought help from other health facilities to no avail. The clinical picture was that of a decompensated PDA. After some initial stabilization, he had surgical ligation of the PDA. Four among others who attended follow-up regularly (two preterm and two term infants) also subsequently had surgical ligation of their ducts between the ages of six and 13 months. They had before surgery been treated with combinations of diuretics, potassium supplements and digoxin in doses earlier stated. Intractable heart failure led to their being sent for surgical ligation of ducts. Two of the preterm infants previously documented as having PDA had by their chronologic age of two months, lost signs of PDA and it was concluded that their PDA had closed. At the point of truncating the study, two other term infants aged seven months and nine months respectively, who had both failed to thrive with signs of refractory heart failure were also being considered for surgical treatment. The industrial dispute precluded this at our centre. It was not known what became of them.

Discussion

Persistence of the ductus arteriosus is one of the commonest congenital cardiac anomalies.[6,8, 15-18] In modern paediatric cardiology and neonatology practices, the gold standard for the diagnosis of PDA is based on a clear demonstration by colour-coded Doppler echocardiography of a systolic retrograde flow in the main pulmonary artery, in addition to a systolic retrograde flow in the thoracic descending aorta.[6-8] Diastolic retrograde flows in both locations would indicate large shunts and an increase beyond 1.3 of the ratio of the left atrium diameter and the aortic root diameter is an adjunct to diagnosis.[7] Spectral tracings of pulsed or continuous wave Doppler interrogations of main pulmonary artery flow patterns would reveal clear antegrade and retrograde flows.[8] A documentation of the peripheral blood pressure preferably by a Doppler method in the neonate with an appropriate sized cuff showing a wide pulse pressure would also corroborate the diagnosis of PDA in current standard practices.[6] However, at the time of carrying out the present study, these facilities did not exist at the centre. Hence, a clinical approach was adopted for the diagnosis of PDA. This report therefore, represents an experience of trying to document a commonly encountered problem in a nursery without the use of modern ancillary diagnostic facilities. Although an increasingly good number of centres in the developing world are now acquiring these diagnostic tools, it is unfortunately the case that the majority of centres in the developing world still lack them. It is hoped by this communication therefore, that some of the difficulties faced by those who provide care for these sick infants would be highlighted. Although in this particular study the precaution of first training the senior residents in the art of clinical recognition of PDA was carried out and a subsequent pre-test showed a complete concordance between them and the consultant, admittedly however, the system would have missed out the so called "silent ducts"[7] and the "haemodynamically insignificant"[7] ducts. From a practice point of

view however, these categories of patent ducts are not known to adversely affect the morbidity and mortality in these infants. Their identification when the facilities exist therefore would in part be academic and would not be the primary focus of the physicians looking after such infants.

Some other conditions are also known to cause a systolic murmur audible in the left mid-infraclavicular area. The presence of such a murmur if considered in isolation may therefore not be synonymous with a PDA. These conditions include a physiologic stenosis at the bifurcation of the main pulmonary artery,[19] ventricular septal defect,[20] valvar pulmonary stenosis[21,22] and functional atrio-ventricular valve regurgitation.[21] However, none of the above-mentioned conditions is associated with bounding peripheral pulses as seen in PDA. The clinical diagnosis of PDA in infants in the present study population can therefore be reasonably assumed to have been accurate. To further buttress this, during the course of follow-up, five of the infants had surgical ligation of their ducts with subsequent relief of their symptoms, and no new identification of PDA was documented among those in whom it had previously not been documented.

In the present study, a significant association was found between prematurity and PDA (p=0.014; Table II). This is in conformity with previous reports which have shown that preterm infants have a particularly higher risk of developing PDA.[3,6,8] The present study also showed a high incidence of PDA among preterm infants (35 per cent), while the US national collaborative study on PDA in the premature infant quoted an overall incidence of 20.2 per cent.[23] Among preterm infants, the VLBW infants in particular, have been found to have a significant incidence of PDA.[6,23] The mean birth weight among the preterm infants with PDA in this study was 1447g while that of those infants without PDA was 1835g; most of the preterm infants with PDA were found to be of very low birth weight (p = 0.028; Table II), lending further credence to the association between LBW, VLBW and occurrence of PDA. The high incidence of PDA in preterm infants has been attributed to the immaturity of and hence, scanty amount of ductal wall smooth muscle component, higher levels of circulating vasodilatory prostaglandins and decreased response to oxygen induced vasoconstriction.[3] The former factor would appear to explain the observation of the 'disappearance' of the murmur and other features previously documented in two of the preterm infants by the chronologic age of two months during the follow-up phase of the study.

Apart from prematurity, some other factors have been documented as predisposing to patency of the ductus arteriosus. These include birth asphyxia, respiratory distress, fluid overload and anaemia.[6-8] Surprisingly however, the present study did not demonstrate any association between birth asphyxia and PDA. This might have been due to the fact that most of the asphyxiated infants in the study had mild birth asphyxia (mean one minute Apgar score = 5) and not moderate or severe birth asphyxia. However, all the seven preterm infants delivered outside UCH, in whom Apgar scores were not recorded had PDA. There were clinical features in these infants that were consistent with severe birth asphyxia, namely, multiple organ dysfunction, hence increased incidence of PDA. It is a known phenomenon that birth attendants tend either to conceal Apgar scores or overestimate it for babies they deliver.[24] In general, Apgar scores do not correlate well with the severity of birth asphyxia[24] and was not indeed designed as a measure of the severity of birth asphyxia.[24] It is no surprise therefore, that a poor association was demonstrated between Apgar scores and the occurrence of PDA in preterm and term infants (p = 0.257 and p = 0.526, respectively). In the absence however, of more specific modalities of assessing severity of asphyxiation in the newborn such as arterial blood gas analysis, Apgar score remains an acceptable option.[24]

In conformity with previous studies, no relationship was found between the sex of these infants and the development of PDA. Persistent ductal shunting is a well-recognized problem for preterm infants with respiratory distress.[3,6-8] This is further confirmed in this study as 71 per cent and 75 per cent respectively, of the preterm and term infants with respiratory distress developed PDA. This calls for aggressive management of all infants with respiratory distress to reduce the incidence of PDA. Such management should include attention to the primary cause of the respiratory distress with the prompt provision of ventilatory support and supplementary oxygen in the event of respiratory failure. Correction of the invariably associated metabolic derangements is also a prime necessity.

All the hospital mortality recorded at one week in this study occurred in preterm infants, and of these, more than half had PDA. The likely causes of death are not included in this report but preterm babies, in whom pulmonary vascular resistance falls rapidly after birth, typically manifest signs of overt cardiac failure in the first week of life[6-8] and may succumb at this stage. This therefore, also calls for aggressive management of such infants especially preterms who show

signs of decompensation from PDA in order to reduce mortality in our neonatal intensive care units. This should include fluid restriction, attempt at medical (pharmacological) closure, failing which, interventional closure techniques should be explored or surgical ligation should be adopted as a last resort.

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