

Overview of Patent Ductus Arteriosus in the Albaha Area, Saudi Arabia: Prevalence, Risk Factors, Types, Clinical Presentation, and Outcome

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Abstract

Background: The ductus arteriosus is a connection between the aorta and pulmonary artery. Normally, it should be closed within several days after birth, but sometimes it remains open due to prematurity or other factors which cause hemodynamic changes. It is more common in preterm infants, among whom the incidence is approximately 30-40%.

Objectives of the study: The aims of this study were to determine the prevalence of patent ductus arteriosus, determine its size by echocardiogram, and define the effects of environmental risk factors which can affect its prevalence and course.

Methodology: A retrospective hospital-based cross-sectional study was conducted in the Pediatric and King Fahad Hospital Albaha, Saudi Arabia, from January 2010 to December 2017, which included all neonates diagnosed as having isolated patent ductus arteriosus (PDA).

Results: A total of 3,000 newborns were screened by echocardiography. Of them, 1,012 (33.73%) neonates had isolated PDA, 960 (32%) were preterm infants, and 52 (1.73%) were full term. There were 593 females (58.59%) and 419 males (41.4%), (OR 1.3). Small PDA was seen in 444 (14.8.1%) patients, moderate in 387 patients (12.91%), and large in 181 (6.1%) patients, 95% CI (177.33-497.33). It was more common in high-altitude areas, with 677 (22.57%) patients coming from high-altitude areas, versus 335 (11.16%) cases from sea-level areas (OR 2). The prevalence was higher in neonates with O positive and A+ blood groups [95% CI (12.9-30.77)]. Spontaneous closure is the usual course and was documented in 75% of cases with no medical treatment. We found that PO ibuprofen was easy to administer, safe, and more effective, with less adverse effects than IV indomethacin and the same outcome of PDA closure.

Conclusion: The prevalence of PDA was high in preterm neonates, and spontaneous closure occurred in about 70% of cases. High altitude was found to be a risk factor associated with increased prevalence of PDA. Small PDA was more common, and PDA was more common in females. Ibuprofen was found to be effective, with less adverse effects than indomethacin.

Keywords: Patent ductus arteriosus; Preterm infants; Indomethacin; Ibuprofen

Background

The ductus arteriosus is a connection between the aorta and pulmonary artery. Normally, it should be closed within several days after birth, but it sometimes remains open due to prematurity or other factors which cause hemodynamic changes. It is more common in preterm infants. The incidence of patent ductus arteriosus (PDA) is approximately 30-40%, in premature and low birth weight infants [1]. The prevalence of PDA in the Albaha area in a previous study was approximately 40% in premature infants and 9.5% for all congenital heart diseases [2]. The incidence reaches 80-90% in very low birth weight (VLBW) infants aged younger than 26 weeks [3]. The spontaneous closure of the ductus arteriosus starts within several hours after birth. It occurs by the end of the first week of life in about 90% of full-term infants and 73% of preterm infants [4]. PDA is more

common in females (2:1). Pulmonary overflow and hemodynamic changes can increase the neonatal morbidities [5]. Pulmonary overload due to left to right shunt can cause lung disease and the stealing of blood from the aorta [6]. The cerebral and mesenteric perfusions are decreased and contribute to the risk of morbidity and complications of PDA, including the risks of developing chronic lung disease (CLD), intraventricular haemorrhage (IVH), upper gastrointestinal bleeding (UGIB), necrotizing enterocolitis (NEC), and oliguria, as well as increased serum creatinine level. Increased incidence of PDA associated with prematurity, RDS, surfactant treatment, asphyxia, rubella, trisomy 13, trisomy 18, high altitude, and the presence of congenital heart disease (CHD). Administration of steroid antenatal and prolonged rupture of membranes can be associated with decreased incidence of PDA. The treatment should consider the underlying pathophysiology [7]. PDA can be divided into small, moderate, and large sizes, as defined by echocardiography, and can also be divided morphologically by cardiac catheterization into type A conical ductus, type B window-like, type C tubular ductus, type D complex ductus,

type E elongated ductus, and type F if the morphology did not fit any other classification based on Krichenko's classification [8-10]. Increasing the arterial PaO₂ and decreasing circulating PGE₂ can help with PDA closure after birth. The functional closure is seen within 24 h in 50%, within 48 h in 90%, within 96 h in 100% [3]. A high altitude between 2438 and 4267 meters results in decreased PaO₂ and oxygen saturation, which can contribute to the patency of ductus arteriosus [11]. Cyclooxygenase inhibitors like indomethacin, ibuprofen, and acetaminophen block the conversion of arachidonic acid to prostaglandin and can help with the closure of PDA [12,13].

Objectives

The aims of this study were to determine the prevalence of PDA, determine the size of PDA by echocardiogram, and define the effects of environmental risk factors which can affect the occurrence and clinical presentation of PDA, like high altitude, blood group, and gender. Additional aims were to evaluate the outcomes of medical treatment with different types of cyclo-oxygenase inhibitors, mainly ibuprofen and indomethacin, and to compare our results with those of other national and international studies in this field.

Methodology

This retrospective hospital-based cross-sectional study was conducted in the Pediatric and Neonatology Department of King Fahad Hospital Albaha, Saudi Arabia. Retrospectively, we reviewed files from January 2010 to December 2017. The study was approved by the hospital's Scientific Research and Ethical Committee and was performed according to the Helsinki Declaration [14]. We screened all of the preterm, term, and low-birth-weight babies who presented with any clinical sign of congenital heart disease (CHD). Only neonates who were diagnosed by echocardiography to have isolated PDA were enrolled in the study. Syndromic babies, septic patients, and patients who had PDA associated with other CHDs were excluded. The infants were considered to have symptomatic PDA if they presented signs of heart failure, respiratory distress, increased oxygen requirements, apnea, tachycardia, bounding pulse, widened pulse pressure, or renal dysfunction. The diagnosis was confirmed by echocardiography through evidence of left-to-right shunting across the ductus arteriosus. Echocardiography screening was done for all included cases after the age of 96 hours of life and, in some cases, was done before then to rule out CHD. The screening was done with a Philips CX50 echocardiography machine. We divided the PDA cases into three types: small: <1.5 mm, moderate: 1.5-3 mm, and large: >3 mm and measured the biventricular function for all included neonates. Systemic hypoperfusion and pulmonary hyperperfusion were diagnosed when the LA:Ao ratio ≥ 1.5 and mitral E/A ratio >1.5 , with the presence of a retrograde flow in the descending aorta [9,10]. The outcomes in our study were the closure of PDA and the presence of any morbidity. P-values, odds ratios, and 95% confidence intervals were the statistical significances calculated to evaluate the results. A P-value <0.05 was considered statistically significant. The Users' Guides to the Medical Literature, third edition, was used to calculate the significant statistical values [15]. The treatment protocol we applied in our unit was intravenous indomethacin in three doses and intervals depending on the patient's age: a first dose of 0.2 mg/kg, then two doses of 0.1 mg/kg after 12 h or 36 h if the infant is either <7 days old or <1250 g, respectively, then three doses of 0.2 mg/kg, and two doses of 0.25

mg/kg if the patient >7 days old or >1250 g. Oral ibuprofen was given in three doses: 10 mg/kg as loading, followed by two doses of 5 mg/kg at 24-hr intervals [4,16]. In some cases, a second course was needed. Treatment was cancelled if the patient developed oliguria, elevated serum creatinine, signs of NEC or UGIB, low platelets, or pulmonary hemorrhage. We randomly selected two groups of patients to compare the outcomes and adverse effects of two treatment modalities. For tiny asymptomatic PDA, fluid restriction was the only management. The patient was transferred for surgical ligation if no response to medical treatment was achieved. The babies' gestational age, weight, blood group, prenatal and postnatal conditions, high-altitude or sea-level altitude of residency, and gender were considered as risk factors in the prevalence and prognosis of ductus arteriosus.

Results

During the last 6 years, the average admission to the Neonatal Intensive Care Unit (NICU) at King Fahad Hospital has been about 600 patients per month. Echocardiography was done for 3000 newborn infants from the NICU and nursery, and on neonates transferred from other centers for cardiology consultation. As seen in Table 1, isolated PDA was diagnosed in 1012 (33.73%) patients, including 960 (32%) preterm infants and 52 (1.73%) full-term patients. Isolated was thus significantly more common in preterm infants. In the patients diagnosed with isolated PDA, 593 were female (58.59%) and 419 were male (41.4%) (OR 1.3). PDA was measured by echocardiography. Small PDA was seen in 444 (14.8.1%) patients, versus moderately sized PDA in 387 (12.91%) patients and large in 181 (6.1%) patients, 95% CI (177.33-497.33). Among the patients, 677 (22.57%) came from a high-altitude areas, while 335 (11.16%) cases came from sea-level areas (OR 2).

We randomly checked the blood group of 150 patients and found that 63 (42%) cases had O positive blood, 40 (26.7%) cases had A positive, 15 (10%) had B positive, 12 (8%) had O negative, 8 had (5.3%) A negative, 7 had (4.7%) AB positive, and 5 had (3.3%) B negative, 95% CI (12.9-30.77). These results need another detailed study to analyze and clarify this point.

Spontaneous closure is the usual course and was documented in 75% of cases with no medical treatment. We reviewed the data of two groups of patients given medical treatment for PDA closure (Table 2): group A, comprising 100 patients treated by PO Ibuprofen, and group B, comprising 100 patients given IV indomethacin. No difference was seen in the prevalence of PDA between females and males in the two groups [OR: 0.96, 95% CI (-0.65-1.79), P-value=0.88]. Also, no significant difference was seen in the closure of PDA between the two treatment modalities. Closure was achieved in 91 (91%) patients and failed in 9 (9%) patients in group A, and achieved in 89 (89%) patients and failed in 11 (11%) patients in group B [OR: 1.3, 95% CI (-0.03-1.73), P-value=0.64]. The oral ibuprofen treatment was slightly more effective. Creatinine serum level elevation was seen in 3 (3%) neonates in group A, and in 8 (8%) neonates in group B, [OR: 0.36, 95% CI (1.2-6.36), P-value=0.12]. Oliguria was seen in 2 (2%) neonates in Group A, and 6 (6%) in Group B, [OR: 0.32, 95% CI (1.26-7.77), P-value=0.14]. UGIB and NEC were not seen in group A but occurred in 3 (3%) neonates in group B, P-value=0.08. It was clear that the PO ibuprofen was easy to administer and safe, with less adverse effects than IV indomethacin but the same outcomes in terms of PDA closure.

Age	PDA	F	M	Large	Moderate	Small	High	Sea level
All Patients	1012 (33.73%)	593	419	181	387	444	677	335
Preterm	960 (32%)	559	401	173	369	418	642	318
Term	52 (1.73%)	34	18	8	18	26	35	17

PDA: Patent ductus arteriosus. F: Female. M: Male

Table 1: Distribution of patients with PDA in the study.

Characteristics	Group A (n=100) Ibuprofen	Group B (n=100) Indomethacin	IV	P-value	OR	95% CI
Mean age (wk)	29.92	29.75		0.71	1.01	
Mean Wt (g)	1140.86	1140		0.76	0.99	
Female	60	61		0.88	0.96	-0.5-1.8
Male	40	39				
PDA closed	91	89		0.64	1.3	-0.3-1.73
PDA not closed	9	11				
Increased serum creatinine	3	8		0.12	0.36	1.2-6.36
Oliguria	2	6		0.15	0.32	1.26-7.77
UGIB	0	3		0.08	-	
NEC	0	3		0.08	-	

PDA: Patent Ductus Arteriosus. NEC: Necrotizing Enterocolitis. UGIB: Upper Gastrointestinal Bleeding. IV: Intravenous. PO: Oral

Table 2: Outcome of medical treatment for PDA by PO ibuprofen and IV indomethacin.

Discussion

A total of 3000 infants were screened in the study. We found a 32% prevalence of PDA in preterm infants in the Albaha area and of 1.73% in term babies, with a female-to-male ratio of 1.3:1, which is the same as the prevalence rate mentioned in national and international studies [1,17]. Spontaneous closure was documented in 73% of cases. PDA was more prevalent among patients living in high-altitude areas (22.57%), while seen in 11.16% of patients living in sea-level areas. Echocardiography was found to be a non-invasive and useful test for evaluating cardiac function, structures, and the measurements of the PDA. Small PDA was seen in 444 (14.81%) patients, moderate PDA was seen in 387 (12.91%) patients, and large PDA was seen in 181 (6.1%) patients. As mentioned in Table 2, no significant difference was seen in the closure of PDA between the two treatment modalities in our study, which was the same result as found in other international papers [12,13].

We found that ibuprofen was as effective as intravenous indomethacin but has less side effects and simple administration, and is cost effective. This result was the same as found in other international studies [18,19]. PDA closure was achieved in 91% of infants treated by oral ibuprofen and failed in 9% in group A, while intravenous indomethacin was given to patients in group B, for whom closure was achieved in 89% of cases and failed in 11%, (P-value: 0.64). The oral ibuprofen treatment was slightly more effective. Elevated

creatinine serum level was seen in 8% of the infants in group B, versus 3% of the infants in group A (P-value 0.36). Oliguria occurred in 6% of infants in Group B, and 2% in Group A (P-value 0.15). Upper GI bleeding and NEC were seen in 3% of patients in group B while no cases were seen in group A, (P-value 0.08). We randomly checked the blood group in 150 patients and found that the prevalence of PDA was somewhat higher in the neonates who had blood groups O positive and A positive. These results were statistically not significant, 95%CI (12.9–30.77), and need another study with a larger sample to analyze and clarify this point. No published studies regarding this issue were found for comparison.

Conclusion

The prevalence of PDA in preterm infants is high, and the majority of cases (70%) closed spontaneously in the first few days of life. Small PDA is more common, and PDA is more common in females. Ibuprofen was effective when compared with indomethacin in closing PDA, with less adverse effects and no significant differences. High altitude was a risk factor associated with increased prevalence of PDA. PDA was diagnosed more in neonates who had O positive and A positive blood groups. Large prospective studies are needed to clarify the risk factors that contribute to the outcomes of patent ductus arteriosus.

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