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ORIGINAL ARTICLE

Patent ductus arteroisus: a villain or a random condition in pre-term infants?

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Abstract

Objective: To analyze newborns weighing less than 1500g at birth who developed complications like bronchopulmonary dysplasia, retinopathy of prematurity, peri-intraventricular hemorrhage, pulmo-nary hemorrhage and necrotizing enterocolitis with or without patent ductus arteriosus (PDA). The aim was to establish a causal relationship between them. **Method:** Search in the database of the Bra-zilian Network of Neonatal Research of newborns from the Hilda Brandão Maternity Hospital at Santa Casa de Belo Horizonte - MG, between 2014-2019. It included babies who were born or were admitted to the maternity ward with birth weight between 401 and 1500g or gestational age of 22 weeks and 0 days to 29 weeks and 6 days. **Results:** It was observed that for all complications, the absolute num-ber of cases was considerably higher in the presence of PDA. However, in our sample, after the statis-tical analises, there was no causal relationship between the events studied (patent ductus arteriosus X complications). **Conclusion:** The presence of some association between patent ductus arteriosus and diseases and complications inherent to prematurity is indisputable. However, as suggested in other case series, in this study, a causal relationship between PDA and the studied comorbidities was not established. It suggests that maybe all the conditions (including the patency of the canal) are just mo-re common in a group of severe preterm infants. The absence of a causal association leads us to re-flect on the PDA closure treatment, opting for less interventionist and more selective approaches.

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INTRODUCTION

The ductus arteriosus (DA) is a conduit linking the pulmonary artery to the aorta that develops from the sixth week of gestation[1]. It is through the DA that the blood that reaches the pulmonary artery, already oxygenated in the placenta, is diverted to systemic circulation. This arrangement allows oxygen to make it to tissues in a context in which the lungs are not yet functioning. Normally, functional closure of the DA occurs within 48 hours in full-term newborns and within 72 hours in 90% of the infants born after more than 30 weeks of gestation[2]. When the DA remains open for more than 72 hours, a diagnosis of patent ductus arteriosus (PDA) is considered[2].

PDA is more prevalent in females, affecting 1:2,000 to 1:5,000 live births[3,4]. Incidence varies depending on gestational age (GA) and birth weight (BW). In newborns, the incidence is 57:100,000 live births and PDA is commonly associated with other potentially related congenital heart lesions[4]. Incidence is substantially higher in preterm newborns, as PDA is seen in 31:100 infants born weighing between 501g and 1500g. The lower the GA and the birth weight, the higher the incidence and time for which the DA remains patent[4]. In these babies, PDA is a frequent complication of hyaline membrane disease. In 80% of extremely preterm infants (born after less than 28 weeks of gestation), the DA remains patent for as long as three days after birth[2].

PDA is not necessarily linked to clinical symptoms. However, the sequestration of systemic blood flow through the DA may cause hypotension and reduced organ perfusion (hemodynamically significant ductus arteriosus), potentially affecting the bowel and causing necrotizing enterocolitis (NEC)[2]. Poor cerebral perfusion may predispose patients to developing periventricular leukomalacia (PVL) and periventricular/intraventricular hemorrhage (PVH/IVH)[2]. Moreover, increased blood flow to the lungs may cause pulmonary hemorrhage (PH) with acute and chronic ventilatory repercussions, including bronchopulmonary dysplasia (BPD)[2].

The lower the birth weight, the greater the chances of occurrence of clinical repercussions. In low birth weight (LBW) preterm infants born weighing less than 2,500g, incidence ranges from 10 to 42%. Incidence peaks to 85% in extremely low birth weight (ELBW) preterm infants born weighing less than 1,000g[4].

PDA and its repercussions are often associated with high morbidity and mortality, especially among preterm infants. For this reason, in an attempt to mitigate or prevent adverse outcomes, early interventional measures are often adopted. However, the role of PDA in complications often attributed to it is still debatable. Moreover, there is insufficient evidence that drug therapy or surgery reduces the occurrence of these complications[5,6].

In light of the controversy around the association between PDA and complications often attributed to it, the authors of this study analyzed the medical charts of very low birth weight (VLBW) preterm infants born weighing less than 1500g, with or without PDA, who developed BPD, retinopathy of prematurity (ROP), PVH/IVH, NEC and PH, in order to verify whether a causal relationship could be established between PDA and these complications.

METHODS

This observational, retrospective, cross-sectional study included the medical records of 422 newborns seen at the Hilda Brandão Maternity Hospital of the Santa Casa de Belo Horizonte - MG, from January 2014 to December 2019. Newborn data were obtained from the Brazilian Network for Neonatal Research (RBPN) database, which contains information about all babies born or admitted to the maternity hospital with birth weight ranging from 401 to 1500 grams or gestational ages from 22 weeks and 0 days to 29 weeks and 6 days.

Preterm infants of both sexes were selected based on the following inclusion criteria: infant listed in the RBPN either born or admitted to the Hilda Brandão Maternity Hospital in the period from January 2014 to December 2019 with any of the following complications: BPD, ROP, PVH/IVH, HP, or NEC. Newborns who died in the delivery room or within 12 hours of birth and infants with one or more of the complications listed above without a diagnosis of PDA were excluded. A total of 202 patients were selected and included in the study.

Patient data were transcribed to an Excel® 2010 spreadsheet and double-checked by the authors. The spreadsheet was then exported to SPSS® 20.0 for Windows. Initial exploratory descriptive analysis was performed by calculating frequencies. To test the association between variable "patent ductus arteriosus" and variables related to complications, Pearson's chi-squared test was used adopting a 5% significance level. *P*-values <0.05 were deemed statistically significant.

The Research Ethics Committee of the Santa Casa de Belo Horizonte Hospital approved the study and granted it certificate no. 43950021.0.0000.5138.

RESULTS

Table 1 shows the incidence of complications (BPD, ROP, PVH/IVH, HP or NEC) seen in the patients included the study.

PVH/IVH and BPD were the complications with the highest recorded incidence, with 63.8% and 40.6% respectively. The other complications (NEC, ROP and HP) had incidence ranging from 13.4% to 17.8%. Fifty-four infants (26.7%) had at least one of the complications, but no mention about the presence or absence of BPD. Thus, the incidence of BPD may have been underestimated and could have been as high as 66%, if the infants with this information missing in their charts actually had the condition. Since the RBPN database defines presence of BPD based on need for oxygen at 36 weeks corrected gestational age, most of the infants with no data about BPD

Table 1. Incidence of complications in preterm infants born at the Hilda Brandão Maternity Hospital of the Santa Casa de Belo Horizonte, Minas Gerais, 2014-2019.

Complications		N	%
Pulmonary hemorrhage	No	168	83,2
	Yes	34	16.8
Necrotizing enterocolitis	No	175	86,6
	Yes	27	13.4
Periventricular/intraventricular hemorrhage	No	64	31.7
	Yes	129	63.8
	No data	09	4.5
Retinopathy	No	107	53.0
	Yes	59	29.2
	No data	36	17.8
Bronchopulmonary dysplasia	No	66	32.7
	Yes	82	40.6
	No data	54	26.7

Source: Brazilian Neonatal Research Network (RBPN), 2014-2019.

may actually be cases of discharge, death, or referral before this postmenstrual age. However, since the field in question was left blank for these infants, we cannot state that they had BPD. A few charts also had missing information about ROP and PVH/IVH, however in a much smaller proportion, which makes bias a less relevant issue.

The search for complications was followed by the categorization of each infant based on the presence or absence of a patent ductus arteriosus. The infants born in our maternity hospital in the study period (2014-2019) were diagnosed with PDA based on transthoracic echocardiography. Our protocols establish that every newborn with a GA of less than or equal to 30 weeks or with signs of heart disease (e.g.: murmur) on physical examination must undergo transthoracic echocardiography. The RBPN database only shows whether the infants were diagnosed with a patent ductus arteriosus. There is no data about the echocardiographic parameters of each ductus arteriosus or other information that might allow the categorization of patients into cases of PDA with or without hemodynamic repercussions. Table 2 shows the incidence of complications for infants with and without PDA.

Table 2 shows that the absolute number of complications was considerably higher in patients with PDA. However, the p-value calculated via the chi-squared test was greater than 0.05 across the board. Therefore, we found no significant differences between the groups in our population for presence of PDA and complications or a correlation between PDA and higher incidence of complications.

DISCUSSION

In the fetus, the ductus arteriosus, which is well developed by the first trimester of pregnancy, is responsible for diverting almost all the cardiac output of the right ventricle (approximately 55% of total cardiac output) that reaches the pulmonary arteries to the descending aorta[1]. Through the DA, blood from the right ventricle (partially oxygenated by placental circulation) reaches systemic circulation, with only a small portion of the total volume of blood not diverted by the DA circulating in the lungs. The lungs, still not oxygenated and with high vascular resistance, are thus protected against volume overload.

As the newborn begins to breathe, blood oxygen saturation increases significantly, initiating a sharp drop in pulmonary blood flow resistance, while the removal of the placenta causes an increase in systemic vascular resistance[1]. The reversal of these resistances causes a shunt through the ductus arteriosus now in the opposite direction, from left to right (which would cause volume overload in the lungs and left ventricle), but only transiently. Increased arterial oxygen concentration, which has a vasoconstrictor effect, together with decreased relaxation response of the DA wall to prostaglandins (due to the lower sensitivity of receptors present in the DA, and the lower synthesis and higher clearance of prostaglandins in full-term neonates)[7], promote the functional closure of the DA.

In full-term newborns, the functional closure of the DA begins approximately 12 hours after birth, while permanent closure occurs after five to seven days, though in some cases it may take up to 21 days[7]. Since the sensitivity of the DA to the constrictive effect of oxygen is directly related to GA, in preterm newborns the ductus arteriosus remains open for a longer period of time. The more preterm the newborn, the more frequent the occurrence of PDA. Other common findings in preterm infants are: higher prostaglandin levels in the first weeks of life; greater sensitivity to prostaglandins; complications such as hypoxia and acidosis; and incomplete formation of smooth muscle of the vascular wall, which also contributes to the occurrence of PDA.

Among preterm infants, PDA is primarily seen in babies born weighing less than 1,000g. According to Yang et al. (2013)[8], as many as 58% of the preterm infants born weighing less than 1000g and 68% of the babies born with a GA of less than 30 weeks are diagnosed with PDA. Nevertheless, preterm infants with PDA do not necessarily develop clinical manifestations. Although 90% of the newborns with PDA have murmurs[4], hemodynamic repercussions are diagnosed in 10 to 42% of the newborns with PDA weighing less than 2,500g at birth[9], with percentages growing with lower GA and birth weight.

The repercussions arising from the non-closure of the DA result from the diversion of blood flow through it (left-right shunt), which, as explained above, leads to increased pulmonary flow and decreased systemic flow. The blood shunted from the aorta to the pulmonary trunk may correspond to half or even two thirds of the cardiac output when there is no physiological closure of the DA[3]. Increased blood flow into the pulmonary capillaries may cause extravasation and lung edema, which deteriorate ventilatory conditions and lead to PH, a severe complication, or BPD, a chronic repercussion[2]. Impaired systemic circulation may cause hypotension and significantly

Table 2. Incidence of complications in preterm newborns with and without a patent ductus arteriosus, born at the Hilda Brandão Maternity Hospital of the Santa Casa de Belo Horizonte, Minas Gerais, 2014-2019.

Complications		Canal arterial patente		OR (95% CI)	*P**
		Não N (%)	Sim N (%)		
Pulmonary hemorrhage	No	41 (20.2)	127 (62.8)	1.24 (0.50-3.07)	0.633
	Yes	07 (3.7)	27 (13.3)		
Necrotizing enterocolitis	No	41 (20.2)	134 (66.3)	0.87 (0.34-2.21)	0.777
	Yes	07 (3.7)	20 (9.8)		
Periventricular/intraventricular hemorrhage	No	18 (9.5)	46 (23.8)	1.55 (0.77-3.10)	0.214
	Yes	26 (13.4)	103 (53.3)		
Retinopathy	No	27 (16.2)	80 (48.1)	1.87 (0.81-4.31)	0.135
	Yes	09 (5.6)	50 (30.1)		
Bronchopulmonary dysplasia	No	19 (12.8)	47 (31.7)	1.80 (0.83-3.91)	0.131
	Yes	15 (10.3)	67 (45.2)		

OR= Odds Ratio, CI= Confidence Interval
*Chi-squared test
Source: Brazilian Neonatal Research Network (RBPN), 2014-2019.

reduce the diastolic perfusion of several organs, particularly the brain, kidneys, and bowel. Low cerebral blood flow may cause PVL and PVH/IVH, which cause high morbidity. NEC may occur in the bowel, and acute kidney injury may also develop. The frequency of complications reported in the literature in infants with PDA varies. A Brazilian study described respiratory distress syndrome, sepsis, and PVH/IVH as the most prevalent comorbid conditions (seen in more than 90% of the infants), with NEC affecting just over 14% of the study population[4]. PDA has been described in the literature as a risk factor for the development of ROP, a retinal proliferative vasculopathy that culminates in partial or total visual impairment[10].

The association of PDA with the comorbid conditions linked to prematurity mentioned in this article (ROP, NEC, PVH/IVH, PH, BPD) is unquestionable. For decades, studies have described the coexistence of PDA with these complications. In our study, such association is also demonstrated. Most of the preterm infants in our population with any of the comorbidities listed above had PDA. Infants with PH accounted for 16.8% of our population; in this subgroup, 27 of the 34 infants (79%) also had PDA. BPD was seen in 40.2% of our population; in this subgroup, 67 of 82 infants weighing less than 1,500 grams at birth (81%) also had PDA. The existence of an association is apparently obvious, as is the ensuing conclusion that treatment might lead to decreased morbidity and mortality. However, there is more to consider.

Despite the proven increase in morbidity and mortality in preterm infants associated with PDA, meta-analyses discussing the effectiveness of drug therapy for patent ductus arteriosus showed no reduction in neonatal morbidity and described additional treatment-related complications[11]. Thirty-five randomized trials have been conducted to analyze the effects of PDA closure treatment on the respiratory system. In 2018, SANKAR et al.[11] reported that three of the 35 trials described shorter times on a ventilator or on oxygen therapy for infants treated with indomethacin; 22 showed no difference in use of a ventilator by treated and untreated infants; and seven reported increased use of oxygen, surfactants, and longer time on mechanical ventilation among treated preterm infants. A retrospective study conducted on an American database covering 13,853 infants weighing less than 1,500 grams at birth (Pediatric Hospital Information System Database - PHIS) looked at outcomes after a decrease of 11% per year in PDA closure interventions in the period ranging from 2005 to 2014. Fewer interventions were followed by increases in the number of cases of BPD, PVL, ROP and AKI; despite the higher rate of complications, survival also increased. A study including the medical records of 61,520 preterm infants born after 23 to 30 weeks of gestation also showed increased survival after a decrease in interventions to treat PDA, with no increase in the rates of NEC, ROP, and PVH/IVH; the only increase was seen in the rates of BPD in preterm infants born after 23 and 24 weeks of gestation[11].

Reflections about what to do in cases of PDA must take into account the information available in the literature, which was supported by the findings of the present study. The co-occurrence of PDA and severe comorbid conditions linked to prematurity does not necessarily mean that PDA caused these conditions. NEC, BPD, PVH/IVH, PH, and ROP have been correlated to several other risk factors inherent to prematurity. Thus, a preterm newborn with PDA may present several risk factors for the development of NEC, for example, such as an immature gastrointestinal tract, sepsis, prolonged fasting, deprivation of breast milk, which may occur or not in conjunction with PDA. As with NEC and other comorbid conditions of prematurity that have different risk factors and causes, PDA will almost always be more prevalent in severely involved newborns (lower GA and birth weight), although it

does not always cause these comorbid conditions. Evidence of poorer outcomes with aggressive treatment of PDA, especially surgery, along with a 50% chance of developing post ligation cardiac syndrome leading to increased incidence of NEC and BPD and 33% mortality, reinforce this idea[2].

Despite the seemingly endless discussion, it has been established that early and generalized approaches to patent ductus arteriosus, using either drug therapy or surgery, do not yield better outcomes, which is probably explained by the inexistence of a causal relationship between PDA and other present comorbid conditions. There is, however, a group of patients, which includes extremely preterm infants (born after less than 26 weeks of gestation) and infants with significant hemodynamic dysfunction after the second week of life, who might benefit from PDA closure treatment[11]. Moreover, echocardiographic findings such as DA diameter, maximum left-to-right transductal flow velocity, left ventricular cardiac output, and mitral flow during atrial contraction have been associated with the identification of patients with increased chances of death and development of chronic lung disease[12]. The ideal management of PDA in preterm infants revolves around careful selection of hemodynamically significant cases of PDA affecting extremely preterm infants, combined with relevant clinical findings, although selection is difficult and often subjective.

Once the need for intervention has been defined, conservative measures such as management of oxygen saturation, with a target residing between 90-95%; adjustment of PEEP (positive end-expiratory pressure) in mechanical ventilation; blood pressure control to avoid hypertension; and control of fluid supply according to sodium and fluid balance are recommended[2]. Drug therapy may be offered with ibuprofen or paracetamol, both with comparable efficacy and different side effects that require case-by-case analysis. If drug therapy fails or cannot be prescribed, surgery should be considered.

CONCLUSION

Studies have historically associated several comorbid conditions with PDA and proposed different approaches and therapies. PDA gained a bad reputation in neonatal intensive care units as series and reports associated it with events such as PH, refractory arterial hypotension, PVH/IVH, BPD and NEC. The rationale seems obvious. If PDA is associated with higher morbidity and mortality, therefore we should close it. However, evidence accumulated over the years showed that mortality did not decrease after closure, and contrary to expectations, many outcomes were poorer and led to increases in the rates of NEC, BPD, and other neurodevelopmental complications.

Evidence available in the literature and results from studies similar to ours, in which a causal relationship between PDA and various perinatal complications could not be established, indicate a clear need to adopt a more judicious approach to PDA. Today, aggressive, early and generalized treatment proves inadequate.

In 2015, El-Khuffash, et al.[12] published a multicenter study with 141 preterm infants with PDA, in which for the first time a score was proposed to determine which patients were at greater risk of death or developing chronic lung disease and, consequently, might benefit from PDA closure. The results, obtained through echocardiographic parameters, had a sensitivity of 92% and specificity of 87% in the identification of the best candidates for treatment, representing a potential turning point in the treatment of patent ductus arteriosus.

Additional studies focusing on the establishment and validation of criteria and scores to help in the decision to treat infants with PDA must be encouraged. Careful identification of the group of newborns who might benefit from PDA closure with positive impacts on their development and less risk of adverse effects should be the goal of neonatologists today. While such identification is not possible, conservative management devised to minimize the impact of a patent ductus arteriosus without necessarily closing it, should be preferred.

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