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Persistent Ductus Arteriosus in Critically Ill Preterm Infants

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ABSTRACT

Introduction: Persistent ductus arteriosus (PDA) is found with increased incidence in preterm infants, significantly affecting neonatal morbidity and mortality rates.

Aim: To evaluate the association between the presence of PDA and the severity of clinical condition at birth in critically ill preterm infants, with gestational ages (GA) ≤ 32 weeks and severe respiratory distress.

Methods: All preterm infants with GA ≤ 32 weeks admitted to the neonatal intensive care unit (NICU) of the Clinical County Emergency Hospital, Sibiu between 1 January 2010 and 31 December 2015 were included in the study. These were categorized as Group 1 [Preterm infants with PDA; n=154] and Group 2 [Preterm infants without PDA; n=186]. Epidemiological and clinical data were collected in the National Registry for Respiratory Distress Syndrome for all children, and data related to prenatal period, clinical characteristics at birth i.e GA, weight, gender, Apgar scores, and clinical features such as resuscitation at birth, surfactant administration, need and duration of respiratory support, neonatal sepsis, complications associated with prematurity, and death, were analyzed.

Results: Group 1 infants had significantly lower GA and birth weights, were more often out born (p=0.049, HR 1.69), and had significantly lower Apgar scores at 1 and 10 minutes (p=0.022, p=0.000). They presented a significantly higher need for surfactant administration (42.9% vs 24.7%, p<0.0001) and respiratory support (96.8% vs 90.3%, HR 3.19, p=0.019 for need of CPAP and 22.1% vs 10.8%, HR 2.35, p=0.004 for mechanical ventilation). Duration of respiratory support was also significantly higher in the Group 1 (7.6%±7.5 vs. 5.1±3.8 days, p<0.0001 for CPAP and 20.1±22.5 vs. 12.0±15.7 days, p<0.0001 for mechanical ventilation).

Conclusion: In very preterm infants, PDA may be associated with a critical clinical condition leading to serious complications. The presence of PDA after the seventh day of life was associated with an increased need for respiratory support, both CPAP and mechanical ventilation, increased severity of the respiratory distress syndrome, requiring a longer duration of respiratory support, and increased the hospitalization length. In very preterm infants, PDA presence was also associated with a higher rate of severe complications and death, indicating the need for a careful and proper management of these critical cases in neonatal intensive care units.

Keywords: persistent ductus arteriosus, prematurity, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage

■ INTRODUCTION

Ductus arteriosus (DA), described for the first time by Galen in the first century is an important vascular structure of the fetal circulation, connecting the proximal ascendant aorta to the pulmonary artery root, close to the left pulmonary branch artery [1,2]. After birth, as part of the transition to extra uterine life, the ductus closes due to increased arterial oxygen pressure, decreased pressure of the pulmonary blood flow, decreased concentration of prostaglandin E2, and decreased number of the prostaglandin E2 receptors [3,4]. At term, spontaneous functional closure of DA occurs in 50% of the infants at 24 hours, in 90% of the cases at 48 hours, and in 100% of the cases at 72 hours of life [5,6]. Anatomical closure of the ductus occurs in 2-3 weeks [2]. Closure of DA often fails in preterm infants, mostly due to developmental immaturity [2,6].

The term "patent ductus arteriosus" is an umbrella term covering all physiological and pathological situations related to an open DA [7]. Persistent ductus arteriosus (PDA) defines a patent ductus arteriosus at seventy-two hours after birth [8,9].

In "term infants," PDA occurs in 0.3-4/1000 live births at the end of the neonatal period, representing 5-10% of the congenital heart defects [2,10,11]. Sometimes PDA accompanies congenital ductal-dependent heart defects and closure of the PDA soon after birth may precipitate clinical deterioration [12]. In premature infants, PDA incidence is inversely associated with gestational age (GA) and birth weight (BW), the incidence varying between 20-70% in very low birth weight infants (VLBW) [3,6,8,13-20].

Multiple risk factors have been described in association with PDA such as lower GA and BW [14-16,21,22], chorioamnionitis and neonatal sepsis, [3,15,22-25], maternal diabetes mellitus, [14,26] antepartum hemorrhage, multiple pregnancy, male gender [14], small for gestational age (SGA), [27] lower Apgar scores, need for resuscitation at birth, asphyxia [16], severe respiratory distress syndrome (RDS) [16,22,28,29], excessive fluid administration during the first days of life [30], Furosemide administration [31], decreased platelets number during the first day of life [22,32], oxygen administration [16], lower oxygen saturation targets [33,34], surfactant administration [16,28,35,36], increased duration of mechanical ventilation and respiratory support [22], metabolic acidosis [16], phototherapy [37], and high altitude [6].

In preterm infants, during the neonatal period, PDA is a multifactorial condition, most often concomitant with respiratory distress syndrome, often significantly affecting the haemodynamics and compromising blood flow and oxygenation with short and long-term consequences. In the short term, PDA is associated with decreased blood pressure [5,8], decreased renal function [5], cardiac congestive failure [18,37,38], pulmonary haemorrhage [8,39], apnea and ventilator-dependency [6,38], bronchopulmonary dysplasia (BPD) [5,14,20,21,25,34,41,42], necrotizing enterocolitis (NEC) [8,9,11,19,20,34,39,43,44], intraventricular hemorrhage (IVH) [5,19,20,39,42,45,46], periventricular leukomalacia (PVL) [5], retinopathy of prematurity (ROP), cerebral palsy [24], delayed growth [11], and increased mortality rate [6,34,45,47-50].

The aim of this study was to evaluate the association between the presence of PDA and the severity of the clinical condition in critically ill preterm infants with GA ≤ 32 weeks and severe respiratory distress syndrome at birth.

METHODS

Study population

All preterm infants with GA ≤ 32 weeks admitted to the neonatal intensive care unit (NICU) of the Clinical County Emergency Hospital Sibiu between 1 January 2010 and 31 December 2015 were included in the study. Epidemiological and clinical data were collected from the National Registry for RDS, which is a large Romanian registry that collects epidemiological data, information regarding RDS severity and treatment, and on short-term outcome in preterm infants with GA ≤ 32 weeks.

PDA was considered to exist if ductal flow was visualized by colour Doppler echocardiography after the 7th day of life, irrespective of its caliber and haemodynamic significance. The preterm infants included in the study were divided into two groups, according to the presence of PDA. Group 1 included patients with PDA (n=154), and Group 2 included patients without PDA (n=186). Fifty-one preterm infants who did not survive to discharge (40 from the Group 1 and 11 from the Group 2) were excluded from the analysis, since deaths frequently occurred during the first days of life, before reaching the seven days necessary to define a PDA as a pathological condition.

The following data was extracted from the National Registry:
a) Data related to prenatal period - maternal prenatal conditions, pregnancy complications, antenatal corticosteroid administration, preterm rupture of the membranes, pregnancy type, delivery mode;
b) Clinical characteristics at birth - GA, BW, SGA, gender, Apgar scores at 1 and 5 minutes;
c) Clinical characteristics associated with the critical condition of the preterm infant: birth resuscitation and peripheral oxygen saturation during resuscitation at birth, surfactant administration, need and duration of respiratory support, neonatal sepsis, complications associated with prematurity (bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage, severe retinopathy of prematurity, neonatal sepsis), and death.

BPD was diagnosed if positive-pressure respiratory support with any fraction of inspired oxygen (FiO_2) or

supplemental oxygen were needed at 36 weeks corrected age, since we used continuous positive air pressure (CPAP) with room air for weaning from mechanical ventilation and CPAP was stopped when the patients achieved respiratory stability. All other definitions used for neonatal conditions are based on the Vermont-Oxford Trials Network [51].

The study was conducted in accordance with the principles stipulated in the Declaration of Helsinki. All the subject parents agreed with processing of newborn data and all the study procedures were carried out following approval of the institution where the newborns were treated.

Statistical analysis

Data are reported as values, mean (SD), and percentages. SPSS 10.0 for Windows was used for data analysis. The independent t-test was used for scale variables while Fisher's exact test or chi-square test (where appropriate) were used for the analysis of categorial variables.

Statistical significance was set at α=0.05. The odds ratio was calculated, and confidence intervals (CI) of 95% were used.

■RESULTS

During the study period, 391 preterm infants with GA≤32 weeks were admitted in the neonatal intensive care unit of the Clinical County Emergency Hospital Sibiu, of whom 194 were diagnosed with PDA (49.6%). From the 340 preterm infants who survived to day seven postpartum, 154 were diagnosed with PDA after the seventh day while in 186 infants, PDA was not identified by echocardiography. For the purpose of the study, data of the preterm infants surviving up to discharge was analyzed.

A. Prenatal characteristics of the study populations

The presence of PDA was associated with a decreased rate of prolonged rupture of the amniotic membranes and decreased gestational age at prenatal corticosteroid prophylaxis (Table 1). No significant differences were seen between infants with and without PDA as regards the presence and types of complications during pregnancy, pregnancy type, delivery mode, and antenatal corticosteroid therapy (Table 1).

B. Clinical characteristics at birth in the study population

The mean GA in Group 1 was significantly lower than the mean GA in Group 2 (p<0.0001)], as was true the mean

Table 1. Maternal, pregnancy and delivery data

	Group 1 (PDA)		Group 2 (no PDA)		p	HR [95% CI]
	No.	Value	No.	Value		
Corticosteroid therapy						
Prenatal corticosteroids (n/%)	154	82 (53.2)	186	104 (55.9)	0.624	0.89[0.58-1.38]
Complete course (n/%)	82	49 (59.2)	104	73 (70.2)	0.138	0.63[0.34-1.16]
Number of doses (mean±SD)	82	2.6±1.3	105	2.5±1.3	0.699	-
Time elapsed from initiation of corticosteroid prophylaxis to delivery (hours) (mean±SD)	82	11.4±22.1	104	15.6±34.4	0.341	-
Complications during pregnancy						
Any complication (n/%)	154	33 (21.4)	186	35 (18.8)	0.550	1.18[0.69-2.00]
Diabetes mellitus (n/%)	154	0 (0)	186	1 (0.5)	-	-
Antenatal hemorrhage (n/%)	154	6 (3.9)	186	3 (1.6)	0.193	2.47[0.61-10.06]
Pregnancy-induced hypertension (n/%)	154	10 (6.5)	186	13 (7.0)	0.857	0.92[0.39-2.17]
Eclampsia (n/%)	154	0 (0)	186	4 (2.2)	-	-
Chorioamnionitis (n/%)	154	0 (0)	186	4 (2.2)	-	-
Type of pregnancy						
Multiple pregnancy (n/%)	154	48 (31.2)	186	44 (23.7)	0.121	1.46[0.90-2.36]
Second twin (n/%)	48	29 (60.4)	44	25 (56.8)	0.730	1.16[0.50-2.66]
ART pregnancy (n/%)	154	9 (5.8)	186	6 (3.2)	0.243	1.86[0.65-5.35]
Delivery						
Rupture of the amniotic membranes > 18 hours (n/%)	154	28 (18.2)	186	52 (28.0)	0.034	0.57[0.34-0.96]
Cesarean section (n/%)	154	48 (31.2)	186	48 (25.8)	0.276	1.30[0.81-2.09]

Legend: SD- standard deviation, ART- assisted reproductive techniques

BW [p<0.0001)] (Table 2). No significant differences were seen between Group 1 and Group 2 with regards to gender, ponderal index, and SGA status (Table 2).

Group 1 had lower Apgar scores at one and ten minutes, but no significant difference was found between groups regarding the need for resuscitation at birth (Table 3). Interestingly, despite having similar mean peripheral oxygen saturations during resuscitation, Group 2 infants received significantly increased oxygen concentrations at birth (Table 3).

C. Severity of the clinical condition in the critically ill preterm infants

The severity of RDS was increased in Group 1 as compared to Group 2. Group 1 presented a significantly higher need for surfactant administration (p<0.0001) and respiratory support [p=0.019], and Continuous Positive Airways Pressure (CPAP) and mechanical ventilation [p=0.004] Duration of respiratory support was also significantly increased in the Group 1 for CPAP and for mechanical ventilation. p<0.0001) (Table 3).

Premature infants in Group1 had significantly increased rates of bronchopulmonary dysplasia (BPD) (p=0.002, HR 2.94), intraventricular hemorrhage (IVH) (p=0.050, HR 1.56), and severe retinopathy of prematurity (ROP)(p=0.056). No significant associations were found between PDA and neonatal sepsis and necrotizing enterocolitis (NEC). The presence of PDA was also associated with a significantly increased rate of death (20.6% vs. 5.6%, p<0.0001, HR 4.39). No difference was found between the study groups as regards necrotizing enterocolitis, periventricular leukomalacia, or severe retinopathy of prematurity. Both early and late onset sepsis were recorded to a greater extent in

Table 2. Neonatal characteristics

	Group 1 (PDA)		Group 2 (no PDA)		p	HR [95% CI]
	No.	Value	No.	Value		
Gestational age (weeks) (mean±SD)	154	29.7±2.0	186	30.4±1.7	0.0001	-
Birthweight (g) (mean±SD)	154	1297.4±327.6	186	1458.0±317.4	0.0001	-
Male gender (n/%)	154	86 (55.8)	186	101 (54.3)	0.777	1.06[0.69-1.63]
Ponderal index (mean±SD)	154	1.96±0.33	186	1.95±0.32	0.596	-
SGA (n/%)	154	84 (54.5)	186	102 (54.8)	0.957	0.99[0.64-1.52]

Legend: SD- standard deviation, SGA- small for gestational age

Table 3. Neonatal status at delivery and respiratory distress syndrome

	Group 1 (PDA)		Group 2 (no PDA)		P	HR [95% CI]
	No.	Value	No.	Value		
Birth resuscitation						
Need for resuscitation at birth (n/%)	154	98 (63.6)	186	121 (65.1)	0.787	0.94[0.60-1.74]
FiO2 during resuscitation (%) (mean±SD)	98	84.8±29.7	121	92.5±22.8	0.030	-
Peripheral oxygen saturation during resuscitation	93	88.1±4.9	106	89.0±5.3	0.221	-
Apgar scores at 1 minute (mean±SD)	151	6.3±2.0	185	6.7±1.8	0.022	-
Apgar scores at 5 minutes (mean±SD)	146	7.6±1.4	178	7.8±1.1	0.087	-
Apgar scores at 10 minutes (mean±SD)	140	8.0±0.9	164	8.4±0.7	0.0001	-
Apgar scores at 20 minutes (mean±SD)	28	8.2±0.6	68	8.2±0.7	0.880	-
Respiratory distress syndrome management						
Need for surfactant administration (n/%)	154	66 (42.9)	186	46 (24.7)	0.0001	2.28[1.44-3.62]
Surfactant dose (mg/kg)(mean±SD)	66	166.4±33.6	46	171.8±31.5	0.398	-
INSURE strategy (n/%)	154	51 (33.1)	186	35 (18.8)	0.002	2.14[1.30-3.51]
Need for oxygen therapy (n/%)	154	139 (90.3)	186	168 (90.8)	0.863	0.94[0.45-1.94]
Oxygen therapy length (days) (mean±SD)	139	19.0±34.5	168	8.4±14.5	0.0001	-
Need for CPAP (n/%)	154	149 (96.8)	186	168 (90.3)	0.019	3.19[1.16-8.81]
CPAP support duration (days) (mean±SD)	149	7.6±7.5	169	5.1±3.8	0.0001	-
Need for mechanical ventilation (n/%)	154	34 (22.1)	168	20 (10.8)	0.004	2.35[1.29-4.29]
Duration of mechanical ventilation (days) (mean±SD)	34	20.1±22.5	20	12.0±15.7	0.0001	-

Legend: FiO2- fraction of inspired oxygen, SD- standard deviation, INSURE- INtubate-SURfactant-Extubation on continuous positive airway pressure support strategy, CPAP- continuous positive airway pressure

Table 4. Complications during hospitalization

	Group 1 (PDA)		Group 2 (no PDA)		p	HR [95% CI]
	No.	Value	No.	Value		
Bronchopulmonary dysplasia (n/%)	154	26 (16.9)	186	12 (6.5)	0.002	2.94[1.43-6.06]
Necrotizing enterocolitis (n/%)	154	3(1.9)	186	1 (0.5)	0.231	3.67[0.38-3.57]
Intraventricular hemorrhage (n/%)	154	62 (40.3)	186	56 (30.1)	0.050	1.56[0.99-2.45]
Periventricular leukomalacia (n/%)	154	6 (3.9)	186	4 (2.2)	0.344	1.84[0.51-6.66]
Severe retinopathy of prematurity (n/%)	154	3 (1.9)	186	0 (0)	0.056	-
Early onset sepsis (n/%)	154	25 (16.2)	186	20 (10.8)	0.138	1.61[0.85-3.02]
Late onset sepsis (n/%)	154	21 (13.6)	186	27 (14.5)	0.817	0.93[0.50-1.72]
Any infection (n/%)	154	46 (29.8)	186	47 (25.2)	0.831	1.05[0.65-1.70]
Hospitalization length (days) (mean±SD)	154	52.9±26.4	186	44.1±18.5	0.0001	-
Death (n/%)	194	40 (20.6)	197	11 (5.6)	0.0001	4.39[2.18-8.85]

Legend: SD- standard deviation.

the Group 1 than Group 2 (16.2% vs. 10.8% for early onset sepsis and 13.6% vs. 14.5% for late-onset sepsis). However, the differences were not statistically different. The presence of PDA was also associated with a significantly increased rate of death in Group 1 than Group 2 (p<0.0001), (Table 4).

■ Discussions

In preterm infants, PDA is diagnosed significantly more often than in term infants, 40-60% according to gestational age in preterm infants [17,18,49] versus 57/10.000 live births in term infants [7,20], and is associated with considerably increased morbidity and mortality [14]. Functional closure of DA in preterm infants with GA≥30 weeks gestation occurs towards the fourth day of life, while in those with GA<30 weeks or with RDS the incidence of PDA is about 65% [5,19,51]. Instead of analyzing only infants with significant PDA we have chosen to define and analyze PDA only if the ductus was seen on echocardiography after the first week of life. Therefore, the incidence reported in our study corresponds to data reported in the literature.

Patent ductus arteriosus, associated risk factors and clinical presentation at birth in very preterm infants

Among the factors significantly influencing the persistence of DA, GA is the most often cited. [3,6,13-16,20,21,52] Koch et al. [19] evaluated the direct relationship between GA and spontaneous closure of DA showing that for each gestational week after 23 weeks, the odds for spontaneous closure of the ductus increases with a ratio of 1.5. Studies also demonstrate that the incidence of PDA increases with a decrease in

BW [3,6,13-16,19,24,42,43,52,53]. In our study, in accordance with published data, infants with PDA had significantly lower mean BW and GA (p<0.05).

Male gender was reported by Hammoud et al. as a risk factor for PDA. However, in accord with Nizarali et al. the current results found no difference between the study groups regarding gender [14,16]. Nor was any difference found between infants with and without PDA when comparing the mean ponderal index and the proportions of SGA infants even though SGA was reported in other studies as a risk factor for PDA [27,49].

Prenatal corticosteroid prophylaxis decreases the risk for PDA [14,16,49,54,55], even if administered after chorioamnionitis [24]. In the present study, similar proportions of infants with and without PDA received prenatal corticosteroids, and even if more infants received a complete course, the difference between the two groups was not significant p>0.050. This may also be explained by the similar mean number of corticosteroid doses and by the insignificant difference between mean time elapsed from prophylaxis initiation to delivery.

Diabetes mellitus was reported by Hammoud et al. as a risk factor for PDA in preterm infants aged < 34 weeks gestation [14]. They also found that antepartum haemorrhage occurred more often in premature infants with PDA. Many studies linked chorioamnionitis to PDA in preterm infants [3,15,23-25,56]. In these cases, inflammation increases cyclo-oxygenase activity and prostaglandin E2 production causing PDA [56]. Pregnancy-induced hypertension and eclampsia are associated with decreased incidence of PDA as these conditions are characterized by accelerated pulmonary

maturation [14,15,57]. We have found no difference between preterm infants with and without PDA when analyzing the complications during pregnancy: diabetes mellitus, antenatal hemorrhage, pregnancy-induced hypertension, eclampsia, and clinical chorioamnionitis. Most probably these results are due to the small number of complications noted in the present study. Also, only cases of clinical chorioamnionitis were considered, as data regarding histological amnionitis were not available. In a meta-analysis comprising 23 studies and 17.708 preterm infants, Park et al. showed a lack of association between PDA and clinical chorioamnionitis [24].

The study performed by Hammoud et al. was the only one found that reported an association between PDA and multiple pregnancies [14]. They indicated that a multiple pregnancy has four times the risk of PDA. We also found PDA more often in preterm infants from multiple pregnancies, 31.2 versus 23.7%, but the difference was not significant. The PDA incidence was similar in the second twin in both study groups.

No information was found in the literature with regards to associations between PDA and assisted reproductive techniques or delivery mode. The current study data shows that very preterm infants conceived using assisted reproductive techniques may have an increased incidence of PDA compared to those naturally conceived (p>0.05). In larger preterm infants, delivery by cesarean section is associated with an increased risk of PDA [58]. A similar trend was seen in our groups of very preterm infants, but the difference was not statistically significant. A more detailed analysis of the reasons for performing cesarean section may reveal why PDA is more often seen in preterm infants delivered by cesarean section compared to vaginal birth.

Hypoxia and low Apgar scores were associated with increased incidence of PDA [16,59]. Compared to preterm infants without PDA, Group1compared to Group 2 in the present study had significantly lower mean Apgar scores at 1 and 10 minutes, lower scores at 5 minutes, and similar scores at twenty minutes.

Patent ductus arteriosus and resuscitation at birth in very preterm infants

The need for resuscitation at birth was cited by Nizarali et al. as a risk factor for PDA [16]. There was no difference between Group 1 and Group 2 with regards to the need for resuscitation at birth. This may be due to the continuous change of the resuscitation protocols, according to national and international guidelines, which occurred, during the study period, acceptance of lower oxygen saturations in the first minutes of life, and more extensive use of positive pressure ventilation with T-piece resuscitator in very preterm infants [60]. Nevertheless, we noted that infants without PDA after the first week of life were resuscitated at birth with significantly increased oxygen concentrations (p=0.030) while no difference was seen between the mean peripheral oxygen saturation. It can be speculated that increased FiO_2 during resuscitation may have triggered PDA closure since increased arterial oxygen pressure is one of the most important factors contracting DA [4].

Respiratory distress syndrome and patent ductus arteriosus in very preterm infants

In very preterm infants, one of the most important risk factors for PDA, cited in the literature, is RDS. Pegoli reported a PDA incidence of 80% in preterm infants with RDS and Smith [6] hypothesized that increased circulating prostaglandin E2 concentrations during RDS are responsible for ductus arteriosus persistence [61,62]. In agreement with data reported by other authors, the need for surfactant administration, which is taken to reflect the severity of RDS, was significantly increased in preterm infants with PDA after the first week of life (p=0.000), [16,28,35,36,49]. According to Clyman et al. surfactant alters pulmonary vascular resistance, favouring early left-to-right shunting through the DA [49]. No difference was found between the mean doses of surfactant administered (p=0.398) between the study groups. The increased proportion of preterm infants with PDA treated using the INSURE strategy (INtubate-SURfactant-Extubate on CPAP) is explained only by the appliance of national and European guidelines for RDS treatment recommending a non-invasive approach in preterm infants that do not require assisted ventilation at birth. Similarly, according with current recommendations, a very high proportion of the preterm infants in both study groups were treated using CPAP support, (Table 3) and an increased proportion of infants with PDA needed mechanical ventilation (p=0.004), and mean duration of oxygen therapy, CPAP support, and mechanical ventilation were significantly increased compared to premature infants without PDA (p<0.05) demonstrating that increased severity of RDS is associated with higher risk for PDA after the seventh day of life [16,21,22,60,63] (Table 3).

Numerous studies have demonstrated that PDA significantly influences morbidity and mortality of the very preterm infants. [6,11,43,45,47,63]. In the short term, PDA is associated with arterial hypotension, myocardial dysfunction and systemic perfusion [5,8,38], renal functional disturbances [5,19,39], and pulmonary hemorrhage [40,64,65].

As in other studies the current data showed a significant association between PDA and BPD (p=0.002) (Table 4) [6,9,15,20,21,25,41,42,47,66-69]. An almost similar risk was reported by Marshall et al. in VLBW infants (BW <1500 g) [69]. In preterm infants with RDS, PDA induces an interstitial and alveolar pulmonary edema, decreases pulmonary compliance, increases the need and length of mechanical ventilation and oxygen needs, thus increasing the risk for BPD [5,42].

Patent ductus arteriosus and necrotizing enterocolitis in very preterm infants

Ductus arteriosus persistence was also associated with an increased risk of NEC in very preterm infants, and other studies [11,21,43,44,47,70]. The current study also showed an increased incidence of NEC in preterm infants ≤ 32 weeks gestation, but the low number of NEC cases may explain the lack of significance of this association (Table 4). Predisposition to NEC in preterm infants with PDA is due to diastolic blood stealing from the superior mesenteric artery and abdominal aorta through DA with secondary intestinal hypoperfusion [5,42,43].

Patent ductus arteriosus, intraventricular hemorrhage and periventricular leukomalacia in very preterm infants

A significant PDA also affects the cerebral blood flow, mostly during diastole, a possible pathway for IVH and PVL [42,46]. A link between PDA and IVH has been reported in many studies, as in the current report where there was an increased risk for IVH in Group 1 compared to Group 2 [20,40,46,47,68] (Table 4).

Patent ductus arteriosus and severe retinopathy of prematurity in very preterm infants

Only one study reporting a significant association between PDA and ROP was found in the literature, but after adjusting for GA, the association was attributed only to GA [72]. Only three preterm infants with severe ROP needed laser therapy during the current study period. Since the mean GA and BW were significantly lower in Group 1, it may be concluded that GA and BW are important contributory factors.

Patent ductus arteriosus and sepsis in very preterm infants

Even though some authors reported an increased incidence of PDA in preterm infants with early and late neonatal infections, no correlation between the incidence of PDA and neonatal infections even if early and late infections were aggregated, (p>0.05) despite the fact that higher proportions of preterm infants with PDA developed early neonatal sepsis and any neonatal sepsis [3,25] (Table 4).

Mortality associated with patent ductus arteriosus in very preterm infants

The death rate is significantly increased in preterm infants with PDA, increasing with decreasing GA and in association with lack of antenatal corticosteroid prophylaxis [53].

This is a similar risk of death in preterm infants ≤32 weeks gestation with PDA after the first week of life and a significantly increased mean duration of hospitalization, (p<0.05) as reported in the current study (Table 4). Significantly lower GA, BW, more severe RDS, more frequent severe complications of prematurity, BPD, NEC, IVH, ROP, are significant contributors to the increased rate of death and prolonged hospitalization and PDA was associated with all these factors in our study.

Considerations related to study protocol

The classic definition of PDA implies failed closure of DA after 72 hours of life [8,9]. Most of the studies in the literature evaluated risk factors only haemodynamically significant PDA and its influence on neonatal morbidity and mortality. We have chosen to evaluate the clinical and pathological correlations of PDA after the first week of life, regardless of size and hemodynamic influence, in very preterm infants (≤32 weeks gestation). However, we have found the same clinical associations, lower GA and BW, lower Apgar scores, severe RDS including need for surfactant administration and respiratory support, prolonged oxygen therapy and respiratory support (both CPAP and mechanical ventilation) - and pathological correlations - BPD, IVH, severe ROP, and death - as demonstrated by others in evaluating hemodynamically significant PDA in very preterm infants.

In agreement with previous studies the current study reported, in very preterm infants, the same clinical associations, i.e. lower GA and BW, lower Apgar scores, severe RDS the need for surfactant administration and respiratory support, prolonged oxygen therapy and respiratory support, with pathological states i.e. - BPD, IVH, severe ROP, and death.

More studies are needed, most probably stratified on gestational age, to identify the most important risk factors for each GA and to develop more successful management strategies, to more clearly define which preterm infants need treatment, the best moment for therapeutic interventions, and the best therapeutic approach for a better long-term outcome. Interventional strategies for prevention of unfavorable outcome of PDA in very preterm critically ill infants must also focus on clinical and pathological correlations of PDA not only on PDA prophylaxis and therapy.

■ Conclusions

In very preterm infants, delivered at ≤ 32 gestational weeks, PDA can be associated with a critical clinical condition leading to serious complications. The presence of PDA after the 7th day of life is associated with an increased need for respiratory support, both by CPAP and mechanical ventilation and an increased severity of the respiratory distress syndrome, requiring a longer duration of respiratory support and prolonging the hospitalization length. In very preterm infants, PDA is also associated with significantly higher rates of severe prematurity associated complications and death, indicating the need for a careful and appropriate management of these critical cases in the neonatal intensive care units.

■ Disclosure of conflicts of interest

None to declare

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