PERSISTENT DUCTUS ARTERIOSUS – AN IMPORTANT RISK FACTOR FOR NEONATAL MORBIDITY AND MORTALITY IN VERY LOW BIRTH WEIGHT PRETERM INFANTS

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Abstract

Introduction: Ductus arteriosus (DA), an important vascular structure during fetal life, persists with increased incidence in preterm infants as gestational age (GA) and birth weight (BW) decreases and significantly alters the neonatal course. Severe perinatal complications of prematurity are occurring more often in association with persistent ductus arteriosus (PDA), increasing the neonatal mortality rate and negatively affecting the long-term outcome. *Aim:* To evaluate the impact on neonatal morbidity and mortality of PDA in very low birth weight preterm infants (VLBW) with GA ≤ 32 weeks. *Material and methods:* All VLBW 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 in the National Registry for Respiratory Distress Syndrome and comparatively analyzed using SPSS 10.0 for Windows; p was considered statistically significant if < 0,05 (confidence interval 95%). *Results:* 391 preterm infants with GA ≤ 32 weeks were admitted in the NICU, of whom 262 had BW ≤ 1500g. Of the 262 VLBW infants forming the study group 151 were diagnosed with PDA (57.3%). VLBW preterm infants with PDA had significantly lower GA and birth weights (p<0.05), were more often outborn (p=0.008, OR 2.26), and had significantly lower Apgar scores at 1, 5, and 10 minutes (p<0.05). Also, they needed more often surfactant (p=0.010, OR 1.92), mechanical ventilation (p=0.001, OR 2.59), longer oxygen therapy, and respiratory support (p<0.05). VLBW preterm infants with PDA had increased rates of bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), severe intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and severe retinopathy of prematurity (ROP) (p>0.05) but only the association with NEC was statistically significant (p=0.012, OR 5.57). Also, PDA was associated with increased risk of death in VLBW preterm infants (p=0.001, OR 3.40). Persistence of DA was associated with increased risk for unfavorable long term outcome as revealed by the association with a composite outcome comprising BPD, NEC, severe IVH, PVL, ROP, and death) - p=0.000, OR 2.81. No significant associations were found between PDA and neonatal sepsis. *Conclusion:* In accordance with data in the literature, PDA occurred in more than half of the VLBW infants and was associated with lower GA and BW, lower Apgar scores, and more severe respiratory distress syndrome. Also, PDA was associated with an increased incidence of neonatal mortality and increased the rates of the most severe complications of prematurity, increasing significantly the risks for unfavorable long-term outcome.

Key words: persistent ductus arteriosus, prematurity, very low birth weight infants, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, neonatal mortality.

Introduction

Ductus arteriosus (DA) is an important vascular structure connecting the proximal ascending aorta with the root of the pulmonary artery, close to the left pulmonary artery origin[1]. Closure of DA the is an important process of the cardiovascular and pulmonary adaptation process after birth, influenced by many factors: increased arterial oxygen pressure, decreased pressure of the pulmonary blood flow, decreased concentrations of prostaglandin E2, and decreased number of prostaglandin E2 receptors are favoring the contraction of DA while hypoxia, acidosis, increased pulmonary resistance, increased sensibility to vasodilator effect of prostaglandin E2 and nitric oxide, down regulation of their receptors, and increased volume of fluids administered during the first days of life are hindering DA contraction[2-4]. Spontaneous functional closure of the DA occurs in 50% of the cases at 24 hours, in 90% of the cases at 48 hours, and in almost 100% of the cases at 72 hours of life in term infants[1,5], while anatomical closure is accomplished in about 2-3 weeks[1]. Failure of DA closure in preterm infants is attributed mostly to developmental immaturity[1,6].

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The term "patent ductus arteriosus" is assigned to describe both physiological and pathological situations when DA is open while the term "persistent ductus arteriosus" (PDA) defines a patent DA after the first 72 hours of life[7,8].

An incidence of 0.3-4/1000 live births at the end of the neonatal period was reported for PDA in infants delivered at term, representing 5-10% of all congenital heart defects[1,9]. A much higher incidence of PDA is reported in preterm infants, the rates increasing as GA and BW are decreasing[6], varying between 20-70% in very low birth weight infants (VLBW)[2,7,10-22].

In preterm infants, PDA is a multifactorial condition often affecting significantly the neonatal development, influencing hemodynamics by compromising the blood flow and oxygenation of all organs and systems. Decreased blood pressure with subsequent hypotension[7,23], renal dysfunction[24], cardiac congestive failure[17,18,25], pulmonary hemorrhage[7,21,26], apnea and prolonged duration of mechanical ventilation[25,27], feeding intolerance[6,9] are cited as effects of PDA during the first days of life, effects that are significantly contributing to increased rates of bronchopulmonary dysplasia (BPD)[7,19,22,25,26,28-34], necrotizing enterocolitis (NEC)[2,7-9,17-19,22,32,33,35-37], intraventricular hemorrhage (IVH)[17-20,22,32,33], periventricular leukomalacia (PVL)[38], retinopathy of prematurity (ROP)[39], and death[19,22,23,32,40-43]. On long-term, these severe conditions associated with prematurity are associated with increased risk for neurodevelopmental deficits and cerebral palsy[6,16,20,22,32,42] and delayed physical growth[9].

Unfortunately, currently there is no consensus as regards the management of PDA in preterm infants as most of the studies evaluating the influence of different therapeutic strategies - conservative management (including fluid restriction during the first days of life, waiting for spontaneous DA closure, and treatment of large PDA significantly influencing the respiratory support), early, presymptomatic or symptomatic pharmacological treatment, or surgical ligation[11] - showed that some therapeutic strategies may decrease the rate of conditions associated with PDA (BPD, NEC, IVH, ROP) and death but have no influence on long-term outcome of these infants[33,42,44-48]. Therefore, a better understanding of PDA influence on the preterm infants development is still needed in order to decrease its impact on short and long term prognosis.

Material and methods

All preterm infants with BW ≤ 1500 g (VLBW) and GA ≤ 32 weeks admitted to the neonatal intensive care unit (NICU) of the Clinical County Emergency Hospital Sibiu, a regional level III unit, between 1 January 2010 and 31 December 2015 were included in the study. Epidemiological and clinical data were collected retrospectively for 2010 and prospectively in 2011 in the National Registry for RDS. PDA was considered if ductal flow was visualized by color Doppler echocardiography after the 7th day of life, irrespective of its caliber and hemodynamic significance. The Romanian National Registry for RDS prospectively collects epidemiological data, information regarding birth, RDS severity and treatment, and on short term outcome in preterm infants with GA ≤ 32 weeks. For the present study we extracted and analyzed the following information: a) prenatal - maternal prenatal conditions, pregnancy complications, antenatal corticosteroid administration, preterm rupture of the membranes, pregnancy type, delivery mode, presentation; b) neonatal characteristics and data - GA, BW, ponderal index, SGA, gender, Apgar scores at 1 and 5 minutes, birth resuscitation and peripheral oxygen saturation during resuscitation at birth, surfactant administration, need and duration of oxygen therapy and respiratory support, neonatal sepsis, complications associated with prematurity (BPD, NEC, IVH, PVL, ROP, apnea of prematurity, neonatal sepsis), and death. All definitions used for neonatal conditions are based on the Vermont-Oxford trials network[49] except for BPD. 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. This definition was chosen since the protocol of our unit includes using continuous positive air (CPAP) pressure with room air as the method of choice for weaning from mechanical ventilation and CPAP is stopped when the patient achieves respiratory stability.

The VBLV preterm infants included in the study were divided into two groups: with and without PDA. Data are reported as values, mean values, standard deviations (SD), and percentages. SPSS 10.0 for Windows was used for data analysis. 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. A $p < 0.05$ was considered statistically significant. Odds ratio were calculated using confidence intervals (CI) of 95%.

Results

During the 6 years 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 262 had BW ≤ 1500 g (VLBW) and comprised the final study group. The VLBW preterm infants in the study group had a mean GA of 28.8 ± 2.2 weeks (23-32 weeks gestation) and a mean BW of 1138.3 ± 243.7 g (500-1500 g). Of these 262 VLBW preterm infants 151 were diagnosed with PDA (57.3%) after the seventh day of life.

The mean GA of the preterm infants diagnosed with PDA was significantly lower than the mean GA of those without PDA - 28.5 ± 2.3 weeks versus 29.3 ± 1.9 weeks -, and significantly lower BW - 1085.4 ± 259.8 g versus 1210.2 ± 199.6 g - (Table 1). Presence of PDA was associated with decreased rate of prolonged rupture of the amniotic membranes (> 18 hours) and decreased gestational age at prenatal corticosteroid prophylaxis (Table 2). No significant differences were seen between infants with and without PDA as regards the gender, ponderal index, SGA status, presence and types of complications during

pregnancy, pregnancy type, delivery mode, and antenatal corticosteroid therapy (Table 2). A more than 2 fold increased risk for PDA was noted in association with delivery in lower grade hospitals and neonatal transfer to our level III unit after birth (Table 2). Lower Apgar scores at 1, 5 and 10 minutes were found in VLBW preterm infants with PDA but no significant difference was found between groups regarding the need for resuscitation at birth (Table 3). No differences were noted as regards the mean peripheral oxygen saturations and oxygen concentrations used during resuscitation at birth (Table 3). Severity of RDS was increased in very preterm infants with PDA, as revealed by increased need for surfactant administration and for mechanical ventilation, and prolonged length of CPAP respiratory support and oxygen therapy, although no difference in the need for oxygen therapy (Table 3). Severe conditions associated with prematurity as BPD, IVH grade III and IV, PVL grad II or III, ROP (requiring laser therapy) occurred more often in VLBW preterm infants but the stronger correlation was found between PDA and NEC and apnea of prematurity (Table 4). Also, presence of any of BPD, severe IVH, severe PVL, and severe ROP - conditions associated with unfavorable neurodevelopmental outcome - was associated with DA persistence (Table 4). No difference was found between the study group as regards neonatal sepsis, irrespective of the onset (Table no.4). PDA was also associated with a significantly increased rate of death (Table no. 4).

Table 1. Neonatal characteristics.

	No PDA		PDA		p	OR [95% CI]
	No.	Value	No.	Value		
Gestational age (weeks) (mean±SD)	111	29.3±1.9	151	28.5±2.3	0.003	-
Birth weight (g) (mean±SD)	111	1210.2±199.6	151	1085.4±259.8	0.000	-
Male gender (n/%)	111	55 (49.5)	151	86 (57.0)	0.236	1.35[0.82-2.20]
Ponderal index (mean±SD)	111	1.95±0.31	151	1.97±0.35	0.620	-
SGA (n/%)	111	64 (57.7)	151	84 (55.6)	0.745	0.92[0.56-1.51]

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

Table 2. Maternal, pregnancy and delivery data.

	No PDA		PDA		p	OR [95% CI]
	No.	Value	No.	Value		
Corticosteroid therapy						
Prenatal corticosteroids (n/%)	111	63 (56.8)	151	72 (47.7)	0.148	0.69[0.42-1.14]
Complete course (n/%)	63	25 (39.7)	72	29 (40.3)	0.944	0.97[0.49-1.95]
Number of doses (mean±SD)	63	2.7±1.3	72	2.6±1.3	0.570	-
Gestational age at corticosteroid prophylaxis (weeks) (mean±SD)	63	29.4±1.6	72	28.1±2.2	0.000	-
Time elapsed from initiation of corticosteroid prophylaxis to delivery (hours) (mean±SD)	63	14.8±24.5	72	18.5±39.4	0.528	-
Complications during pregnancy						
Any complication (n/%)	111	23 (20.7)	151	30 (19.9)	0.866	0.95[0.52-1.74]
Diabetes mellitus (n/%)	111	1 (0.9)	151	0 (0)	-	-
Antenatal hemorrhage (n/%)	111	3 (2.7)	151	5 (3.3)	0.778	1.23[0.29-5.27]
Pregnancy-induced hypertension (n/%)	111	10 (9.0)	151	12 (7.9)	0.760	0.87[0.36-2.10]
Eclampsia (n/%)	111	3 (2.7)	151	1 (0.7)	0.185	0.24[0.02-2.34]
All types of maternal hypertension (n/%)	111	10 (2.7)	151	13 (10.2)	0.991	0.99[0.42-2.3]
Chorioamnionitis (n/%)	111	4 (3.6)	151	1 (0.7)	0.086	0.18[0.02-1.62]
Type of pregnancy						
Multiple pregnancy (n/%)	111	34 (30.6)	151	49 (32.5)	0.756	1.09[0.64-1.84]
Second twin (n/%)	34	18 (52.9)	49	28 (5.1)	0.709	1.18[0.49-2.86]
ART pregnancy (n/%)	111	5 (4.5)	151	5 (3.3)	0.620	0.73[0.20-2.57]
Delivery						
Outborn (n/%)	111	18 (16.2)	151	46 (30.5)	0.000	2.26[1.23-4.17]
Rupture of the amniotic membranes > 18 hours (n/%)	111	36 (32.4)	151	21 (13.9)	0.000	0.34[0.18-0.62]
Cesarean section (n/%)	111	35 (31.5)	151	41 (27.2)	0.442	0.81[0.47-1.38]

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

Table 3. Neonatal status at delivery and respiratory distress syndrome.

	No PDA		PDA		p	OR [95% CI]
	No.	Value	No.	Value		
Birth resuscitation						
Need for resuscitation at birth (n/%)	111	80 (72.1)	151	115 (76.2)	0.456	1.24[0.71-2.16]
FiO_2 during resuscitation (%) (mean±SD)	79	86.9±28.8	115	91.4±23.5	0.228	-
Peripheral oxygen saturation during resuscitation	68	87.5±9.5	106	85.2±8.5	0.105	-
Apgar score at 1 minute (mean±SD)	110	6.2±2.1	148	5.5±2.2	0.007	-
Apgar score at 5 minutes (mean±SD)	106	7.5±1.5	145	6.9±1.5	0.011	-
Apgar score at 10 minutes (mean±SD)	98	8.2±0.9	141	7.7±1.2	0.001	-
Apgar score at 20 minutes (mean±SD)	40	7.7±0.9	32	7. ±1.4	0.539	-
Respiratory distress syndrome management						
Need for surfactant administration (n/%)	111	46 (41.4)	151	87 (57.6)	0.010	1.92[1.17-3.16]
Surfactant dose (mg/kg)(mean±SD)	46	168.5±36.6	87	170.2±32.8	0.783	-
INSURE strategy (n/%)	111	33 (29.7)	151	62 (41.1)	0.060	1.65[0.98-2.77]
INSURE failure (n/%)	33	9 (27.3)	62	34 (54.8)	0.010	3.24[1.30-8.08]
Need for oxygen therapy (n/%)	111	107 (96.4)	151	144 (95.4)	0.682	0.77[0.22-2.69]
Oxygen therapy length (days) (mean±SD)	107	11.6±17.5	144	21.5±36.3	0.010	-
Need for CPAP (n/%)	111	106 (95.5)	151	142 (94.0)	0.606	0.74[0.24-2.28]
CPAP support duration (days) (mean±SD)	106	6.1±4.7	142	8.1±7.9	0.028	-
Maximum FiO2 on CPAP (%) (mean±SD)	106	45.6±23.4	142	48.0±22.8	0.406	-
Maximum PEEP on CPAP (mmHg) (mean±SD)	106	6.3±0.3	142	6.3±0.3	0.979	-
Need for mechanical ventilation (n/%)	111	22 (19.8)	151	59 (39.1)	0.001	2.59[1.47-4.59]
Duration of mechanical ventilation (days) (mean±SD)	22	11.3±15.2	59	15.1±21.2	0.439	-

Legend: FiO_2 - fraction of inspired oxygen, SD - standard deviation, INSURE - INtubate-SURfactant-Extubate, CPAP - continuous positive airway pressure, PEEP - positive end-expiratory pressure

Table 4. Complications during hospitalization.

	No PDA		PDA			
	No.	Value	No.	Value	p	OR [95% CI]
Bronchopulmonary dysplasia (n/%)	111	13 (11,7)	151	28 (18,5)	0.134	1,71[0,84-3,49]
Apnea of prematurity (n/%)	111	17 (15.3)	151	41 (27.2)	0.023	2.06[1.10-3.86]
Necrotizing enterocolitis (n/%)	111	2 (1.8)	151	14 (9.3)	0.012	5.57[1.24-25.03]
Intraventricular hemorrhage (n/%)	111	40 (36.0)	151	70 (46.4)	0.095	1.53[0.93-2.53]
Severe intraventricular hemorrhage (n/%)	111	4 (3.6)	151	13 (8.6)	0.105	2.52[0.80-7.95]
Periventricular leukomalacia (n/%)	111	3 (2.7)	151	7 (4.6)	0.422	1.75[0.44-6.92]
Severe retinopathy of prematurity (n/%)	111	0 (0)	151	3 (2)	-	-
Early onset sepsis (n/%)	111	16 (14.4)	151	30 (19.9)	0.253	1.47[0.76-2.86]
Late onset sepsis (n/%)	111	20 (18.0)	151	24 (15.9)	0.651	0.86[0.45-1.65]
Any neonatal sepsis (n/%)	111	35 (31.5)	151	50 (33.1)	0.788	1.07[0.64-1.82]
Hospitalization length (days) (mean±SD)	111	48.3±22.1	151	48.6±33.5	0.951	-
Combined severe complications of prematurity (n/%)	111	24 (21.6)	151	66 (43.7)	0.000	2.81[1.62-4.90]
Death (n/%)	111	10 (9.6)	151	38 (25.2)	0.001	3.40[1.61-7.16]

Legend: SD - standard deviation

Severe conditions associated with prematurity as BPD, IVH grade III and IV, PVL grad II or III, ROP (requiring laser therapy) occurred more often in VLBW preterm infants but the stronger correlation was found between PDA and NEC and apnea of prematurity (Table 4). Also, presence of any of BPD, severe IVH, severe PVL, and severe ROP - conditions associated with unfavorable neurodevelopmental outcome - was associated with DA persistence (Table 4). No

difference was found between the study group as regards neonatal sepsis, irrespective of the onset (Table no.4). PDA was also associated with a significantly increased rate of death (Table no. 4).

Discussions

Failure of DA closure is reported significantly more often in preterm infants than in term infants - 40-60% according to gestational age in preterm infants[14-16] versus 57/10.000 live births in term infants[19,50] - and is associated with considerably increased morbidity and mortality[11]. In preterm infants with GA ≥30 weeks gestation, functional closure of DA occurs towards the fourth day of life, while in those with GA <30 weeks or with significant RDS the incidence of PDA is about 65%[5,18,51]. We have chosen to define and analyze PDA only if the ductus was seen on echocardiography after the first week of life even though the classic definition states that PDA defines failed closure of DA after 72 hours of life[7,8] since in our study we did not evaluate the size and hemodynamic significance of the ductus. Therefore, the incidence reported in our study - 57.3% - in VLBW preterm infants includes all types of PDA, irrespective of size (small, moderate, or large) and hemodynamic significance (silent or with significant shunt). In a study on 272 VLBW infants with GA < 30 weeks surviving more than 28 days after birth, Al Nemri[3] reported a PDA incidence of 46% while other reported rates between 21.9 and 33%[7,13,15,18,35]. The difference between the rates reported in the literature and the rate found in our study group may be explained by definition criteria used in our study.

Persistence of DA is a multifactorial condition, but low GA and BW are by far the most often risk factors cited[2,6,9-13,18,19,28,29,35,52-54]. The direct relationship between GA and spontaneous closure of DA was evaluated by Koch et al.[18] who showed that for each gestational week after 23 weeks the odds for spontaneous closure of the ductus increases with a ratio of 1.5. A significantly lower mean BW and GA was associated with PDA in VLBW preterm infants in our study ($p<0.05$) (Table 1), in accordance with data published in the literature.

A higher occurrence rate of PDA in male infants was reported by some authors[11,41] but, in accordance with Nizarali et al.[13] we have found no difference between VLBW preterm infants with and without PDA. In other studies[16,55], SGA status was reported as a risk factor for PDA. Our analysis of the study groups did not revealed any difference between the proportions of SGA infants and the mean ponderal index (Table 1).

Antenatal corticosteroid prophylaxis decreases the risk and severity of RDS[56]. There also studies reporting a decreased risk for PDA after prenatal administration of corticosteroids[11,13,16,57,58]. A relatively small proportion of infants in our groups benefited from antenatal corticosteroid prophylaxis (56.8% of VLBW infants without PDA and 47.7% of infants with PDA) and even smaller proportion of the preterm infants received a complete course of steroids (39.7% of 63 VLBW infants without PDA and 40.3% of those with PDA) (Table 2). This may explain, together with the significantly lower mean GA when corticosteroid prophylaxis was initiated and relatively short interval between rupture of amniotic membranes and birth, and between steroid administration and delivery (Table 2), why antenatal corticosteroid prophylaxis had no influence on PDA occurrence in our study.

Maternal conditions as diabetes mellitus[11], chorioamnionitis[2,12,34,52,59,60], and antenatal hemorrhage[11] were reported in association with increased risk for PDA. Increased immaturity of all organs and systems may explain delayed cardiovascular adaptation with failed closure of DA in infants delivered by mothers with diabetes mellitus[61,62]. We weren't able to analyze such correlations since we had only one VLBW infant born from a pregnancy complicated by maternal diabetes in our study. No difference was found between groups as regards antenatal maternal hemorrhage (Table 2). In chorioamnionitis, inflammation increases cyclo-oxygenase activity and prostaglandin E2 production causing PDA[60] explaining the link found by many authors between chorioamnionitis and PDA[2,12,34,52,59,60]. The limited number of maternal chorioamnionitis registered in our groups and the fact that we considered only cases of clinical chorioamnionitis (since data about histological amnionitis were not available) may explain the lack of correlation between this condition and PDA in our VLBW preterm infants. But, a meta-analysis comprising 23 studies and 17.708 preterm infants done by Park et al.[52] have also shown a lack of association between PDA and clinical chorioamnionitis - OR 1.28 [95%CI 1.00-1.64]. On the contrary, pregnancy-induced hypertension and eclampsia were associated with decreased incidence of PDA[11,12,63], probably due to accelerated fetal pulmonary maturation in these conditions[11]. Even when counting together all types of maternal hypertension - pregnancy-induced or pre-existent - we have found no difference between VLBW infants with and without PDA (Table 2).

We have found in the literature only one study reporting and association between PDA and multiple pregnancy. Hammoud et al.[11] showed a four fold risk for PDA in infants born from multiple pregnancies (OR 3.8 [95%CI 1.5-12.4]). In our groups, no association was found between PDA and multiple pregnancy and birth rank (PDA occurred with similar incidence in the second twin, known to have a more complicated postnatal course than the first one) (Table 2).

No information was found in the literature as regards PDA incidence according to pregnancy type - naturally occurring or by assisted reproductive techniques - and to delivery mode - cesarean section versus vaginal delivery - in VLBW preterm infants. We weren't able to demonstrate that such correlations exists in VLBW preterm infants (Table 2). Delivery in a lower level neonatal unit and postnatal transfer to our unit significantly increased the risk for PDA in VLBW preterm infants - OR 2.26 [95% CI 1.23-4.17] - and this may be explained by a number of factors, including reduced access to modern equipment, lesser experience in carrying VLBW infants (births attended by obstetricians or midwives or pediatricians without neonatal training), lack or

insufficient training in neonatal stabilization and transport, delayed transfer, etc.

In a study of 318 VLBW infants less than 32 weeks gestation, Nizarali et al.[13] identified the need for resuscitation at birth as a risk factor for PDA - OR 13.1[95% CI 3.11-55.1]. As expected, a great proportion of VLBW infants in both our study groups - with and without PDA - required resuscitation procedures at birth (Table no. 3). Continuous adaptation of the resuscitation protocols to national and international guidelines during the study period - as use of lower oxygen concentrations during resuscitation, monitoring of peripheral oxygen saturation, 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 in latest years - may explain our results.

Nevertheless, we noted that VLBW infants without PDA after the first week of life were resuscitated with slightly lower oxygen concentrations. This observation deserves a more detailed approach since currently FiO_2 of 21-30% are recommended for preterm infant's resuscitation[64,65].

An increased incidence of PDA was reported in association with hypoxia and low Apgar scores[13,66]. We have also found that VBLB infants with PDA had significantly lower mean Apgar scores at 1, 5, and 10 minutes ($p<0.05$) (Table 3).

Presence and severity of RDS is an important risk factor for PDA, PDA incidence of 80% being cited by Pegoli[41] in preterm infants with RDS. According to Smith[67], increased circulating prostaglandin E2 concentrations during RDS are responsible for ductus arteriosus persistence. The need for surfactant administration, reflecting in most of the cases the severity of RDS, was significantly increased in VLBW preterm infants with PDA compared to those without PDA ($p=0.010$, OR 1.92[95% CI 1.17-3.16] (Table 3), similar with data reported by other authors[13,16,68-70]. According to Clyman et al.[16], surfactant alters pulmonary vascular resistance, favoring early left-to-right shunting through DA. The administered dose of surfactant did not influenced PDA (Table 3). Compliance to national[71] and European guidelines for RDS treatment[72] - recommending non-invasive approach (INSURE strategy) in preterm infants that do not require assisted ventilation at birth - explains the proportions of VLBW infants treated using INSURE strategy (INtubate-SURfactant-Extubate on CPAP) but association between PDA and INSURE strategy failure ($p=0.010$, OR 3.24 [95% CI 1.30-8.08] may be due to both to a more severe or complicated RDS course or to an improper selection of cases for INSURE strategy. A strong tendency for non-invasive approach to RDS is also demonstrated by the high proportions of VLBW infants treated using CPAP in both study groups (Table 3), according to experts recommendations[72]. Also, biases due to CPAP management were excluded since no difference was found as regards FiO2 and positive end-expiratory pressure (PEEP) used on CPAP support in the study groups (Table 3). Similar with data reported by other authors[13,28,73], a significantly increased proportion of VLBW infants with PDA needed mechanical ventilation ($p=0.001$). Also, VLBW preterm infants had significantly increased duration of oxygen therapy, and CPAP support compared to those without PDA ($p<0.05$) (Table no. 3), all these data suggesting that increased severity of RDS was associated with increased risk for PDA after the first week of life in VLBW preterm infants.

Neonatal morbidity and mortality is significantly influence by PDA in preterm infants, according to numerous studies[6,9,22,32,35,74].During the first days of life, PDA is associated with arterial hypotension, myocardial dysfunction and systemic perfusion[5,7,75], renal functional disturbances[5,17,18], pulmonary hemorrhage[21,76,77], apnea and prolonged duration of mechanical ventilation[11,25,27], and feeding intolerance[10,11].

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[5,29]. Contrary to other studies[6,8,12,19,22,26,28,29-31,33,34,78], we have found no significant association between PDA and BPD ($p>0.05$) (Table no. 4) most probably because most of the cited studies used the classic definition of PDA and evaluated the influence of hemodynamically significant PDA while we included in the study all types of PDA, irrespective of size and hemodynamic significance, diagnosed after the first week of life.

An increased risk for apnea was signaled in preterm infants with PDA in some studies[11,25,27]. In our study, PDA doubled the risk for apnea of prematurity (OR 2.06 [95% CI 1.10-3.86]) (Table 4).

An increased risk for NEC in preterm infants with PDA was reported[9,22,28,37,79] due to diastolic blood stealing from the superior mesenteric artery and abdominal aorta through DA with secondary intestinal hypoperfusion[5,29,35]. Ductus arteriosus persistence was also associated with a 1.8 fold increased risk for NEC in very preterm infants in the study performed by Dollberg et al.[35]. In our batch of VLBW preterm infants, PDA increased the risk for NEC by 5.57 times (Table 4). Different approach to enteral feeding - minimal enteral nutrition, type of milk used, progression of feedings, etc. - may also be responsible for this increased risk for NEC.

Cerebral blood flow is also affected by significant PDA, mostly during diastole[29], a pathway considered responsible for IVH and PVL occurrence[20]. An increased incidence of IVH[19-22,33] and PVL[80] was reported in association with PDA. We have also found an increased rate of IVH and severe IVH (grade III and IV according to Papile[81]) and severe PVL (grade II and III according to deVries[82]) in VLBW preterm infants with PDA compared to those without PDA (Table no. 4) but the numbers failed to reach statistical significance, most probably due to low number of cases.

During the study period, only 3 cases of severe ROP (needing laser therapy) were registered in VLBW infants, all of them diagnosed with PDA and other severe complications

of prematurity, with gestational ages of 24 weeks (1 case) and 27 weeks (2 cases). We found only one study reporting a significant association between PDA and ROP - OR 2.41 [95% CI 1.08-5.38] but after adjusting for GA, the association was attributed only to GA[83]. It is most probably that occurrence of severe ROP in our cases was multifactorial, with a great contribution of GA and co-existent morbidities.

Same as in chorioamnionitis, an increased incidence of PDA was reported in preterm infants with early and late neonatal infections[2,34]. Our analysis showed no correlations between PDA and neonatal infections, analyzed separately or together ($p>0.05$). A trend for increased rate for early neonatal infections was observed in VLBW preterm infants with PDA compared to those without PDA (19.9% versus 14.4%) (Table no. 4).

Persistence of DA in VLBW preterm infants was associated, in our study, with increased risk for unfavorable neurodevelopmental long-term outcome since as revealed by the association with a combined outcome comprising BPD, NEC, severe IVH, PVL, ROP and death) ($p=0.000$, OR 2.81 [95% CI 1.62-4.90]) (Table 4).

Finally, we are reporting an 3.4 fold increased risk for death in VLBW preterm infants with PDA compared to those without PDA after the first week of life. Numerous studies are also demonstrating a significantly increased risk of death in preterm infants with PDA[6,16,22,32,42,84] - 4-8 times higher[22,40] -. Despite the significantly lower GA, BW, the more severe RDS, and the more frequent association with severe complications of prematurity - BPD, NEC, IVH, ROP, apnea of prematurity - no significant differences were seen in the hospitalization length, most because an important number of VLBW infants with PDA died before the first month of life.

Conclusions

Most of the studies in the literature evaluated risk factors only for hemodynamically significant PDA and its influence on neonatal morbidity and mortality, defining PDA as failed closure of DA after the first 72 hours of life. Our choice was to evaluate the impact of PDA on neonatal morbidity and mortality, when PDA was diagnosed after the first week of life, regardless of size and hemodynamic influence, in VLBW preterm infants (≤32 weeks gestation). Comparing the baseline maternal and neonatal characteristics we have found that PDA is associated with significantly lower GA and BW, Apgar scores, and with more severe RDS. Not surprisingly, in VBLW preterm infants, PDA was also associated with increased rates of conditions associated with prematurity - BPD, apnea of prematurity, NEC, IVH, PVL, severe ROP - and death. However, a significantly increased risk was demonstrated only for NEC, apnea of prematurity, and death. The relatively low incidence of BPD, severe IVH, severe PVL, and severe ROP is one plausible explanation for lack of association of PDA with these conditions along with defining PDA in our study.

Correlation of PDA with increased neonatal morbidity and mortality are still unclear: result of the left-to-right shunting, result of PDA treatment or simple consequences of prematurity[35]. Controversies still exists regarding the best management for PDA in preterm infants as most of the studies evaluating the influence of different therapeutic strategies - conservative management (including fluid restriction during the first days of life, waiting for spontaneous DA closure, and treatment of large PDA significantly influencing the respiratory support), early, presymptomatic or symptomatic pharmacological treatment, or surgical ligation[5] - failed to demonstrate an influence on long-term outcome of these infants[33,42,44-48]. More studies are needed to identify pathways for PDA involvement in the occurrence and development of comorbidities associated with prematurity. Also, studies of the most important risk factors, stratified on gestational age, are needed in order to develop more successful management strategies, to more clearly define who and when PDA treatment is needed, and which is the best therapeutic approach for a better long-term outcome. Improvement of the outcome of VLBW preterm infants with PDA must include also successful prophylaxis and therapy of the complications of prematurity.

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