Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 03/07/2018
Approved on: 07/28/2018

ORIGINAL ARTICLE

Epidemiological description of preterm neonates weighing less than 1500 grams with a patent ductus arteriosus

Anelise Maria Fonseca Pinheiro[1], Anna Christina do Nascimento Granjeiro Barreto[2], Melina Tertulino de Lima[3], Fernanda Priscila Soares da Costa Menezes[4], Márcia Silva Moisés Filgueira de Negreiros[4]

Keywords:
Patent Ductus Arteriosus,
Neonatology,
Preterm,
Epidemiology.

Abstract

Objective: To provide an epidemiological description of neonates with very low birth weight diagnosed with patent ductus arteriosus (PDA) at the neonatal intensive care unit (NICU) of a teaching maternity hospital in 2015. **Methods:** This cross-sectional study included the records of neonates admitted to the NICU assessed by a pediatric cardiologist in 2015. The population comprised all neonates weighing less than 1500 grams at birth diagnosed with a PDA with records of prenatal care, epidemiological data, neonatal morbidities, and treatment. Descriptive statistical analysis was performed on software package PSPP version 1.0.1. **Results:** The study enrolled 28 neonates. More than two thirds (67.8%) of the neonates with a PDA weighed less than 1000 grams. Ibuprofen was prescribed to 25% of the neonates to treat PDA. Late-onset sepsis was seen in 89.3% of the patients. Mechanical ventilation was offered to 89.3% of the neonates and 64.2% were dependent on oxygen therapy at the age of 28 days. **Conclusions:** Most of the patients were on mechanical ventilation and most relied on oxygen therapy at the age of 28 days. Prevalence of a PDA was higher in neonates with extremely low birth weight. Few patients required drug therapy. Sepsis was a frequent event in individuals with a PDA. Larger prospective studies are required to refine the assessment of risk factors, treatment, and the short- and long-term morbidity of patients diagnosed with PDA.

[1] Resident Doctor of the Neonatology Program at Maternity School Januário Cicco - MEJC / UFRN.
[2] PhD - Neonatologist at the Januário Cicco School Maternity Hospital of the Federal University of Rio Grande do Norte.
[3] Pediatric Cardiologist - Pediatric Cardiologist at the Januário Cicco School Maternity Hospital of the Federal University of Rio Grande do Norte.
[4] Neonatologist at the Januário Cicco School Maternity Hospital of the Federal University of Rio Grande do Norte.

Correspondence to:
Anelise Maria Fonseca Pinheiro.
Federal University of Rio Grande do Norte, Januário Cicco School Maternity Hospital, Department of Education and Research, Neonatology Residency. Rua Raimundo Chaves, nº 2189, Candelária, bl D, Apto 301, Natal, RN, Brasil. CEP: 59064-390. E-mail: anelisepinheirof@gmail.com

INTRODUCTION

The ductus arteriosus (DA) is a blood vessel present in the developing fetus that bypasses the fetus's non-functioning lungs and diverts blood flow into systemic circulation. During adaptation to postnatal life, pulmonary vascular resistance and pulmonary blood pressure decrease and systemic vascular resistance increases, thereby changing the direction of flow away from the DA and into the aorta and pulmonary artery. This change happens via complex processes involving cord clamping, breathing and alveolar ventilation, production of endogenous mediators in the pulmonary vascular endothelium, etc. In full-term babies and preterm neonates, the DA usually closes within the first week of life. Non-closure of the DA by the end of the first week of life defines the diagnosis of patent ductus arteriosus (PDA).[1,2] Preterm neonates often suffer with late closure of the DA.[3]

PDA is a disorder seen in approximately a third of the neonates with a gestational age at birth (GAB) of less than 30 weeks, with proportions growing to as much as 70% for neonates with a GAB of less than 28 weeks.[4] The primary mechanism at play in preterm neonates is vascular wall immaturity. This finding has been correlated with various comorbidities such as neonatal sepsis and pulmonary hemorrhage, although the causal links between PDA and other conditions have not been clearly established.[5,6]

The Brazilian Neonatal Research Network reported an incidence of 48.5% of PDA in 441 preterm neonates with very low birth weight. The proportion went up to 58% when only neonates weighing less than 1000 grams were considered.[7]

The clinical symptoms seen in preterm neonates are usually unspecific and may have a late onset.[2] Transthoracic echocardiography is the gold standard diagnostic method for PDA, since it is a widely available, painless test that can be carried out on the bedside, in addition to assisting in the definition of which patients will require further treatment, as described by Curty and Castilho.[8]

PDA has been associated with hemodynamic repercussions and increased patient morbidity and mortality. However, little is known about the risks and benefits of the various existing therapies proposed for the condition.[9] The discussion of whether or not patients with a PDA require therapy has involved controversial opinions and ambiguous findings derived from different management options.[10] Clyman et al.[11] argued that therapy to close the DA in neonatal life might not be needed. Harkin et al.[12] found a significant association between treatment for PDA and severe morbidity, with significant increases in cases of severe bronchopulmonary dysplasia (BPD). Despite the reported consequences, more studies are required to define the risks of not treating patients with hemodynamic repercussions.[13]

Although drug therapy with ibuprofen or indomethacin has been prescribed to neonates with PDA and hemodynamic repercussions, reports showing unfavorable neurologic outcomes and increased morbidity as a result of drug therapies or surgery have led to a decrease in the prescription of these drugs in the treatment of PDA.[14] Prophylactic therapy with ibuprofen or indomethacin has been discouraged in view of the high proportion of neonates (60%) experiencing spontaneous closure of the ductus arteriosus and drug side effects. There is no long-term evidence of decreased mortality or impaired neurological development.[2,15]

Ligation may be considered in patients with a large PDA producing hemodynamic repercussions, dependence on mechanical ventilation, and in cases of failed drug therapy. The procedure must be prescribed judiciously, since it has its risks and potential complications.[4] Various studies have associated ligation with development of chronic lung disease regardless of gestational age at birth.[16]

Percutaneous closure of the PDA is a well-established procedure for infants, but more information is needed on populations of preterm neonates with gestational ages of less than 32 weeks.[17,18]

Given the relevance of PDA for preterm neonates, our study aimed to provide an epidemiological description of neonates with the condition to support better planning capabilities and improve the training provided to multidisciplinary care teams involved in the management of patients with a PDA by offering them adequate and up-to-date diagnostic and treatment methods to ultimately improve the care provided to patients with the condition.

METHODS

Study population

Our study included neonates weighing less than 1500 grams diagnosed with a PDA admitted to the NICU of a teaching maternity hospital in the city of Natal, in the state of Rio Grande do Norte, Brazil, in 2015.

Study design

This retrospective observational cross-sectional study included the medical records of every neonate admitted to the NICU of our service and assessed by a pediatric cardiologist in 2015.

Ethical considerations

This study is the continuation of a previous study approved by the Research Ethics Committee of our institution. It was assigned permit no. CAAE 59459116.9.0000.5292.

Exclusion criteria

Patients with congenital heart defects associated to a PDA and individuals with missing information on their medical records were excluded.

Study variables

The patients were described based on the following variables: sex; type of delivery; weight vs. GAB; prenatal prescription of steroids to the mother; history of infection; history

of respiratory distress syndrome (RDS); presence of repercussions from the PDA; type of treatment for PDA; necrotizing enterocolitis (NEC); periventricular leukomalacia (PVL); intracranial hemorrhage (HIC); pulmonary hemorrhage; and BPD.

Quantitative variables included maternal age; number of prenatal visits; APGAR scores at 1 and 5 minutes after birth; birth weight; gestational age at birth; time on mechanical ventilation; time on oxygen therapy; and age at resolution.

Weight and GAB were categorized based on the Intergrowth charts.[19] Patients categorized as appropriate for gestational age (AGA) had weight and stature between the 10th and 90th percentiles; patients categorized as small for gestational age (SGA) had weight and stature below the 10th percentile; and patients categorized as large for gestational age (LGA) had weight and stature greater than the 90th percentile.

Length of gestation was assessed based on the date of the last period or on first-trimester fetal ultrasound scans in cases where the date of the last period was unknown.

Diagnosis of PDA with hemodynamic repercussions was based on clinical criteria and echocardiography findings. Clinical criteria (Chart 1) included increased need for respiratory support; inability to wean the patient from mechanical ventilation; hypotension and/or congestive heart failure.[20] Echocardiography findings (Chart 2) included a DA with an internal diameter greater than 1.5 mm; presence of turbulent flow with increased systolic flow velocity in the pulmonary artery (velocity > 1.3 m/s suggestive of pulmonary hyperflow); assessment of the Doppler flow velocity curve of the DA; dilated left heart chambers; and a left atrial-to-aortic root diameter ratio (LA/Ao) > 1.4 (Figure 1). Assessment of the Doppler flow velocity curve of the DA indicates the presence of hemodynamic repercussions when peak systolic flow in the DA is four times greater than peak diastolic flow. Every neonate with a GAB of less than 28 weeks weighing less than 1000 grams and babies with symptoms such as murmurs, dyspnea, or cyanosis undergo examination by echocardiography in the maternity hospital where our study was carried out. The institution's database did not mention the age at which the neonates had their echocardiograms taken.

In regard to PDA therapy, the database contained information on whether patients were treated with ibuprofen, but not on how old they were at the time of treatment.

Neonatal sepsis was defined based on the guidelines of the Brazilian Health Regulatory Agency (Anvisa). Early sepsis was characterized as presence of signs of infection (based on clinical, laboratory, microbiology testing) within the first 48 hours of life, whereas late-onset sepsis was described when signs of infection were seen after the first 48 hours of neonatal life.[21]

ICH was diagnosed when patients had alterations in transfontanellar ultrasound scans based on the classification developed by Papile.[22] Absence or presence of PVL was also assessed via transfontanellar sonography. Pulmonary hemorrhage was characterized by history of bleeding through the endotracheal tube and need to increase mechanical ventilation (MV) parameters. Patients relying on oxygen therapy at 28 days of life were diagnosed with BPD.[23] Neonates showing clinical, laboratory, or imaging signs of NEC were diagnosed with the condition according to the criteria described by Bell in 1978.[24] Time on mechanical ventilation was recorded for invasive (conventional MV) and noninvasive mechanical ventilation. Noninvasive mechanical ventilation was characterized by the non-use of invasive devices (such as an endotracheal tube) during ventilation.

Statistical and descriptive analysis including calculation of measures of central tendency for quantitative variables (mean, median, 25th percentile, 75th percentile, and standard error) and proportions for categorical variables was performed on software package *PSPP version 1.0.1.* The Kolmogorov-Smirnov test was used to test whether variables followed a normal distribution.

RESULTS

The institution in which our study was carried out is a referral center for high-risk pregnancies, neonates with heart conditions, and preterm neonates in the State of Rio Grande do Norte, Brazil. An estimated 30% of the deliveries performed in this center involve preterm neonates, a population with a higher incidence of PDA. In 2015, 58 of the 121 neonates admitted to the hospital's NICU and examined by a pediatric cardiologist were diagnosed with a PDA, 32 weighing less than 1500 grams. Four subjects were excluded from the study for presenting heart conditions unrelated to having a PDA. The study's final population comprised 28 neonates.

More than two thirds (67.8%) of the neonates diagnosed with a PDA weighed less than 1000 grams.

The included neonates had 27.3 weeks of gestational age and weighed 869.39 grams on average at birth (Table 1). More than half of the subjects (53.6%) were males. Seven neonates (25%) were treated for PDA with ibuprofen (Table 2).

Chart 1. Clinical criteria used to assess repercussions from a patent ductus arteriosus.

Increased need for respiratory support
Inability to wean the patients from mechanical ventilation
Hypotension and/or congestive heart failure

Chart 2. Echocardiography findings used to assess repercussions from a patent ductus arteriosus.

Ductus arteriosus with an internal diameter > 1.5 mm
Presence of turbulent flow with increased systolic flow velocity in the pulmonary artery
Assessment of the Doppler flow velocity curve of the DA
Dilated left heart chambers
LA/Ao > 1.4

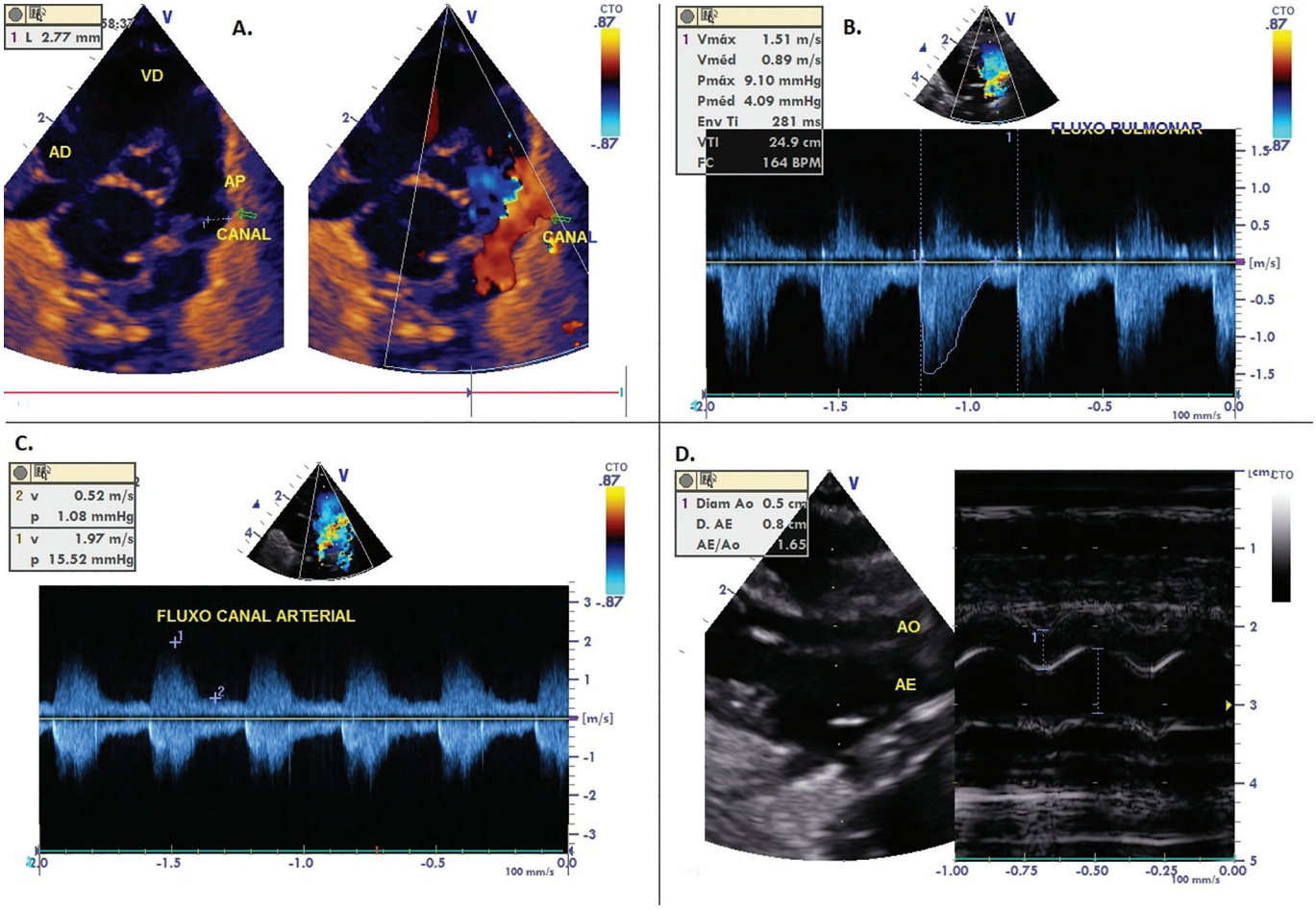


Figure 1. Echocardiogram of a preterm neonate with a PDA with hemodynamic repercussion: A) PDA measuring 2.77 mm; B) Doppler assessment of systolic flow velocity in the pulmonary artery > 1.3 m/s, suggesting pulmonary hyperflow; C) assessment of the Doppler flow velocity curve showing a peak systolic flow (1) four times greater than the peak diastolic flow (2) supporting the existence of a PDA with hemodynamic repercussion; D) Left atrial-to-aortic root diameter ratio (LA/Ao) > 1.4.

None of the patients was prescribed indomethacin therapy or ligation. More than two thirds of the neonates (67.9%) were born from cesarean sections and seven mothers (25%) had pregnancy-induced hypertension (PIH). Twenty-five neonates (89.3%) were categorized as AGA, while 10.7% were considered SGA. Prenatal steroids were prescribed in eleven cases (39.3%). Nine neonates (32.1%) had pulmonary hemorrhage and 22 (78.6 %) were prescribed surfactants. Transfontanellar sonography was performed in 23 patients; one did not undergo ultrasound examination and the records of four neonates were unspecific about it. Some degree of periventricular/intraventricular hemorrhage (PVH/IVH) was seen in 11 patients (39.3%). Late-onset sepsis was observed in 25 neonates (89.3%). Twelve patients (42.9%) were diagnosed with early sepsis. None of the neonates had NEC, but data on NEC was missing for 25% of the included subjects. MV was prescribed to 25 neonates (89.3%) and 18 (64.2%) relied on oxygen therapy 28 days after birth (BPD). None of the patients died. All subjects progressed to closure of the ductus arteriosus or to PDA without hemodynamic repercussion.

DISCUSSION

Although based on a small population, our study showed that most of the neonates diagnosed with a PDA required mechanical ventilation. Härkin et al[12] reported that conventional mechanical ventilation is an independent risk factor for neonates with a PDA requiring treatment.[12] Lung disease and mechanical ventilation increase pulmonary vascular resistance, thereby increasing pressure in the ductus arteriosus and keeping it open, in addition to decreasing the effectiveness of vasoconstriction by affecting the production of endothelin-1 and other peptides such as bradykinin and thromboxane A2, and reducing circulating prostaglandin levels.[25]

The greater proportion of neonates with a PDA and extremely low birth weight (67.8%) is consistent with the literature. The incidence of PDA has been described as being inversely related to GAB and birth weight. The incidence of PDA in Brazil is 58% in neonates weighing less than 1000 grams.[7]

Infection promotes patency of the ductus arteriosus and compromises response to cyclooxygenase inhibitors on

Table 1. Epidemiological description of 28 neonates diagnosed with PDA at a school maternity hospital in Natal, Brazil, in 2015.

Variable	N	Mean	Median	Standard Error	25th Percentile	75th Percentile
Birth weight (grams)	28	869.39	804.00	233.400	678.50	1066.50
Gestational age at birth (weeks)	28	27.304	27.400	2.6020	24.500	28.200
Maternal age (years)	28	26.00	27.59	6.459	24.00	34.00
Number of prenatal visits	28	4.43	4.00	1.938	3.00	6.50
1-minute APGAR score	28	5.68	6.00	2.610	4.00	8.00
5-minute APGAR score	28	7.76	8.00	1.508	7.00	9.00
Time on mechanical ventilation (days)	28	25.22	21.00	19.540	10.00	36.00
Time on oxygen therapy (days)	28	42.38	37	22.953	27.50	51.50
Age at resolution (days)	28	77.44	83	26.646	51.25	93.75

Table 2. Epidemiological description of 28 neonates diagnosed with PDA at a school maternity hospital in Natal, Brazil, in 2015 - categorical variables.

Variable	N	Yes (%)	No (%)
Prenatal steroids	28	39.3	60.7
Pulmonary hemorrhage	28	32.1	67.9
Mechanical ventilation	28	89.3	10.7
Oxygen therapy 28 days after birth	28	64.2	35.8
Prescription of surfactant	28	78.6	21.4
Prescription of ibuprofen	28	25	75
Intraventricular hemorrhage	24	45.8	54.2
Early sepsis	28	42.9	57.1
Late-onset sepsis	28	89.3	10.7
Enterocolitis	28	0	100
Mother with pregnancy-induced hypertension	28	25	75

account of the release of circulating prostaglandins.[7] Nearly nine in ten (89.3%) of the neonates included in our study had late-onset sepsis, a finding that supports the existence of the aforementioned association.

Seven neonates (25%) were prescribed drug therapy to treat PDA. However, fewer patients have been treated for PDA. The literature indicates that therapy does not decrease mortality or the incidence of BPD and exposes neonates to undesired drug side effects.[12] The abolition of drug therapy and surgery has not been supported in the literature yet, although evidence suggests that treatment does not improve long term outcomes.[15,19]

Reports of symptom improvement in neonates progressing to heart or respiratory failure on account of left-to-right shunt and pulmonary hyperflow after closure of the DA call for rigorous assessment of the repercussions of a PDA before a decision is made about treating the patient or not. It is important to attempt conservative measures such as restricting water intake, prescribing diuretics, offering transfusion of packed red blood cells, and adjusting mechanical ventilation parameters (permissive hypercapnia to decrease pulmonary vasodilation; higher positive end-expiratory pressure to increase pulmonary pressure and decrease flow; and decrease time on mechanical ventilation).[26]

A study reported that exposure to a symptomatic PDA for various days did not increase the incidence of BPD.[16] A more recent publication reported a lower incidence of BPD in patients with a PDA treated conservatively compared to neonates treated with indomethacin or ligation.[13] In our study, 20 patients with a PDA were analyzed for BPD and 64.2% relied on oxygen therapy 28 days after birth. This may indicate that PDA increased the incidence of BPD, but time on mechanical ventilation may also induce the onset of BPD; therefore, a solid association between PDA and BPD cannot be derived.

Multiple trials failed to describe the long-term benefits of PDA closure, thus suggesting that a number of outcomes connected to PDA such as severe RDS, BPD, NEC, ICH, PVL, and death may be associated with PDA on account of other factors such as prematurity and infection.[26,27] According to Adzick [28], closure of the PDA may not alter the outcome of these conditions.

A case-control study enrolling 177 neonates with very low birth weight and gestational ages at birth > 25 weeks found evidence that PDA did not significantly affect the morbidity and mortality of neonates with very low birth weight. BPD was one of the analyzed morbidities.[25]

The following conclusions may be drawn from our study: most of the studied patents were on mechanical ventilation and relied on oxygen therapy 28 days after birth; the prevalence of PDA was higher among neonates with extremely low birth weight; drug therapy was prescribed to few patients; sepsis was a frequent finding in patients with a PDA. Our study enrolled a relatively small population, since it included only neonates weighing less than 1500 grams born in 2015 at our hospital, some of which had died before assessment by a pediatric cardiologist and were thus not included in the study. Additional prospective studies with larger populations

are required to improve the assessment of risk factors, treatment, and short- and long-term morbidity associated with PDA.

REFERENCES

1. Gillam-Krakauer M, Mahajan K. Patent Ductus Arteriosus. StatPearls. Treasure Island (FL): StatPearls Publishing; 2019.
2. Sallmon H, Koehne P, Hansmann G. Recent Advances in the Treatment of Preterm Newborn Infants with Patent Ductus Arteriosus. Clin Perinatol. 2016;43(1):113-29.
3. Deshpande P, Baczynski M, McNamara PJ, Jain A. Patent ductus arteriosus: The physiology of transition. Semin Fetal Neonatal Med. 2018;23(4):225-31. DOI: https://doi.org/10.1016/j.siny.2018.05.001
4. Gournay V. Prise en charge du canal artériel du prématuré: une approche factuelle. Arch Pediatr. 2017;24(2):175-9.
5. Oncel MY, Erdeve O. Oral medications regarding their safety and efficacy in the management of patent ductus arteriosus. World J Clin Pediatr. 2016;5(1):75-81.
6. Oncel MY, Erdeve O. Safety of therapeutics used in management of patent ductus arteriosus in preterm infants. Curr Drug Saf. 2015;10(2):106-12.
7. Luca AKC, Betilin MR, Rugolo LMSS. Nova abordagem da Persistência do Canal Arterial. In: Sociedade Brasileira de Pediatria; Procianoy RS, Leone CR, orgs. PRORN Programa de Atualização em Neonatologia: Ciclo 10. Porto Alegre: Artmed Panamericana; 2013.
8. Curty C, Castilho M. Utilização do ecocardiograma no diagnóstico de persistência de canal arterial na Maternidade Escola da UFRJ. Resid Pediátr. 2011;1(2):15-8.
9. Gudmundsdottir A, Johansson S, Håkansson S, Norman M, Källen K, Bonamy AK. Timing of pharmacological treatment for patent ductus arteriosus and risk of secondary surgery, death or bronchopulmonary dysplasia: a population-based cohort study of extremely preterm infants. Neonatology. 2015;107(2):87-92.
10. Prescott S. Near infrared spectroscopy and patent ductus arteriosus in the preterm neonate: A systematic review. J Neonatal Nurs. 2017;23(1):9-27. DOI: http://dx.doi.org/10.1016/j.jnn.2016.07.002
11. Clyman RI, Liebowitz M. Treatment and Nontreatment of the Patent Ductus Arteriosus: Identifying Their Roles in Neonatal Morbidity. J Pediatr. 2017;189:13-7.
12. Härkin P, Marttila R, Pokka T, Saarela T, Hallman M. Morbidities associated with patent ductus arteriosus in preterm infants. Nationwide cohort study. J Matern Fetal Neonatal Med. 2018;31(19):2576-83. DOI: 10.1080/14767058.2017.1347921
13. Sung SI, Chang YS, Chun JY, Yoon SA, Yoo HS, Ahn SY, et al. Mandatory Closure Versus Nonintervention for Patent Ductus Arteriosus in Very Preterm Infants. J Pediatr. 2016;177:66-71.e1. DOI: http://dx.doi.org/10.1016/j.jpeds.2016.06.046
14. Janz-Robinson EM, Badawi N, Walker K, Bajuk B, Abdel-Latif ME; Neonatal Intensive Care Units Network. Neurodevelopmental Outcomes of Premature Infants Treated for Patent Ductus Arteriosus: A Population-Based Cohort Study. J Pediatr. 2015;167(5):1025-32.e3.
15. Sehgal A, McNamara PJ. International perspective on management of a patent ductus arteriosus: Lessons learned. Semin Fetal Neonatal Med. 2018;23(4):278-84. DOI: http://dx.doi.org/10.1016/j.siny.2018.03.002
16. Chorne N, Leonard C, Piecuch R, Clyman RI. Patent Ductus Arteriosus and Its Treatment as Risk Factors for Neonatal and Neurodevelopmental Morbidity. Pediatrics. 2007;119(6):1165-74. DOI: 10.1542/peds.2006-3124
17. Backes CH, Cheatham SL, Deyo GM, Leopold S, Ball MK, Smith CV, et al. Percutaneous Patent Ductus Arteriosus (PDA) Closure in Very Preterm Infants: Feasibility and Complications. J Am Heart Assoc. 2016;5(2).pii:e002923.
18. Rodríguez Ogando A, Planelles Asensio I, de la Blanca ARS, Ballesteros Tejerizo F, Sánchez Luna M, Gil Jaurena JM, et al. Surgical Ligation Versus Percutaneous Closure of Patent Ductus Arteriosus in Very Low-Weight Preterm Infants: Which are the Real Benefits of the Percutaneous Approach? Pediatr Cardiol. 2018;39(2):398-410.
19. Villar J, Cheikh Ismail L, Victora CG, Ohuma EO, Bertino E, Altman DG, et al.; International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet. 2014;384(9946):857-68.
20. Yeh TF, Goldbarg HR, Henek T, Thalji A, Pildes RS. Intravenous indomethacin therapy in premature infants with patent ductus arteriosus. Causes of death and one-year follow-up. Am J Dis Child. 1982;136(9):803-7.
21. Brasil. Agência Nacional de Vigilância Sanitária (ANVISA). Gerência de Vigilância e Monitoramento em Serviços de Saúde (GVIMS) Gerência Geral de Tecnologia em Serviços de Saúde (GGTES). Critérios Diagnósticos de Infecção Associada à Assistência à Saúde Neonatologia. Segurança do Paciente e Qual em Serviços Saúde [Internet]. Brasília: ANVISA; 2017 [acesso 2018 Fev 5]. Disponível em: http://portal.anvisa.gov.br/documents/33852/3507912/Caderno+3+-+Critérios+Diagnósticos+de+Infecção+Associada+à+Assistência+à+Saúde+Neonatologia/9fa7d9be-6d35-42ea-ab48-bb1e068e5a7d
22. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978;92(4):529-34.
23. Bancalari E, Abdenour GE, Feller R, Gannon J. Bronchopulmonary dysplasia: clinical presentation. J Pediatr. 1979;95(5 Pt 2):819-23.
24. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978;187(1):1-7.
25. Tauzin L, Joubert C, Noel AC, Bouissou A, Moulies ME. Effect of persistent patent ductus arteriosus on mortality and morbidity in very low-birthweight infants. Acta Paediatr. 2012;101(4):419-23.
26. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? J Perinatol. 2010;30(4):241-52. DOI: http://dx.doi.org/10.1038/jp.2010.3
27. Gonzalez A, Sosenko IR, Chandar J, Hummler H, Claure N, Bancalari E. Influence of infection on patent ductus arteriosus and chronic lung disease in premature infants weighing 1000 grams or less. J Pediatr. 1996;128(4):470-8.
28. Adzick NS, Harrison MR, deLorimier AA. Surgical clip ligation of patent ductus arteriosus in premature infants. J Pediatr Surg. 1986;21(2):158.