



ORIGINAL ARTICLE

Effects of therapeutic approach on the neonatal evolution of very low birth weight infants with patent ductus arteriosus^{☆,☆☆}

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☆ Please cite this article as: Sadeck LS, Leone CR, Procianoy RS, Guinsburg R, Marba ST, Martinez FE, et al. Effects of therapeutic approach on the neonatal evolution of very low birth weight infants with patent ductus arteriosus. J Pediatr (Rio J). 2014. <http://dx.doi.org/10.1016/j.jpmed.2014.04.010>

☆☆ Study linked to 16 units from the Brazilian Neonatal Research Network: Universidade de São Paulo (USP); FIOCRUZ/Instituto Fernandes Figueira (IFF); Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS)/Hospital São Lucas (HSL), UNESP (Universidade Estadual Paulista)/Faculdade de Medicina de Botucatu (FMB); Universidade Federal do Rio Grande do Sul (UFRGS)/Hospital de Clínicas de Porto Alegre (HCPA); Universidade Federal de São Paulo (UNIFESP)/Escola Paulista de Medicina (EPM); Universidade de São Paulo (USP), Ribeirão Preto; Universidade Estadual de Campinas (UNICAMP)/Hospital da Mulher Prof. Dr. José Aristodemo Pinotti (CAISM); Universidade Estadual do Rio de Janeiro (UERJ)/Hospital Universitário Pedro Ernesto (HUPE); Universidade Federal de Minas Gerais (UFMG)/Hospital de Clínicas (HC); Universidade Federal do Paraná (UFPR)/Hospital de Clínicas (HC); Faculdade de Ciências Médicas de Minas Gerais (FCMMG)/Maternidade Hilda Brandão (MHB); Universidade Federal de Uberlândia (UFU)/Hospital de Clínicas (HC); Universidade Estadual de Londrina (UEL)/Hospital Universitário (HU); Instituto de Medicina Integral Professor Fernando Figueira (IMIP); Universidade Federal do Maranhão (UFMA)/Hospital de Clínicas (HU).

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<http://dx.doi.org/10.1016/j.jpmed.2014.04.010>

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Received 28 October 2013; accepted 3 April 2014

KEYWORDS

Preterm;
Very low birth
weight;
Ligation;
PDA management

Abstract

Objective: to analyze the effects of treatment approach on the outcomes of newborns (birth weight [BW] < 1,000 g) with patent ductus arteriosus (PDA), from the Brazilian Neonatal Research Network (BNRN) on: death, bronchopulmonary dysplasia (BPD), severe intraventricular hemorrhage (IVH III/IV), retinopathy of prematurity requiring surgical (ROP_{sur}), necrotizing enterocolitis requiring surgery (NEC_{sur}), and death/BPD.

Methods: this was a multicentric, cohort study, retrospective data collection, including newborns (BW < 1000 g) with gestational age (GA) < 33 weeks and echocardiographic diagnosis of PDA, from 16 neonatal units of the BNRN from January 1, 2010 to Dec 31, 2011. Newborns who died or were transferred until the third day of life, and those with presence of congenital malformation or infection were excluded. Groups: G1 – conservative approach (without treatment), G2 – pharmacologic (indomethacin or ibuprofen), G3 – surgical ligation (independent of previous treatment). Factors analyzed: antenatal corticosteroid, cesarean section, BW, GA, 5 min. Apgar score < 4, male gender, Score for Neonatal Acute Physiology Perinatal Extension (SNAPPE II), respiratory distress syndrome (RDS), late sepsis (LS), mechanical ventilation (MV), surfactant (< 2 h of life), and time of MV. Outcomes: death, O₂ dependence at 36 weeks (BPD_{36wks}), IVH III/IV, ROP_{sur}, NEC_{sur}, and death/BPD_{36wks}. Statistics: Student's *t*-test, chi-squared test, or Fisher's exact test; Odds ratio (95% CI); logistic binary regression and backward stepwise multiple regression. Software: MedCalc (Medical Calculator) software, version 12.1.4.0. *p*-values < 0.05 were considered statistically significant.

Results: 1,097 newborns were selected and 494 newborns were included: G1 - 187 (37.8%), G2 - 205 (41.5%), and G3 - 102 (20.6%). The highest mortality was observed in G1 (51.3%) and the lowest in G3 (14.7%). The highest frequencies of BPD_{36wks} (70.6%) and ROP_{sur} were observed in G3 (23.5%). The lowest occurrence of death/BPD_{36wks} occurred in G2 (58.0%). Pharmacological (OR 0.29; 95% CI: 0.14-0.62) and conservative (OR 0.34; 95% CI: 0.14-0.79) treatments were protective for the outcome death/BPD_{36wks}.

Conclusion: the conservative approach of PDA was associated to high mortality, the surgical approach to the occurrence of BPD_{36wks} and ROP_{sur}, and the pharmacological treatment was protective for the outcome death/BPD_{36wks}.

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PALAVRAS-CHAVE

Prematuridade;
Muito baixo peso;
Ligadura cirúrgica;
Canal arterial

Efeitos da abordagem terapêutica da persistência de canal arterial sobre a evolução neonatal de recém-nascidos de extremo baixo peso

Resumo

Objetivo: analisar os efeitos da terapêutica adotada para o canal arterial (CA) em recém-nascidos (RN) < 1.000g admitidos em unidades neonatais (UN) da Rede Brasileira de Pesquisas Neonatais (RBPN), sobre os desfechos: óbito, displasia broncopulmonar (DBP), hemorragia intraventricular grave (HIVIII/IV), retinopatia da prematuridade cirúrgica (ROP_{cir}), enterocolite necrosante cirúrgica (ECN_{cir}) e o desfecho combinado óbito e DBP.

Métodos: estudo multicêntrico, de coorte, coleta de dados retrospectiva, incluindo RN de 16 UN da RBPN de 01/01/2010 a 31/12/2011, PN < 1.000 g, idade gestacional (IG) < 33 semanas e diagnóstico ecocardiográfico de PCA. Excluídos: óbitos ou transferências até o terceiro dia de vida, infecções congênicas ou malformações. Grupos: G1 – conservadora (sem intervenção medicamentosa ou cirúrgica), G2 – farmacológica (indometacina ou ibuprofeno) e G3 – cirúrgico (com ou sem tratamento farmacológico anterior). Analisou-se: uso de esteroide antenatal, parto cesárea, PN, IG, Apgar5' < 4, sexo masculino, SNAPPE II, síndrome do desconforto respiratório

(SDR), sepse tardia, ventilação mecânica (VM), surfactante < 2 horas de vida, tempo de VM e os desfechos: óbito, dependência de oxigênio com 36 semanas (DBP_{36s}), HIV III/IV, ROP_{cir}, ECN_{cir} e óbito/DBP_{36s}. Estatística: Teste *t-Student*, Qui-Quadrado ou teste Exato de Fisher. Testes de Regressão Binária Logística e Regressão Múltipla Stepwise Backward. MedCalc (Medical Calculator) software, versão 12.1.4.0.p < 0,05.

Resultados: foram selecionados 1.097 RN e 494 foram incluídos: G1-187 (37,8%), G2-205 (41,5%) e G3-102 (20,6%). Verificou-se: maior mortalidade (51,3%) no G1 e menor no G3(14,7%); maior frequência DBP_{36s} (70,6%) e ROP_{cir} (23,5%) no G3; maior frequência de óbito/DBP_{36s} no G2 (58,0%). As abordagens farmacológica (OR-0,29; 95%, IC-0,14-0,62) e conservadora (OR-0,34; 95%, IC- 0,14-0,79) foram protetoras somente para o desfecho óbito/DBP_{36sem}.

Conclusão: em RN com PCA, a abordagem conservadora relacionou-se à maior mortalidade, a cirúrgica à ocorrência de DBP_{36s} e ROP_{cir}, enquanto o tratamento farmacológico mostrou-se protetor para o desfecho óbito/DBP_{36sem}.

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Introduction

The approach of patent ductus arteriosus (PDA) in the neonatal period has been widely discussed in the literature, both regarding the best time to detect it, as well as the conduct to be used in the presence of DA, particularly in preterm newborns (PNBs) of low birth weight, considering its implications for the evolution of these newborns.

While the DA is an essential structure during the intrauterine period, responsible for the deviation of the pulmonary circulation to the aorta and maintaining the fetal systemic blood flow, its persistence after birth may trigger a series of events, culminating with heart failure.¹ Particularly in infants with birth weight (BW) below 1,000g, patent ductus arteriosus (PDA) with hemodynamic effects may be associated with greater morbimortality,² resulting in higher risks of heart failure, duration of mechanical ventilation, bronchopulmonary dysplasia (BPD),³ intraventricular hemorrhage (IVH),⁴ and necrotizing enterocolitis (NEC).⁵

However, a considerable percentage of PDAs will close spontaneously,^{6,7} or may remain patent without causing significant symptoms.⁷ Consequently, early start of the treatment may unnecessarily expose NBs to prostaglandin inhibitors or surgical ductus ligation, which are associated with adverse effects.⁸ This situation might be prevented if preterm infants more likely to undergo spontaneous PDA closure are identified.

Conduct related to the management of PDA in PNBs has been highly variable in the literature, resulting in many studies, especially in infants with birth weight (BW) < 1,000g.⁸

To date, there is not enough evidence to define the best approach to PDA in PNBs.⁹⁻¹¹ Although pharmacological treatment with indomethacin or ibuprofen has been proven effective in PDA closure, no improvement was observed in evolution when the following events were analyzed: death, BPD, and necrotizing enterocolitis (NEC). Most published clinical trials focused on PDA closure with pharmacological or surgical approach.¹²

Considering the current knowledge and existing questions on the treatment option to be used in the presence of PDA, whether conservative, pharmacological, or surgical, the present study aimed to assess the effects of these approaches in infants weighing less than 1,000g admitted

to neonatal intensive care units (NICUs) of the Brazilian Neonatal Research Network (BNRN) in 2010 and 2011, on the occurrence of the following outcomes: death, BPD, severe intraventricular hemorrhage (IVH III/IV), retinopathy of prematurity requiring surgery (ROP_{sur}), necrotizing enterocolitis requiring surgery (NEC_{sur}), and the combined outcome of death and BPD.

Methods

A multicenter, cohort study was performed with retrospective data from BNRN, which included infants admitted at 16 BNRN NICUs from January 1st, 2010 to December 31st, 2011.

The newborns were selected according to the following inclusion criteria: BW: 400-999g, gestational age (GA) < 33 weeks, and echocardiographic diagnosis of PDA, regardless of hemodynamic effects. Newborns who died or were transferred up to the third day of life and those diagnosed with congenital infections or malformations were excluded.

The NBs included in the study were divided into study groups according to the therapeutic management of PDA: G1 - conservative approach (without medication or surgical intervention), G2 - pharmacological approaches (treatment with indomethacin or ibuprofen), and G3 - surgical approach (surgical ligation, regardless of whether or not the NB had previously received prostaglandin inhibitor).

The variables analyzed were **perinatal conditions:** use of antenatal steroids and Cesarean delivery; **birth conditions:** birth weight, gestational age, adequate birth weight for gestational age, considering small for gestational age (SGA) as PNBs with weight below the 5th percentile of the Alexander et al.¹³ curve, Apgar 5 min. < 4, and male gender; **neonatal outcome:** Score for Neonatal Acute Physiology Perinatal Extension (SNAPPE II) risk score, respiratory distress syndrome (RDS), late-onset neonatal sepsis (LONS) (positive blood culture), need for mechanical ventilation, duration of mechanical ventilation, and surfactant administration up to 2 hours of life; and **primary outcomes:** death, oxygen dependence at 36 weeks (BPD_{36wks}), IVH III/IV according to the classification of Papille, ROP_{sur}, NEC_{sur}, and the combined outcome death/BPD_{36wks}.

This study was approved by the Ethics Committee of the Institution (Ethics Committee for Research Project Analysis

of the Clinical Board of Hospital das Clínicas and Faculdade de Medicina da Universidade de São Paulo) through research protocol 1383/09 and later adopted by the other institutions.

Statistical Analysis

Categorical data are shown with frequency distribution, and continuous data using mean and standard deviation, as indicated. The univariate analysis of categorical variables used the chi-squared or Fisher's exact test, when indicated, whereas Student's *t*-test was used for continuous variables. To calculate the risk, after determining the odds ratio (95% CI), logistic binary regression and backward stepwise multiple regression were performed using MedCalc (Medical Calculator) software, version 12.1.4.0. The statistical significance level was set at 5% ($p < 0.05$).

Results

A total of 1,097 newborns with BW = 400 to 999 g and GA < 33 weeks were admitted in 16 NICUs of the BNRN during the study period. Of these, 220 were excluded due to death or transfer during the first three days of life, malformations, and congenital infections; 494 newborns met the inclusion criteria with echocardiographic diagnosis of PDA and no information regarding the presence of symptoms.

The infants were subdivided according to the therapeutic approach, into: G1 - 187 (37.8%), G2 - 205 (41.5%), and G3 - 102 (20.6%) (Fig. 1).

The characteristics of the population according to each study group is shown in Table 1; it can be observed that there were differences between the groups in relation to the GA, mean SNAPPE II score, frequency and time of mechanical ventilation, and occurrence of LONS.

Regarding the analyzed outcomes, it was observed that mortality was higher in G1 (51.3%), while it was lower in G3 (14.7%). The highest incidence of BPD_{36wks} (70.6%) and ROP_{sur} (23.5%) was observed in G3, while the combined outcome death/BPD_{36wks} was less frequent in G2 (58.0%). It was not possible to analyze the effects of the therapy used on the occurrence of NEC_{sur}, due to the very small number of cases, although a statistically significant difference was observed between G1 and G2 (Table 2).

The multivariate regression analysis showed no influence of the type of therapeutic approach on the probability of death or the occurrence of BPD_{36wks} alone, rather only for the combined outcome death/BPD_{36wks}. However, the following were identified as risk factors for the outcome of death: NEC_{sur} (OR 5.64, 95% CI: 1.03 to 30.7) and IVH-III/IV (OR 3.62, 95% CI: 1.30 to 10.11). For the male gender (OR 2.59, 95% CI: 1.33 to 5.02), LONS (OR 1.88, 95% CI: 1.00 to 3.54), GA (OR 1.49, 95% CI: 1.22 to 1.81), and time of MV (OR 1.04, 95% CI: 1.02 to 1.07) were factors related to the presence of BPD_{36wks}. BW alone was a protective factor against the outcomes death and BPD_{36wks} (OR 0.99, 95% CI: 0.99 to 0.99) (Table 3).

Regarding the combined outcome of death/BPD_{36wks}, the following were identified as risk factors: male gender (OR 3.24, 95% CI: 1.73 to 6.18) and LONS (OR 2.53, 95% CI: 1.42 to 4.52), while the protective factors were:

pharmacological treatment (OR 0.29, 95% CI: 0.14 to 0.62), conservative approach (OR 0.34, 95% CI: 0.14 to 0.79), and BW (OR 0.99, 95% CI: 0.99 to 0.99).

Discussion

The survival of preterm infants without sequelae has been the objective of perinatal care of these at-risk NBs. Among the factors that may influence their evolution, PDA has been considered a risk factor with important consequences. Therefore, the need to define a therapeutic approach in the presence of PDA that can ensure greater control of these complications has increased, particularly in infants with lower BW.

In the present study, conducted with NBs weighing less than 1,000 g at birth and with PDA, the protection of conservative and pharmacological treatments for the combined outcome death/BPD_{36wks} was demonstrated, although the conservative treatment was related to higher mortality. Male gender was also identified, together with LONS, GA, and time of mechanical ventilation, as factors associated with the presence of BPD_{36wks}. The death outcome was associated with the presence of NEC_{sur} and IVH III/IV.

The infants included in this study, although constituting a group at high risk for the events analyzed herein, as they had on average, less than 28 weeks of gestational age and BW lower than 800 grams, might have had this risk attenuated, because two-thirds of them received antenatal corticosteroids and were born with good vital signs. In the postnatal period, although more than 90% developed RDS and required mechanical ventilation, approximately 70% received surfactant within 2 hours of life. However, the occurrence of LONS in approximately half of the newborns may have contributed to the higher frequencies BPD_{36wks}, especially in G3, which corresponded to 65.7% of the NBs.

Due to the high frequency of antenatal corticosteroid use in the analyzed groups, with no difference between them, it was not possible to assess the influence of these drugs on the analyzed outcomes.

Considering the study groups, it was observed that they differed in relation to GA, which was lower in the group that required surgical ligation of the PDA, which also showed a higher frequency of late-onset sepsis, characterizing a higher risk of BPD_{36wks} and ROP_{sur}, according to the results obtained. Nevertheless, higher mortality was observed in the group receiving conservative treatment, which probably explains the lower frequency of the other complications in this group, and the option for non-pharmacological or surgical treatment due to clinical conditions of the NBs. The group that received pharmacological treatment had the lowest SNAPPE II score, which characterizes lower risk of morbimortality and also, possibly, the occurrence of the assessed outcomes.

In general, the treatment of PDA shows a wide variation between services, especially due to the lack of consistent data regarding the best clinical approach. It remains unclear whether there are advantages among the several existing proposals in the literature: prophylactic treatment in children under a specific gestational age; early treatment at symptom onset, or later when the PDA has significant hemodynamic effects, in relation to the immediate

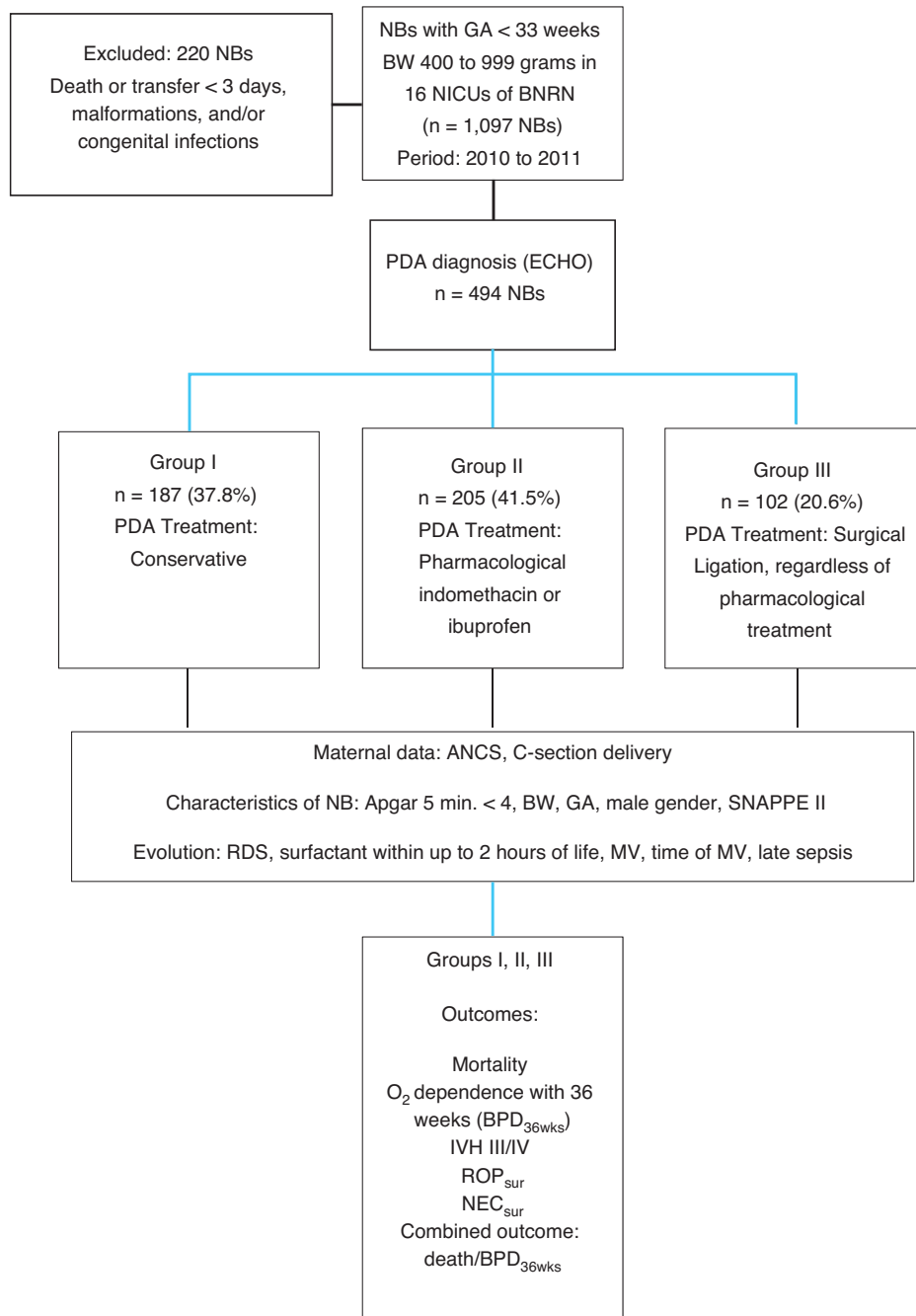


Figure 1 Study design.

BNRN, Brazilian Neonatal Research Network; PDA (ECHO), patent ductus arteriosus diagnosed by echocardiogram; ANCS, antenatal corticosteroids; BW, birth weight; GA, gestational age; SNAPPE II, Score for Neonatal Acute Physiology Perinatal Extension; RDS, respiratory distress syndrome; MV, mechanical ventilation; BPD, bronchopulmonary dysplasia; IVH III/IV, intraventricular hemorrhage grade III/IV; ROP_{sur} , retinopathy of prematurity with surgical procedure; NEC_{sur} , necrotizing enterocolitis with surgical procedure.

clinical effects and long-term results, particularly regarding BPD.^{8,14-17} However, there are potential complications of the pharmacological treatment of PDA, such as renal dysfunction and intestinal perforation, as well as those arising from surgical ligation, such as cardiopulmonary dysfunction.

In this study, comparing the three forms of therapeutic approach, it can be observed that infants treated with prostaglandin inhibitors (indomethacin or ibuprofen)

demonstrated less BPD, ROP_{sur} , NEC_{sur} , and death/ BPD_{36wks} , especially when compared to those who underwent surgical ligation. When we considered the outcomes death and BPD_{36wks} separately, the type of medical or surgical approach did not influence them, while conservative treatment was associated with higher mortality. However, in the analysis of the combined outcome (death/ BPD_{36wks}), the pharmacological and conservative treatments were protective factors.

Table 1 Birth status and in-hospital evolution of the population, according to the study groups, between 2010 and 2011.

Characteristics	G1 n = 187	G2 n = 205	G3 n = 102	p G1 x G2	p G1 x G3	p G2 x G3
ANCS	130 (69.5)	161 (78.5)	70 (68.6)	0.054 ^a	0.981 ^a	0.079 ^a
C-section	121 (64.7)	136 (66.3)	59 (57.8)	0.815 ^a	0.306 ^a	0.183 ^a
Mean BW (g) (SD)	772.0 (142.3)	804 (121.6)	781.0 (118.5)	0.017	0.555	0.117
Mean GA in weeks (SD)	27.6 (2.2)	27.4 (1.9)	26.6 (1.8)	0.307	< 0.001	< 0.001
Male gender n (%)	91 (48.7)	90 (43.9)	48 (47.1)	0.399 ^a	0.890 ^a	0.688 ^a
Apgar 5 min. < 4 n (%)	13 (6.9)	3 (1.5)	3 (2.9)	0.013 ^b	0.247 ^b	0.615 ^b
SGA < 5% n (%)	49 (26.2)	32 (15.6)	13 (12.7)	0.013 ^a	0.012 ^a	0.619 ^a
Mean SNAPPE II (SD)	43 (22.1)	34 (18.6)	40 (19.5)	< 0.001	0.177	0.026
RDS n (%)	167 (89.3)	182 (88.8)	95 (93.1)	0.996 ^a	0.391 ^a	0.314 ^a
LONS n (%)	83 (44.4)	95 (46.3)	67 (65.7)	0.774 ¹	< 0.001 ^a	0.002 ^a
Surfactant ≤2 h n (%)	118 (63.1)	140 (68.3)	66 (64.7)	0.329 ^a	0.886 ^a	0.616 ^a
MV n (%)	171 (91.4)	195 (95.1)	101 (99.0)	0.159 ^a	0.007 ^a	0.107 ^a
Mean time of MV (days) (SD)	16.8 (20.1)	20.4 (20.7)	44.8 (32.4)	0.044	< 0.001	< 0.001

ANCS, maternal use of antenatal corticosteroids; BW, birth weight; GA, gestational age; SGA < 5%, birth weight below the 5th percentile% of the Alexander et al.¹³ curve; SNAPPE II, Score for Neonatal Acute Physiology Perinatal Extension; SD, standard deviation; RDS, respiratory distress syndrome; LONS, late-onset neonatal sepsis confirmed by positive blood culture; surfactant < 2 h, surfactant administration within 2 hours of life; MV, need for mechanical ventilation.

^a Chi-squared test.

^b Fisher's exact test.

Table 2 Univariate analysis of outcomes analyzed according to the studied groups.

Outcomes	G1 n = 187	G2 n = 205	G3 n = 102	p G1 x G2	p G1 x G3	p G2 x G3
Death n (%)	96 (51.3)	58 (28.3)	15 (14.7)	<0.001 ^a	< 0.001 ^a	0.013 ^a
BPD _{36wks} n (%)	48 (25.7)	65 (31.7)	72 (70.6)	0.227 ^a	< 0.001 ^a	< 0.001 ^a
IVH III/IV n (%)	37 (19.8)	35 (17.1)	23 (22.5)	0.573 ^a	0.688 ^a	0.317 ^a
ROP _{sur} n (%)	10 (5.3)	16 (7.8)	24 (23.5)	0.417 ^b	< 0.001 ^b	< 0.001 ^b
NEC _{sur} n (%)	14 (7.5)	3 (1.5)	5 (4.9)	0.005 ^b	0.465 ^b	0.120 ^b
Death/BPD _{36wks} n (%)	134 (71.6)	119 (58.0)	83 (81.4)	0.007 ^a	0.098 ^a	< 0.001 ^a

BPD_{36wks}, bronchopulmonary dysplasia with oxygen dependence at 36 weeks corrected by gestational age; IVH III/IV, intraventricular hemorrhage grade III and IV; ROP_{sur}, retinopathy of prematurity requiring surgical intervention; NEC_{sur}, necrotizing enterocolitis requiring surgical intervention; Death/BPD_{36wks}, combined outcome of death and BPD_{36wks}.

^a Chi-squared test.

^b Fisher's exact test.

These findings agree with those of Mirea et al.¹⁶ who, using multivariate analyses, to attempt to adjust for treatment selection bias, provided evidence of an association between surgical ligation of PDA and increased neonatal mortality or severe morbidity, but conversely, found no effect of treatment with indomethacin when compared to conservative treatment.

Based on the above considerations, the present findings suggest greater protection for the outcomes analyzed in the group treated pharmacologically, although there are

limitations in this analysis, mainly regarding the number of excluded cases and the non-homogeneous distribution of risk factors among the groups, which did not allow assigning the results only to the therapeutic option. Another aspect to be considered is the lack of information concerning the clinical manifestations of PDA and the age at which treatment was established, as well as the possible differences regarding treatment indications in the NICUs. Regarding the protection related to BW, as its OR was close to 1, it had minimal impact on the assessed outcomes.

Table 3 Risk factors identified for outcomes analyzed by backward stepwise multiple regression.

Outcome	Variable	OR (95% CI)	p
Death	BW	0.99 (0.99-0.99)	0.0401
	NEC _{sur}	5.64 (1.03-30.7)	0.0455
	IVH III/IV	3.62 (1.30-10.11)	0.0139
BPD _{36wks}	BW	0.99 (0.99-0.99)	0.0207
	Male gender	2.59 (1.33-5.02)	0.0048
	LONS	1.88 (1.00-3.54)	0.0484
	GA	1.49 (1.22-1.81)	0.0001
	MV duration	1.04 (1.02-1.07)	< 0.0001
Death/BPD _{36wks}	Pharmacological Treatment	0.29 (0.14-0.62)	0.0012
	Conservative Treatment	0.34 (0.14-0.79)	0.0123
	BW	0.99 (0.99-0.99)	0.0001
	Male gender	3.24 (1.73-6.18)	0.0002
	LONS	2.53 (1.42-4.52)	0.0017

NEC_{sur}, necrotizing enterocolitis requiring surgical intervention; IVH III/IV, intraventricular hemorrhage grade III and IV; BPD_{36wks}, bronchopulmonary dysplasia with oxygen dependence at 36 weeks of corrected gestational age; BW, birth weight; GA, gestational age at birth; MV duration, duration of mechanical ventilation; Death/BPD_{36wks}, combined outcome of death or bronchopulmonary dysplasia with oxygen dependence at 36 weeks of corrected gestational age; LONS, late-onset neonatal sepsis; OR, odds ratio; CI, confidence interval.

Even with the aforementioned limitations, these findings indicate the need to conduct more randomized controlled studies to evaluate the possible protective effect of pharmacological treatment in high-risk NBs with PDA.

Collaborators

The following researchers from the Neonatal Units of the Brazilian Neonatal Research Network were responsible for data collection for this research:

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Conflicts of interest

The authors declare no conflicts of interest.

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