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Original article

PDA management in VLBW infants: experience of a level III NICU

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Abstract

Introduction: Hemodynamically significant patent ductus arteriosus (PDA) is a common condition in very low birth weight infants. Therapeutic options include medical therapy and surgical ligation. Medical treatment is based on non-selective inhibitors of cyclooxygenases 1 and 2 (indomethacin and ibuprofen). The debate on the most appropriate treatment for the closure of the PDA is far from being closed, in the light of the currently available evidence.

Aim: The objective of this study was to compare efficacy and safety of indomethacin and ibuprofen.

Methods: All infants < 32 weeks of gestational age or ≤ 1,500 g of birth weight born in "Centro Hospitalar São João" between January 2005 and December 2014 were included. Those with major malformations or genetic disorders, congenital TORCH infections, transferred or deceased before 72 hours of life, outborns, and those with severe pathologies at birth were excluded. The cohort of neonates treated with indomethacin from January 2005 to December 2009 was compared to those treated with ibuprofen from January 2010 to December 2014.

Results: 328 newborns were included in the study: 99 (30.2%) with PDA and 229 (69.8%) without. The median gestational age was 30 weeks and the median birth weight was 1,231 grams. Among the 99 patients with PDA, 21 were treated with indomethacin and 41 received ibuprofen. There was no statistically significant difference in efficacy between groups. There was a higher incidence of thrombocytopenia in the indomethacin group compared to the ibuprofen group, but there was no significant difference in any other PDA-associated comorbidities between groups.

Conclusion: Our study showed that indomethacin and ibuprofen have a similar effect in closing PDA in < 32 weeks preterm infants. We found no significant differences in safety, except for thrombocytopenia. Further studies are necessary to compare both efficacy and adverse events of ibuprofen and indomethacin to identify the optimal pharmacological agent for PDA.

Keywords

Patent ductus arteriosus, ibuprofen, indomethacin, efficacy, morbidities, very low birth weight.

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Introduction

The ductus arteriosus (DA) is a vascular structure that connects the descending aorta to the pulmonary artery. In the foetus, blood oxygenation occurs in the placenta [1]. Thus, in the foetal period, lungs require less blood supply, which corresponds to only 10% of cardiac output [1, 2]. The remaining 90% is derived into the systemic circulation, in part through the DA that allows the shunt of about 55% of the pulmonary artery flow to the descending aorta [1, 2]. After birth, oxygenation becomes dependent on pulmonary circulation. It is essential that DA closes, in a process initially involving a functional occlusion and, thereafter, anatomical closure [2, 3].

However, patent ductus arteriosus (PDA) closure may fail in any newborn, and this is more likely to happen in preterm babies, with an estimated incidence of about 30% in infants with very low birth weight (VLBW, < 1,500 grams) [3,4]. The main factors contributing to keeping DA open in this population are low blood oxygen partial pressure, as well as the endogenous production of prostaglandins and nitric oxide [1].

PDA is defined when the communication between the pulmonary artery and aorta persists beyond 72 hours of life [5]. In general, in the absence of congenital heart disease or pulmonary hypertension, the shunt through the DA is left-to-right, translating the balance between the falling pulmonary pressure and the comparatively high systemic pressure. A PDA with a significant left-to-right shunt results in an excessive blood flow in the pulmonary circulation and a concomitant hypoperfusion in the systemic one. Several studies unequivocally relate this entity to an increased incidence of bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH) and death [5-7]. A DA is defined as hemodynamically significant when, in the presence of a left-to-right shunt, ultrasound criteria of hemodynamic impact (i.e. larger diameter of the DA associated with low velocity of blood through it, dilation of the left heart chambers, and diastolic steal in the systemic circulation) are also identified [5]. The diagnosis of PDA must be prompt, ideally before the onset of clinical signs, especially in preterm babies in whom these signs can appear later [4, 5].

Therapeutic options to manage a significant PDA include medical therapy and surgical ligation. The value of prophylactic treatment is not established, since the potential benefits do not outweigh the associated side effects, and there is a possibility of spontaneous closure whereby many newborns would be treated unnecessarily [1, 4]. Medical treatment is based on non-selective inhibitors of cyclooxygenases 1 and 2 (indomethacin and ibuprofen), through inhibition of prostaglandins, and this seems to be as effective as surgical closure [8, 9]. However, drug therapy is contraindicated in cases of renal failure, thrombocytopenia, active hemorrhage, NEC and severe sepsis [4, 5]. Due to the potential complications of surgery, surgical ligation is indicated when pharmacological treatment is contraindicated or if it fails [4].

Indomethacin was the first drug used, with the first study of its effectiveness in DA closure being published in 1976 [10]. Later, ibuprofen was investigated in trials and it has increasingly been used in clinical practice. More recently, paracetamol has been introduced as an option in the treatment of PDA, showing very few side effects compared with other medications [11]. Currently, ibuprofen is the only option available in Portugal [5]. A second cycle of treatment is indicated if the first one fails to close the DA [4]. Several studies comparing the safety and efficacy of indomethacin versus ibuprofen demonstrated equal efficacy in DA closure in preterm infants [9, 12]. However, there are studies showing shorter duration of ventilatory support, fewer cases of NEC and a lower incidence of oliguria in the ibuprofen group [9]. Nevertheless, the debate on the most appropriate treatment for the closure of

the DA is still ongoing in the light of the evidence currently available [5].

In this context, the purpose of this study is to compare the efficacy and safety of indomethacin versus ibuprofen whilst also not discarding the null hypothesis.

Methods

Study design: retrospective study conducted between January 2005 and December 2014. In January 2010, local PDA management protocol switched from indomethacin to ibuprofen as the drug of choice for medical treatment. The cohort of neonates treated with indomethacin from January 2005 to December 2009 was compared to those treated with ibuprofen from January 2010 to December 2014.

Patient population: we included all inborn infants with < 32 weeks gestational age or ≤ 1,500 g, admitted to the tertiary level Neonatal Intensive Care Unit (NICU) of "Centro Hospitalar São João". We excluded those with major malformations or genetic disorders; with congenital TORCH infections (Toxoplasmosis; Others such as syphilis, varicella-zoster or parvovirus B19; Rubella; Cytomegalovirus; and Herpes); transferred or deceased before 72 hours; outborns; and those with severe pathologies at birth that did not fit in the previous groups.

All patients below 30 weeks of age were submitted to systematic ultrasound screening between 24 and 72 hours; the remaining population included in the study was submitted to echocardiogram if clinical findings suggested PDA. According to NICU protocol, medical treatment was initiated if a hemodynamically significant PDA was diagnosed (ductal diameter > 1.5 mm, relationship left atrium / aorta diameter > 1.4 and resistance index in anterior cerebral and/or pericallosal arteries > 0.8) and the patient had no contraindication (serum creatinine > 2.5 mg/dL; platelet count < 25,000/mm^3; active bleeding; NEC; severe sepsis). Prophylactic indomethacin or ibuprofen are not used in our institution.

According to local and national protocols, indomethacin was given in intravenous (IV) cycles of three doses (the first 0.2 mg/kg/dose and the two remaining 0.1 mg/kg/dose); ibuprofen is also given in IV cycles of three doses (the first 10 mg/kg/dose and the two remaining 5 mg/kg/dose); the interval between doses was 24 hours [4, 5]. If DA failed to closed or reopened, a second cycle was considered, at least 48 hours after completion of the first cycle [5].

Data was collected from medical records and included demographic factors (sex, gestational age, birth weight); maternal and gestational data (intrauterine growth restriction, previous gestations and deliveries outcomes, antenatal steroids, maternal exposures and diseases, and pregnancy complications); labour data (delivery method, presence of spontaneous labour, duration of rupture of membranes, intrapartum antibiotic therapy, clinical chorioamnionitis, Apgar score at 1st and 5th minute and newborn resuscitation); and NICU clinical data and outcomes (ventilation mode and duration, oxygen therapy, surfactant use and respiratory morbidity, such as respiratory distress syndrome [RDS] and BPD, inotropic/vasopressor use, hemoglobin/hematocrit at birth and anemia, thrombocytopenia, metabolic acidosis, acute renal failure and oliguria, parenteral nutrition and duration, NEC, ROP, IVH, hydrocephalus, periventricular leukomalacia [PVL], early and late onset sepsis, length of hospital stay and death).

Intrauterine growth restriction was defined as a birth weight below the 10th percentile of Fenton's growth charts [13].

Antenatal corticosteroids therapy was performed according to the local protocol of Gynaecology and Obstetrics Department at our hospital. Until February 2014 betamethasone (2 doses of 12 mg separated by 24 hours) was used, and after March 2014 dexamethasone (4 doses of 6 mg every 12 hours) was used. Local NICU protocol for RDS treatment included surfactant therapy with poractant alfa administered in an initial dose of 200 mg/kg and, if required, subsequent doses of 100 mg/kg [14].

RDS was diagnosed by clinical and radiographic features, according to the criteria of the *European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants – 2013 update* [14]. BPD was diagnosed if requirement for supplementary oxygen therapy persisted for at least 28 days after delivery and it was associated with characteristic radiographic features. BPD was classified according to the *National Institutes of Health consensus definition* [15]. NEC was classified according to the modified Bell staging criteria [16, 17]. ROP was diagnosed and graded according to the *International Classification of Retinopathy of Prematurity revisited* [18]. IVH was diagnosed when brain ultrasound demonstrated intraventricular bleeding and was graded according

to the Papile classification [19]. PVL was diagnosed according to the de Vries classification [20]. Sepsis was considered in the presence of positive laboratory findings in a newborn with suggestive clinical findings and it was diagnosed in the presence of a positive blood culture.

The statistical analysis was performed using SPSS® for Windows®, version 23. Continuous variables were characterised by mean (± standard deviation) or median (medium-maximum) if they had symmetric or asymmetric distribution, respectively. Categorical variables were characterised by absolute and relative frequencies. To compare continuous variables, parametric tests (independent t test) or non-parametric tests (Mann-Whitney U test) were used. Chi-squared or Fisher's exact test were used to compare categorical variables. A multivariate analysis by logistic regression was performed to evaluate predictive factors of severity and morbidity. A p-value lower than 0.05 was considered statistically significant.

This study was authorized by the "Centro Hospitalar São João" Ethical Committee.

Results

Six hundred newborn infants < 32 weeks gestational age or ≤ 1,500 g birth weight admitted to the NICU of "Centro Hospitalar São João" were identified during the study period.

Two hundred and seventy two (45.3%) newborns were excluded: 173 (63.6%) outborns, 34 (12.5%) transferred before 72 hours, 26 (9.5%) died before 72 h, 17 (6.3%) with major malformations, 10 (3.7%), with genetic disorders, 4 (1.5%), with congenital TORCH infections, 8 (2.9%) with other severe pathologies (4 with fetal hydrops, 2 with perinatal asphyxia, 1 with severe nephropathy, 1 with hypermethioninemia).

A total of 328 (54.7%) newborns were included in the study: 99 (30.2%) had a PDA diagnosis (51 males and 48 females), and 229 (69.8%) did not (109 males and 120 females). In the group included in the study, the median gestational age was 30 weeks and the median birth weight was 1,231 grams.

PDA patients had a significantly lower gestational age (median 29 versus 31 weeks, $p < 0.001$), lower birth weight (median 1,110 versus 1,280 grams, $p < 0.001$), lower incidence of twin-to-twin transfusion and higher incidence of HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome (**Tab. 1**).

There was a significantly higher incidence of Apgar score lower than 7 at the 1st and 5th minutes, more frequent need of resuscitation and endotracheal intubation, greater need of invasive ventilation and oxygen, a higher number of days with nasal CPAP, and higher use of surfactant in the PDA group. This group also presented higher incidence of pneumothorax, pneumonia, inotropic medication, lower hemoglobin and hematocrit at birth, anemia, thrombocytopenia, metabolic acidosis, acute renal failure, oliguria, RDS, BPD, severe ROP, IVH, hydrocephalus and PVL. This group also showed a higher number of days of parenteral nutrition (median 20.5 versus 12, $p < 0.001$) and a longer hospital stay (median 45 versus 32, $p < 0.001$). Twenty-four (7.3%) infants died in the NICU, with a significant difference between the groups with and without PDA (18.4% versus 2.6%, $p < 0.001$) (**Tab. 2**).

Among the 99 patients with PDA, 21 were treated with indomethacin and 41 received ibuprofen. There was no statistically significant difference between indomethacin and ibuprofen groups in the number of required treatment cycles or in the reopening of PDA. The number of days with nasal CPAP was higher in ibuprofen group (median 34 versus 22, $p = 0.028$) while the number of days with invasive ventilation was higher in indomethacin group (median 21 versus 7, $p = 0.036$). Comparing indomethacin with ibuprofen treatment groups, in the indomethacin treatment group there was a higher incidence of thrombocytopenia and late onset sepsis and lower incidence of PVL (**Tab. 3**).

The multivariate analysis did not show any factors significantly associated with PDA. Regarding adverse events, ibuprofen was associated with a lower risk of thrombocytopenia (OR = 0.29, 95% CI [0.09-0.93], $p = 0.038$) than indomethacin.

Discussion

In this study we observed differences in the population with and without PDA in accordance with the literature, with a higher frequency of lower gestational age and birth weight in the first group [3, 21]. Some differences detected in the frequency of twin-to-twin transfusion and HELLP syndrome are not justified by weight and gestational age differences, because they are diagnosed at any stage of pregnancy. However, they are not described in the literature as factors

Table 1. Demographic and antenatal risk factors related to patent ductus arteriosus (PDA).

	Total (n = 328)	PDA (n = 99)	Without PDA (n = 229)	p-value
Gender, n (%)				
Male	160 (48.8)	51 (51.5)	109 (47.6)	0.515[a]
Female	168 (51.2)	48 (48.5)	120 (52.4)	
Gestational age (weeks), median (min-max)	30 (23-36)	29 (23-35)	31 (23-36)	**< 0.001**[c]
Birth weight (grams), median (min-max)	1,231 (450-2,210)	1,110 (450-2,025)	1,280 (520-2,210)	**< 0.001**[c]
Small for gestational age, n (%)	96 (29.4)	22 (22.4)	74 (32.3)	0.073[a]
Intrauterine growth restriction, n (%)	92 (29.8)	21 (22.8)	71 (32.7)	0.082[a]
Previous gestations, n (%)	140 (45.0)	50 (52.1)	90 (41.9)	0.094[a]
Number of previous gestations, median (min-max)	1 (1-6)	1 (1-5)	1 (1-6)	0.381[c]
Previous deliveries, n (%)	98 (31.8)	34 (35.8)	64 (30.0)	0.318[a]
Number of previous deliveries, median (min-max)	1 (1-6)	1 (1-3)	1 (1-6)	0.219[c]
Multiple gestation, n (%)	121 (36.9)	39 (39.4)	82 (35.8)	0.537[a]
Antenatal steroids, n (%)	280 (88.9)	86 (90.5)	194 (88.2)	0.543[a]
Full first cycle	204 (76.4)	63 (75.9)	141 (76.6)	0.897[a]
Maternal exposures and diseases, n (%)				
Smoking	11 (3.4)	6 (6.1)	5 (2.2)	0.073[a]
Alcohol	1 (0.3)	0 (0)	1 (0.4)	0.999[b]
Drugs	1 (0.3)	1 (1.0)	0 (0)	0.302[b]
Infection	29 (8.8)	7 (7.1)	22 (9.6)	0.458[a]
Medications	84 (29.8)	20 (21.5)	64 (29.0)	0.173[a]
Positive GBS screening	13 (54.2)	5 (62.3)	8 (50.0)	0.679[b]
Autoimmune diseases	13 (4.0)	2 (2.0)	11 (4.8)	0.358[b]
Diabetes mellitus	6 (1.8)	1 (1.0)	5 (2.2)	0.672[b]
Arterial hypertension	25 (7.6)	9 (9.1)	16 (7.0)	0.510[a]
Pregnancy complications, n (%)				
Gestational diabetes	24 (7.3)	4 (4.0)	20 (8.7)	0.168[b]
Pre-eclampsia	56 (17.1)	23 (23.2)	33 (14.4)	0.051[a]
Eclampsia	1 (0.3)	0 (0)	1 (0.4)	0.999[b]
HELLP syndrome	9 (2.7)	6 (6.1)	3 (3.1)	**0.024**[b]
Placental abruption	13 (4.0)	4 (4.0)	9 (3.9)	0.999[b]
Twin-to-twin transfusion	16 (4.9)	1 (1.0)	15 (6.6)	**0.046**[b]
Abnormal umbilical flow	62 (18.9)	15 (15.2)	47 (20.5)	0.254[a]

PDA: patent ductus arteriosus; GBS: group B streptococcus; HELLP syndrome: hemolysis, elevated liver enzymes and low platelet count syndrome.
[a]Chi-square test; [b]Fisher's exact test; [c]Mann-Whitney U test.

favouring the PDA, thus raising the hypothesis that there may be some unidentified factors that can explain this discrepancy.

All the differences between groups with and without PDA observed in the univariate analysis (**Tab. 1** and **Tab. 2**) were not confirmed by multivariate analysis. Possibly, these differences only reflect a significantly more immature population group with PDA (with lower gestational age and birth weight). Thus the PDA is probably just an immaturity marker.

In the literature, PDA is associated with some morbidities (BPD, NEC, ROP, IVH), longer duration of hospitalization, higher mortality; however, our multivariate analysis did not show any of these associations [6, 7].

We found that there was no significant difference between indomethacin and ibuprofen in the efficacy of closure rate, with a similar rate of DA reopening and number of cycles needed, and in hospital mortality. This result is consistent with several other studies showing no differences in treatment efficacy between the two drugs [9, 12, 22-24]. Nonetheless, a retrospective cohort study demonstrated that indomethacin was more efficacious for ductal closure than ibuprofen, although this did not have any impact on outcomes [25].

Univariate analysis showed some differences between groups that were not associated with the different treatment in the multivariate analysis, such as the type and duration of ventilation, and

Table 2. Mode of delivery and neonatal outcomes in relationship to patent ductus arteriosus (PDA).

	Total (n = 328)	PDA (n = 99)	Without PDA (n = 229)	p-value
Delivery, n (%)				
Vaginal	87 (26.5)	35 (35.4)	52 (22.7)	**0.017**[a]
C-section	241 (73.5)	64 (64.6)	177 (77.3)	
Presence of spontaneous labor, n (%)	155 (47.5)	47 (47.5)	108 (47.6)	0.985[a]
Rupture of the membranes > 18 h, n (%)	57 (18.1)	16 (17.0)	41 (18.6)	0.747[a]
Intrapartum antibiotic therapy, n (%)	64 (19.6)	16 (16.3)	48 (21.0)	0.333[a]
Clinical chorioamnionitis, n (%)	25 (7.6)	8 (8.1)	17 (7.5)	0.845[a]
Apgar score, n (%)				
1st min < 7	126 (38.4)	52 (52.5)	74 (32.3)	**< 0.001**[a]
5th min < 7	45 (13.7)	23 (23.2)	22 (9.6)	**0.001**[a]
Resuscitation, n (%)	150 (46.7)	69 (71.1)	81 (36.2)	**< 0.001**[a]
Endotracheal intubation, n(%)	110 (34.0)	52 (53.1)	58 (25.7)	**< 0.001**[a]
Nasal CPAP, n (%)	279 (85.8)	85 (87.6)	194 (85.1)	0.548[a]
Number of days with nasal CPAP, median (min-max)	17.5 (1-79)	26 (1-61)	10.5 (1-79)	**< 0.001**[c]
Invasive ventilation, n (%)	155 (47.4)	71 (71.7)	84 (36.8)	**< 0.001**[a]
Number of days with invasive ventilation, median (min-max)	6 (1-136)	8 (1-88)	4 (1-136)	**0.001**[c]
FiO_2, median (min-max)	0.30 (0.21-1.00)	0.40 (0.21-1.00)	0.21 (0.21-1.00)	**< 0.001**[c]
Number of days of oxygen, median (min-max)	5 (1-147)	8.5 (1-143)	3 (1-147)	**< 0.001**[c]
Surfactant, n (%)	165 (50.3)	79 (79.8)	86 (37.6)	**< 0.001**[a]
1st dose of surfactant (hours), median (min-max)	1.00 (0.07-48)	0.70 (0.07-48)	1.00 (0.07-32)	0.325[c]
Number of doses, median (min-max)	1 (1-4)	2 (1-4)	1 (1-3)	**0.001**[c]
Pneumothorax, n (%)	14 (4.3)	9 (9.2)	5 (2.2)	**0.004**[a]
Pneumonia, n (%)	10 (3.0)	7 (7.1)	3 (1.3)	**0.010**[b]
Amines	33 (10.4)	23 (25.6)	10 (4.4)	**< 0.001**[a]
VSD, n (%)	5 (1.5)	5 (5.1)	0 (0)	**0.002**[b]
ASD, n (%)	4 (1.2)	4 (4.0)	0 (0)	**0.008**[b]
Hemoglobin at birth, mean (± SD)	17.20 (± 2.43)	16.49 (± 2.81)	17.51 (± 2.18)	**0.002**[d]
Hematocrit, mean (± SD)	49.25 (± 6.59)	47.54 (± 7.04)	50.06 (± 6.23)	**0.004**[d]
Anemia, n (%)	145 (44.2)	64 (64.6)	81 (35.4)	**< 0.001**[a]
Thrombocytopenia, n (%)	64 (19.5)	34 (34.3)	30 (13.1)	**< 0.001**[a]
Metabolic acidosis, n (%)	36 (11.0)	21 (21.2)	15 (6.6)	**< 0.001**[a]
Acute renal failure, n (%)	24 (7.3)	20 (20.2)	4 (1.7)	**< 0.001**[b]
Oliguria, n (%)	7 (2.2)	5 (5.5)	2 (0.9)	**0.022**[b]
RDS, n (%)	167 (51.2)	74 (74.7)	93 (41)	**< 0.001**[a]
Degree ≥ 2 (moderate)	58 (51.8)	28 (66.7)	30 (42.9)	**0.015**[a]
BPD, n (%)	34 (10.4)	24 (24.2)	10 (4.4)	**< 0.001**[a]
NEC, n (%)	19 (5.8)	9 (9.1)	10 (4.4)	0.093[a]
Degree ≥ 2	6 (31.6)	2 (22.2)	4 (40.0)	0.628[b]
ROP, n (%)	123 (53.0)	52 (71.2)	71 (44.7)	**< 0.001**[a]
Degree ≥ 2	31 (25.0)	18 (35.3)	13 (17.8)	**0.027**[a]
IVH, n (%)	110 (34.3)	52 (53.6)	58 (25.9)	**< 0.001**[a]
Degree ≥ 3	24 (23.1)	15 (30.6)	9 (16.4)	0.085[a]
Hydrocephalus, n (%)	18 (5.6)	12 (12.4)	6 (2.7)	**0.001**[a]
PVL, n (%)	22 (6.9)	14 (14.4)	8 (3.6)	**< 0.001**[a]
PVL cystic	10 (45.5)	4 (28.6)	6 (75.0)	0.074[b]
Early onset sepsis, n (%)	10 (3.0)	2 (2.0)	8 (3.5)	0.729[b]
Late onset sepsis, n (%)	116 (35.5)	39 (39.4)	77 (33.8)	0.239[a]
Parenteral nutrition, n (%)	326 (99.4)	98 (99.0)	228 (99.6)	0.513[b]
Parenteral nutrition (days), median (min-max)	14 (2-101)	20.5 (5-90)	12 (2-101)	**< 0.001**[c]
Length of hospital stay (days), median (min-max)	35 (4-191)	45 (5-191)	32 (4-154)	**< 0.001**[c]
Deaths, n (%)	24 (7.4)	18 (18.4)	6 (2.6)	**< 0.001**[a]
Day of life, median (min-max)	18 (6-147)	19.5 (6-61)	13 (6-147)	0.626[c]

PDA: patent ductus arteriosus; VSD: ventricular septal defect; ASD: atrial septal defect; RDS: respiratory distress syndrome; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia.

[a]Chi-square test; [b]Fisher's exact test; [c]Mann-Whitney U test; [d]Independent t test.

Table 3. Comparison between Indomethacin and Ibuprofen in newborns with patent ductus arteriosus (PDA).

	Total (n = 99)	Indomethacin (n = 21)	Ibuprofen (n = 41)	p-value
Number of cycles, median (min-max)	1 (1-4)	1 (1-4)	1 (1-3)	0.340[c]
Reopening channel, n (%)	11 (18.3)	4 (21.1)	7 (17.1)	0.730[b]
Nasal CPAP, n (%)	85 (87.6)	15 (75.0)	36 (90.0)	0.145[b]
Number of days with nasal CPAP, median (min-max)	26 (1-61)	22 (6-53)	34 (6-61)	**0.028**[c]
Invasive ventilation, n (%)	71 (71.7)	19 (90.5)	34 (82.9)	0.705[b]
Number of days with invasive ventilation, median (min-max)	8 (1-88)	21 (2-55)	7 (1-88)	**0.036**[c]
FiO_2, median (min-max)	0.4 (0.21-1)	0.7 (0.21-1)	0.4 (0.21-1)	0.173[c]
Number of days of oxygen, median (min-max)	8.5 (1-143)	24 (2-117)	9 (1-143)	0.256[c]
Surfactant, n (%)	79 (79.8)	20 (95.2)	38 (92.7)	0.999[b]
1st dose of surfactant (hours), median (min-max)	0.7 (0.07-48)	1.00 (0.42-48)	0.63 (0.07-36)	0.068[c]
Number of doses, median (min-max)	2 (1-4)	2 (1-4)	2 (1-4)	0.129[c]
Pneumothorax, n (%)	9 (9.2)	2 (9.5)	5 (12.5)	0.999[b]
Pneumonia, n (%)	7 (7.1)	0 (0)	5 (12.2)	0.157[b]
Amines	23 (25.6)	9 (47.4)	8 (22.2)	0.055[a]
VSD, n (%)	5 (5.1)	0 (0)	3 (7.3)	0.545[b]
ASD, n (%)	4 (4.0)	0 (0)	1 (2.4)	0.999[b]
Hemoglobin at birth, mean (± SD)	16.49 (± 2.81)	16.01 (± 3.07)	16.38 (± 2.95)	0.661[d]
Hematocrit, mean (± SD)	47.54 (± 7.04)	45.23 (± 6.76)	46.31 (± 7.41)	0.639[d]
Anemia, n (%)	64 (64.6)	17 (81.0)	31 (75.6)	0.755[b]
Thrombocytopenia, n (%)	34 (34.3)	13 (61.9)	13 (31.7)	**0.023**[a]
Metabolic acidosis, n (%)	21 (21.2)	7 (33.3)	6 (14.6)	0.087[a]
Acute renal failure, n (%)	21 (21.2)	8 (38.1)	8 (19.5)	0.114[a]
Oliguria, n (%)	5 (5.5)	2 (10.0)	2 (5.6)	0.611[b]
RDS, n (%)	74 (74.7)	20 (95.2)	35 (85.4)	0.406[b]
Degree ≥ 2 (moderado)	28 (66.7)	10 (71.4)	12 (70.6)	0.999[b]
BPD, n (%)	24 (24.2)	8 (38.1)	14 (34.1)	0.758[a]
NEC, n (%)	9 (9.1)	4 (19)	3 (7.3)	0.214[b]
Degree ≥ 2	2 (22.2)	2 (50.0)	0 (0)	0.429[b]
ROP, n (%)	52 (71.2)	12 (66.7)	27 (84.4)	0.147[a]
Degree ≥ 2	18 (35.3)	4 (33.3)	13 (50.0)	0.486[b]
IVH, n (%)	52 (53.6)	11 (52.4)	25 (61.0)	0.516[a]
Degree ≥ 3	15 (30.6)	4 (36.4)	5 (22.7)	0.438[b]
Hydrocephalus	12 (12.4)	4 (19.0)	7 (17.1)	0.999[b]
PVL, n (%)	14 (14.4)	1 (4.8)	11 (26.8)	**0.046**[b]
PVL cystic	4 (28.6)	0 (0)	3 (27.3)	0.999[b]
Early onset sepsis, n (%)	2 (2.0)	2 (9.5)	0 (0)	0.111[b]
Late onset sepsis, n (%)	39 (39.4)	15 (71.4)	17 (41.5)	**0.025**[a]
Parenteral nutrition, n (%)	98 (99.0)	20 (95.2)	41 (100)	0.339[b]
Parenteral nutrition (days), median (min-max)	20.5 (5-90)	31.5 (12-78)	25 (7-90)	0.233[c]
Length of hospital stay (days), median (min-max)	45 (5-191)	43 (8-118)	59 (8-191)	0.255[c]
Deaths, n (%)	18 (18.4)	5 (23.8)	6 (15.0)	0.395[a]
Day of life, median (min-max)	19.5 (6-61)	25 (8-31)	21 (8-61)	0.999[c]

PDA: patent ductus arteriosus; VSD: ventricular septal defect; ASD: atrial septal defect; RDS: respiratory distress syndrome; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia.
[a]Chi-square test; [b]Fisher's exact test; [c]Mann-Whitney U test; [d]Independent t test

the incidence of late sepsis and LPV (**Tab. 3**). The fact that the first group (indomethacin group) received more invasive ventilation and the second group (ibuprofen) received more non-invasive ventilation was probably due to changes in unit practices, with the introduction and development of the concept of early CPAP and gentle ventilation, revealing a trend to use less invasive ventilation. The highest incidence of PVL in the second period may be associated with a higher survival of more immature newborns and/or with lower birth weight with improving care. Also, the lower incidence of late sepsis in the group treated with ibuprofen is probably related to

nosocomial infection control measures that have been introduced in the unit in 2010, namely the introduction of chlorhexidine and a creation of a guideline-supported indwelling intravascular central-lines (IICL) insertion checklist, daily access for the need of IICL and promptly removal when no longer essential, as well as regular auditing of implemented strategies.

Regarding the comorbidities associated with indomethacin and ibuprofen, we did not find significant differences with the exception of thrombocytopenia. This association has no parallel in the literature and we cannot demonstrate, in the light of current knowledge, any biological plausibility. However, we emphasize this difference as a possible area of future research. Recent studies demonstrated that PDA closure is not significantly affected by platelet count [26, 27], so even if indomethacin can cause thrombocytopenia, this will probably not affect the closure of the PDA.

To study the renal safety of indomethacin and ibuprofen we used acute renal failure and oliguria, because they are routinely monitored in our NICU. However, we know that these markers are not enough to discriminate between normal and abnormal renal function. Similarly to our study, other retrospective clinical studies did not observe any significant differences in hospital mortality, BPD or renal failure between groups, after adjusting for baseline severity of illness [28]. One meta-analysis in 2015 demonstrated a reduction in duration of ventilator support, in NEC and in risk of oliguria favouring the ibuprofen group [9]. A systematic review noted that with ibuprofen treatment there was a smaller rise in serum creatinine after treatment compared to indomethacin, when both were administered IV [24]. According to other systematic review and meta-analysis of 2007, the only statistically significant clinical risk is the lower incidence of oliguria in the ibuprofen group compared to the indomethacin group [22]. Also, some studies concluded that ibuprofen has fewer effects on renal function [12, 23]. However, a retrospective chart review indicated that both indomethacin and ibuprofen appear to have a similar overall effect on renal function [29]. Some studies concluded that ibuprofen causes a significantly smaller effect on cerebral perfusion and oxygenation than indomethacin, but cerebral perfusion has not been evaluated in our study [30].

One reason that can explain the absence of association between PDA or therapeutic interventions and comorbidities are the limitations of the study. The retrospective and non-randomized design, together with a relatively small number of subjects of a single center are the main limitations of this study, because they limit the power to detect significant differences between groups. Furthermore, we compared two sequential time periods using different drugs, and other changes occurred in the approaches to newborn infants during this period.

Conclusion

In conclusion, our study showed that indomethacin and ibuprofen have a similar effect in closing PDA in < 32 weeks preterm infants. We found no significant differences in safety between them, except for thrombocytopenia (more frequent in the indomethacin group). Further studies are necessary to compare both efficacy and side effects of ibuprofen and indomethacin to identify the optimal pharmacological agent for the medical management of PDA.

Declaration of interest

The Authors declare that there is no conflict of interest.

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