ORIGINAL RESEARCH

Efficacy of Pharmacologic Therapy for Patent Ductus Arteriosus Closure in Preterm Small for Gestational Age Infants

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Abstract

Objective: To determine the association between the degree of intrauterine growth restriction (IUGR) [defined by birth weight (BW) *Z*-score] and the efficacy of pharmacologic patent ductus arteriosus (PDA) closure and the rate of surgical PDA ligation in preterm neonates.

Materials and methods: In this retrospective cohort study, we included neonates born below 30 weeks' gestational age (GA), who received medical treatment for PDA between January 2010 and December 2018. Birth weight *Z*-scores were calculated using Olsen nomograms and classified into three categories: above −0.5; from −0.5 to −2.0; below−2. We compared responses to PDA treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and PDA ligations between these groups utilizing multivariable logistic regression analysis.

Results: Of 769 neonates with PDA, 517 (67.2%) neonates received medical treatment for PDA. Of which, 323 (62.5%) had BW *Z*-score above −0.5, 154 (29.8%) had from −0.5 to −2.0., and 40 (7.7%) had below −2. The efficacy of the first course of NSAIDs for the PDA closure was not different among the three groups (51% vs 49% vs 50%). Multivariable logistic regression analysis showed there was no significant difference in PDA closure rate following the first course of NSAIDs between neonates with BW *Z*-score below −2 and those with BW *Z*-score above −0.5 [adjusted odds ratio (aOR): 0.68; 95% CI: 0.33–1.39] as well as those with BW *Z*-score from −0.5 to −2.0 (aOR: 0.89; 95% CI: 0.59–1.35). However, the odds of PDA ligation were significantly higher among neonates with BW *Z*-scores below −2 (aOR: 2.67, 95% CI: 1.12–6.34) but not among neonates with *Z*-scores from −0.5 to −2.0 (aOR: 1.41; 95% CI: 0.84–2.39), as compared to those with BW *Z*-scores above −0.5.

Conclusion: We observed a similar rate of PDA closure following the first course of NSAIDs between appropriately grown and growth-restricted neonates. However, severe growth restriction (BW *Z*-score below −2) is associated with higher rates of PDA ligation as compared to normally grown infants.

Keywords: Ibuprofen, Indomethacin, Intrauterine growth restriction, Patent ductus arteriosus, Prematurity.

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Introduction

Patent ductus arteriosus is one of the most common cardiovascular conditions encountered in preterm neonates. Approximately 70% of neonates below 28 weeks GA and 80% of neonates born at 24–25 weeks GA are affected with PDA during their neonatal intensive care unit (NICU) stay.[1] A hemodynamically significant PDA (HsPDA) can lead to left-to-right shunting of blood and undesirable pulmonary, renal, and gastrointestinal effects, including pulmonary edema and hemorrhage, congestive cardiac failure, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), feeding intolerance, poor weight gain, bronchopulmonary dysplasia (BPD) and death.[2]

Non-steroidal anti-inflammatory agents such as Indomethacin and ibuprofen are the two commonly used medications for PDA closure, whereas acetaminophen is an emerging potentially less toxic option with similar efficacy to the NSAIDs.[3] The PDA closure rates after an initial course of pharmacologic treatment vary from 48% to 98.5%.[4] In Canada, conservative PDA management in neonates below 32 weeks' gestation has increased from 14% to 38% from 2006 to the year 2012, whereas the surgical treatment rates have decreased from 7.1% to 2.5% during this epoch.[5]

Compared to appropriately grown preterm neonates, IUGR preterm neonates are at increased risk of neonatal mortality and morbidities.[6,7] In most cases, fetuses who show IUGR are delivered small for gestational age (SGA, BW less than tenth percentile for GA).[6] Growth-restricted preterm neonates not only have a higher incidence of significant PDA but also more frequent and earlier hemodynamic consequences of PDA.[8,9] Heymann reported a higher failure rate of indomethacin therapy for PDA closure among SGA neonates in 1987[10] and speculated that this could be due to altered levels of prostaglandins, or differences in receptor number or sensitivity. Few studies have examined the efficacy of pharmacologic PDA closure among neonates based on their

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degree of IUGR, with differing results.[11,12] In a single-center study from France, Madeleneau et al. reported the impact of SGA on the treatment for PDA in extremely preterm infants and concluded that failure of the first course of ibuprofen increased with the degree of growth restriction, reaching a maximum of 12.8-fold higher risk of failure, according to a gradient that intensified with regression adjustments.[11] A multicentre study from the United States reported that SGA infants with *Z*-scores between −2 and −0.5 were more likely to have PDA surgery following indomethacin and/or ibuprofen treatment compared to normally grown infants.[12] Infants with *Z*-scores below −2 had more than 3-fold increased odds of experiencing the composite of PDA surgery following pharmacologic treatment or death, and those with *Z*-scores between −2 and −0.5 had 1.5-fold increased odds.

We hypothesize that preterm growth-restricted infants are less likely to respond to medical treatment for PDA and may need surgical PDA ligation. The objective of this study was to determine the association between the degree of IUGR (defined by BW *Z*-score) and the efficacy of pharmacologic PDA closure and subsequent surgical PDA ligation rate in preterm neonates.

Materials and Methods

In this retrospective cohort study, we included neonates with GA below 30 weeks at birth admitted to the NICU at Foothills Medical Centre in Calgary, Alberta, Canada, between January 2010 and December 2018, who received pharmacological treatment (indomethacin, ibuprofen, or acetaminophen) for PDA. We excluded neonates with major congenital anomalies, neonates who received NSAIDs solely for the purpose of pain management or prophylactic indomethacin for prevention of brain injury, those who died before 48 hours of age or who had primary PDA ligation without any medical treatment. The Conjoint Health Research Ethics Board at the University of Calgary approved this study (REB19-1787).

In our NICU, the decision to treat a PDA was at the discretion of the attending physician and is based on clinical signs and symptoms (such as new onset murmur, wide pulse pressure, systemic hypotension, bounding pulses, and new onset changes in respiratory requirements considered to be due to PDA or clinical deterioration ascribed largely to the PDA), supplemented by echocardiographic confirmation of HsPDA. For this study, HsPDA was defined as a trans-ductal diameter measured at its narrowest dimension of above 1.5 mm, a peak systolic velocity below 1.5 m/second or left atrium (LA) to aortic (Ao) ratio (LA: Ao) above 1.5, as well as either predominantly or complete left-to-right shunting with or without absent or reversed diastolic flow in celiac or superior mesenteric artery.[13,4]

Indomethacin (Indocid P.D.A, Merck Frosst, Kirkland, Canada) is given intravenously in 3 doses at 12-hour intervals with doses varied by age (below 48 hours of life, 0.2, 0.1, and 0.1 mg/kg/dose; 2–7 days of life 0.2 mg/kg for each of the 3 doses; and above 7 days of life, 0.2, 0.25, and 0.25 mg/kg/dose). Ibuprofen is given in 3 doses of 10, 5, and 5 mg/kg/dose at 24-hour intervals. The second course of medical therapy is given for a HsPDA which failed to close on the first attempt. Surgical ligation is indicated if there was a failure to close after ≥2 courses of medication, or in those symptomatic cases with persisting complications from the shunt but with contra-indications to medications. We defined successful pharmacologic closure of PDA if there was the amelioration of clinical symptoms and signs of PDA and/or echocardiographic evidence of PDA closure within 72 hours of treatment.

Data Collection

After ethical approval, eligible neonates were identified from the NICU administrative electronic database and both electronic medical records and paper charts were reviewed. We abstracted demographic characteristics such as GA; BW; sex; antenatal steroids; mode of delivery; singleton vs multiple pregnancy; Apgar scores at birth; antepartum complications; score for neonatal acute physiology (SNAP-II); details of PDA; types of medications, dose, and duration of pharmacotherapy; side effects of treatment (i.e., acute kidney injury defined as urine output below 0.5 mL/kg/hour for above 8 hours or increase in serum creatinine above 30 µmol/L within 72 hours of treatment or above or equal to 50% from baseline, gastrointestinal bleeding), NEC above or equal to stage II by modified Bell staging,[14] surgical PDA ligation, IVH (based on validated classification system),[15] and BPD defined as the need for oxygen or respiratory support at 36 weeks postmenstrual age.

Standard BW *Z*-scores were calculated using Olsen nomograms and classified into three categories: Above −0.5, from −0.5 to −2.0, below−2 (severe IUGR).[16] Infants with *Z*-score above −0.5 constituted the reference group.

Outcome Measures

The primary outcome was the PDA closure rate following the first course of any of the three medications. Secondary outcomes included the proportion of infants needing a second or third course of medication, surgical PDA ligation, and those who had side effects from their pharmacologic treatment (such as gastrointestinal bleeding, intestinal perforation, acute kidney injury, NEC above or equal to stage II), BPD and death during the hospital stay.

Sample Size

A study by Madeleneau et al.[11] showed an 18% difference in the proportion of neonates who closed their PDA after the first course of NSAIDs between categories of infants with BW above −0.5 *Z*-scores, compared to those with BW below −0.5 *Z*-scores. A sample size calculation of 120 neonates in each group (BW category above −0.5 *Z*-scores and the IUGR categories) would be required to find a 20% difference in PDA closure rates between growth-restricted infants and AGA infants at 80% power and alpha error of 5%.

Statistical Analysis

The study cohort was summarized using descriptive statistical methods. We compared the baseline characteristics between the three groups using univariate analysis. Chi-squared tests or Fisher's exact tests for categorical variables were used where appropriate, and the student's *t*-test was employed for continuous variables. Statistical analyses were performed using stata 14 (Stata Corp, College Station, TX). Multivariable logistic regression analysis was performed to evaluate the independent association of BW *Z*-score and response to NSAIDs and subsequent PDA ligation. Covariates included in the regression model include factors that are associated with PDA closure (GA, antenatal steroids, gender), mode of delivery, and illness severity score. A two-tailed $p < 0.05$ was considered statistically significant.

Results

A total of 1,511 preterm neonates were admitted to NICU during the study period. Of which 769 (51%) neonates were diagnosed with PDA. A total of 517 neonates received at least one course of medical treatment for PDA (Flowchart 1). Of 517 included neonates,

Flowchart 1: Flow diagram of the study population

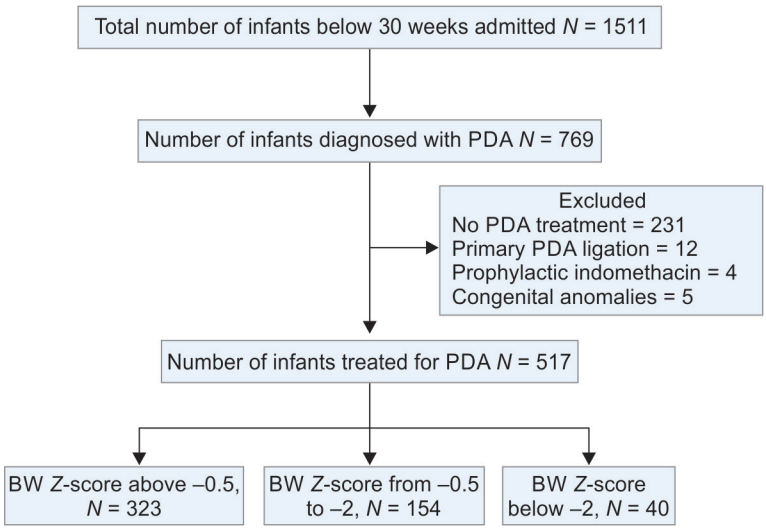

Table 1: Demographic characteristics

	BW Z-score above –0.5, N = 323	*BW Z-score from –0.5 to –2.0, N = 154*	*BW Z-score below –2.0, N = 40*	*p-value*
Maternal				
Maternal age (year)[a] mean	31.1 ± 5.8	31.9 ± 5.04	30.5 ± 5.5	0.145
Hypertension, *n* (%)	16 (4.9)	51 (33.1)	20 (50)	<0.001
Antenatal steroids, *n* (%)	278 (86)	140 (91)	40 (100)	0.01
Cesarean delivery, n (%)	193 (59.7)	103 (66.8)	35 (87.5)	0.002
Neonatal				
GA (week)[a]	25.9 ± 1.7	25.9 ± 1.85	26.6 ± 1.56	0.03
Birth weight (g)[a]	928 ± 222	713 ± 165	538 ± 90	<0.001
Male, *n* (%)	160 (49.5)	79 (51.3)	28 (70)	0.05
Multiples, *n* (%)	90 (27.8)	51 (33.1)	6 (15)	0.07
Apgar score at 5 minutes[b]	7 (6, 8)	7 (6, 8)	7 (5, 8)	0.30
SNAP-II[b]	14 (5, 24)	14 (9, 22)	14 (9, 22)	0.37

[a]Mean ± SD, [b]Median (interquartile range), SNAP-II, Score for acute neonatal physiology, version II

323 (62.5%) neonates had BW *Z*-score above – 0.5; 154 (29.8%) had from – 0.5 to –2.0, and 40 (7.7%) had below –2.

Table 1 shows the comparison of demographic characteristics. Maternal hypertension, exposure to antenatal steroids, and cesarean delivery were significantly higher in BW *Z*-score below –2 group. As expected, the mean GA and BW was significantly different among the three groups. Male gender was also higher among BW *Z*-score below–2 group.

Response to First Course of Medications

Of the 517 neonates, 206 (39.9%) received indomethacin, 301 (58.2%) received ibuprofen, and only 10 (1.9%) infants received acetaminophen as the first course of medication.

The PDA closure rate following the first course of NSAIDs was 51, 49, and 50%, respectively, among the three groups, which was not statistically significant (Table 2).

Patent Ductus Arteriosus Ligation

A total of 90 (17.4%) infants had surgical PDA ligation following medical treatment. There was a trend toward an increased rate of surgical PDA ligation rate with worsening growth restriction (15% vs 20% vs 25%). There was no significant difference in the complication rates and neonatal morbidity among the three groups except for BPD (Table 2). Bronchopulmonary dysplasia was also significantly higher among BW *Z*-score below –2 group as compared to normal growth neonates (85% vs 68%, $p = 0.04$).

Table 3 shows the multivariable logistic regression analysis adjusting for GA, sex, antenatal steroids, mode of delivery, and SNAP-II. There was no significant difference in PDA closure rate following the first course of NSAIDs between neonates with BW *Z*-scores below –2 and those with BW *Z*-score above –0.5, (aOR: 0.68; 95% CI: 0.33–1.39), and those with *Z*-score from –0.5 to –2.0 (aOR: 0.89; 95% CI: 0.59–1.35). However, the adjusted odds of PDA ligation were significantly higher among neonates with BW *Z*-score below –2 (aOR: 2.67, 95% CI: 1.12–6.34) but not among neonates with BW *Z*-score from –0.5 to –2.0 (aOR: 1.41; 95% CI: 0.84–2.39) as compared to BW *Z*-score above –0.5.

Discussion

Our study found a similar efficacy of the first course of NSAID medication in achieving closure of a PDA among the preterm growth-restricted neonates compared to well-grown neonates,

Table 2: Comparison of outcomes

	BW Z-score above –0.5, N = 323	*BW Z -score from –0.5 to –2.0, N = 154*	*BW Z -score below – 2.0, N = 40*	*p-value*
Primary outcome				
Response to the first course of NSAIDs, *n* (%)	164 (51)	75 (49)	20 (50)	0.91
Indomethacin, *n/N* (%)	69/126 (55)	39/64 (61)	10/16 (62.5)	0.65
Ibuprofen, *n/N* (%)	94/193 (49)	36/86 (42)	9/22 (41)	0.50
Acetaminophen, *n/N* (%)	1/4 (25)	0/4 (0)	1/2 (50)	0.33
Secondary outcomes				
Second course NSAIDs, *n* (%)	104 (32)	56 (36)	12 (30)	0.59
Third course NSAIDs, *n* (%)	27 (8.3)	15 (9.7)	4 (10)	0.85
Surgical PDA ligation, *n* (%)	49 (15)	31 (20)	10 (25)	0.17
Acute kidney injury, *n* (%)	31 (9.6)	19 (12.3)	3 (7.5)	0.74
Gastrointestinal bleed, *n* (%)	20 (6.1)	6 (3.9)	2 (5)	0.58
Spontaneous intestinal perforation, *n* (%)	8 (2.4)	7 (4.5)	3 (7.5)	0.18
IVH ≥ grade III, *n* (%)	41 (12.6)	19 (12.3)	1 (2.5)	0.16
NEC ≥ stage II, *n* (%)	33 (10.2)	19 (12.3)	7 (17.5)	0.35
BPD, *n* (%)	220 (68)	114 (74)	34 (85)	0.06

BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NSAID, non-steroidal anti-inflammatory drug; PDA, patent ductus arteriosus

Table 3: Adjusted outcome

Outcome	*Reference*	*BW Z-score from –0.5 to –2.0 (aOR; 95% CI)*	*BW Z-score below –2.0 (aOR; 95% CI)*
Primary outcome			
PDA closure after first course of NSAIDs	BW *Z*-score above –0.5	0.89 (0.59, 1.35)	0.68 (0.33, 1.39)
Secondary outcome			
PDA ligation	BW *Z*-score >–0.5	1.41 (0.84, 2.39)	2.67 (1.12, 6.34)

with closure rates between 49 and 51% for all three groups. However, the preterm growth-restricted neonates with *Z*-score below –2 with PDA had a 2.6-fold increase in odds of surgical PDA ligation as compared to normally grown neonates (*Z*-score above –0.5).

A common problem of studies assessing the potential association of growth restriction with adverse neonatal outcomes is that they do not differentiate between SGA and IUGR, even though the two terms are not synonymous.[17,18] A recent systematic review reporting the association of IUGR/SGA and PDA included 47 studies reported that there was no conclusive evidence of an association between growth restriction and PDA.[19] This finding may be due to marked heterogeneity across the studies in regard to the definition of growth restriction and PDA. For example, when the authors use the definition of SGA as BW less than 10 percentile, there was a significantly reduced risk of PDA (OR: 0.81; 95% 0.66–0.98) but this association disappeared when SGA was defined as BW less than 3 percentile (OR: 1.09; 95% CI: 0.7–1.71).[19]

In contrast to our findings of similar efficacy of PDA closure following the first course of any of these NSAIDs regardless of the birthweight *Z*-score, Madeleneau et al. reported that the success rate of the first course of ibuprofen decreases with increasing severity of growth restriction in France.[11] In their study of 185 neonates (GA from 24 weeks to 27 6/7 weeks), only 18 neonates were BW *Z*-score below –2. The success rate of the first course of ibuprofen was 45% in the study cohort. The risk of failure of the first course of ibuprofen increased with the degree of growth restriction, reaching above 12-fold higher risk of failure with a wide confidence interval (adjusted OR: 12.8; 95% CI: 2.3–70.5). However, there was no significant difference in surgical PDA ligation rate with increasing growth restriction. The two important differences between our study and the study by Madeleneau et al. is that our study had a higher number of SGA infants (194 infants below 30 weeks) as compared to 55 infants (GA below 28 weeks) in their study. Second, our cohort consisted of infants who receive indomethacin and ibuprofen as compared to ibuprofen treatment in their study.

Traditionally, studies on PDA management have often excluded SGA/IUGR subgroups. The SGA status is analyzed as a risk factor for PDA, rather than a predictive factor for treatment failure. In our study, we classified BW standard deviations (SDs) into three categories to reflect the potential continuous pathological effect of worsening growth restriction affecting mortality and neonatal morbidities. Previous epidemiologic studies have described preterm infants' growth restriction status using a –2 SD (or tenth percentile) cut-off for SGA. However, more recent studies show that this definition may no longer be appropriate because it inadequately describes the risks associated with fetal growth restriction based on just a single cut-off value.[20,21] Based on Delphi procedure, the growth restriction

in the newborn is defined as BW less than third percentile or the presence of three out of the 5 following; BW less than 10 percentile; head circumference less than 10 percentile; length less than 10 percentile; prenatal diagnosis of fetal growth restriction and maternal pregnancy information such as preeclampsia or pregnancy-induced hypertension.[18]

In preterm neonates, a persistent PDA is likely due to increased sensitivity of the immature ductus to prostaglandin E2 (PGE2). Also, PGE2 increases the intracellular concentration of cyclic adenosine monophosphate (cAMP), which activates cAMP-dependent protein kinase A (PKA), resulting in vasodilation in the ductus arteriosus. Prostaglandin E2 acts through three G protein–coupled receptors (EP2, EP3, and EP4) that activate adenylyl cyclase. The immature ductus has increased cAMP production because of increased binding of PGE2 to the individual EP receptors and increased potency of cAMP on PKA-regulated paththways.[22]

A previous study showed higher rates of significant PDA within 48 hours of birth among growth-restricted preterm neonates of 26–32 weeks in comparison to non-growth-restricted neonates (65% vs 40%).[8] Growth-restricted preterm neonates are at increased risk of elevated concentrations of inflammation-associated proteins by postnatal day 14.[23] Part of this increased risk might be a consequence of their greater tendency to be exposed to inflammatory stimuli such as sepsis/bacteremia, and prolonged ventilation. This inflammation and likely injury thereof might play a role in modulating response to NSAID treatment. Also, higher pulmonary blood flow is observed in growth-restricted preterm neonates resulting from lower pulmonary vascular resistance due to chronic hypoxia *in utero*. Catecholamines, especially norepinephrine has been shown to increase pulmonary blood flow in fetal lambs.[24,25] This pulmonary vasodilator effect of norepinephrine can be enhanced by glucocorticoids[26] production which is increased in fetuses with IUGR of placental origin.[27]

In a comparative study by Ibara et al., the histologic changes of PDA, such as fragmentation, coagulation necrosis of the intimal elastic lamina, hemorrhage with necrosis, and loosening of elastic fibers and muscles in the tunica media, were seen more frequently in IUGR neonates compared to AGA neonates.[28] These ductal changes may explain why HsPDA has been reported to occur more frequently and at an earlier postnatal age in very preterm growth-restricted neonates.[8,9] Reactivity to ductus arteriosus is also impaired by exposure to chronic fetal hypoxia.

We observed a 2.6-fold increase in surgical PDA closure among neonates with BW *Z*-score below −2. Similarly, Madelenau et al. from France reported a linear relationship between the degree of growth restriction and the need for surgical closure following ibuprofen treatment.[11] Compared to infants with *Z*-scores above −0.5, infants with *Z*-scores between −1.5 and −0.5 had more than 2-fold (OR: 2.6; 95% CI: 1.03–6.8) and infants with *Z*-scores below −1.5 had more than 12-fold (OR: 12.8; 95% CI: 2.3–70.5) increased odds of undergoing surgical closure following the first course of ibuprofen.[11] Boghossian et al.[12] reported higher rates of surgical PDA ligation among preterm SGA neonates after pharmacological treatment with indomethacin or ibuprofen. Compared to neonates with BW *Z*-score below −0.5, surgical PDA ligation following pharmacological treatment was higher among neonates with BW *Z*-score from −2 to −0.5 (OR: 1.23; 95% CI: 1.02–1.47) but this association was not significant for neonates with BW *Z*-score below −2 (OR: 0.83, 95% CI: 0.52–1.33).[12]

Ibuprofen is available as a racemic mixture of R- and S-ibuprofen, with S-ibuprofen being the pharmacologically active drug. The higher requirement of PDA ligation in more growth-restricted neonates might partly be explained by the fact that SGA neonates have been known to have a much higher clearance of S-ibuprofen compared to the appropriate weight for age neonates.[29] Currently used ibuprofen dosing regimens, however, do not consider the enantiomer-specific pharmacokinetics and postnatal day. The dosage of Ibuprofen needs to be adjusted based on BW and postnatal age.[29]

We also observed a significantly higher rate of BPD among growth-restricted infants. This association remained even after adjusting for PDA ligation (aOR 3.27; 95% CI 1.40–9.83). Our finding is similar to previous studies who reported SGA was associated with BPD.[30,31]

The strength of this study was the robust data over nine years from a tertiary care provincial referral NICU in Canada dealing specifically with the population of interest. We followed our PDA treatment guidelines and had a consensus between physicians about when to treat the ductus and with what medications. The pragmatic design of this study was very practical and can relate to the day-to-day practice where we target the HsPDA that is becoming problematic for our infants on an individual case-to-case basis. This goes in favor of the current individualistic approach that many physicians employ toward the ideal management of the ductus arteriosus.

Our study had the limitations of a retrospective design. This is a single-center study and there is an imbalance in the sample size for the three groups. As the study spans a period of nine years, there have been some differences in the relative use of one medication over other medications depending on drug availability locally and elsewhere in the world. There were some changes in ventilation management, especially using non-invasive ventilation during the latter part of the study period. Nonetheless, the treatment approach to PDA was relatively uniform throughout the study period.

Knowing that the commonly used NSAIDs have adverse effects, our study may help inform which neonates are less likely to respond to pharmacologic treatment. This study also highlights that in the smallest birthweight preterm infants, ductal closure is harder to achieve pharmacologically and may cause persistent adverse hemodynamic effects necessitating surgical ductal ligation more often. This might invoke further research into a deeper understanding of the pathophysiology of the underlying mechanisms and could also open new avenues of tackling the symptomatic ductus arteriosus in these infants differently. More research is also needed to elucidate the specific pathways and interactions of prostaglandins in mediating the ductal closure in growth restricted neonates and to identify other factors or unknown confounders that may play a crucial role as there is a paucity of current evidence on this crucial topic.

In conclusion, we observed a similar rate of PDA closure following the first course of NSAIDs between appropriately grown neonates and growth-restricted neonates. However, growth-restricted preterm neonates have higher odds of PDA ligation following pharmacological treatment as compared to appropriately grown preterm neonates with PDA.

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References

1. Benitz WE; Committee on Fetus and Newborn, American Academy of Pediatrics. Patent Ductus Arteriosus in preterm infants. Pediatrics 2016;137(1):10.1542. DOI: 10.1542/peds.2015-3730.
2. Cotton RB, Stahlman MT, Kovar I, et al. Medical management of small preterm infants with symptomatic patent ductus arteriosus. J Pediatr 1978;92(3):467–473. DOI: 10.1016/s0022-3476(78)80451-x.
3. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. Cochrane Database Syst Rev 2018;4(4):CD010061. DOI: 10.1002/14651858.CD010061.pub3.
4. Jain A, Shah PS. Diagnosis, evaluation, and management of Patent Ductus Arteriosus in preterm neonates. JAMA Pediatr 2015; 169(9):863–872. DOI: 10.1001/jamapediatrics.2015.0987.
5. Lokku A, Mirea L, Lee SK, et al. Trends and outcomes of Patent Ductus Arteriosus treatment in very preterm infants in Canada. Am J Perinatol 2017;34(5):441–450. DOI: 10.1055/s-0036-1593351.
6. Fenton TR. A new growth chart for preterm babies: Babson and Benda's chart updated with recent data and a new format. BMC Pediatr 2003;3:13. DOI: 10.1186/1471-2431-3-13.
7. Garite TJ, Clark R, Thorp JA. Intrauterine growth restriction increases morbidity and mortality among premature neonates. Am J Obstet Gynecol 2004;191(2):481–487. DOI: 10.1016/j.ajog.2004.01.036.
8. Rakza T, Magnenant E, Klosowski S, et al. Early hemodynamic consequences of patent ductus arteriosus in preterm infants with intrauterine growth restriction. J Pediatr 2007;151(6):624–628. DOI: 10.1016/j.jpeds.2007.04.058.
9. Robel-Tillig E, Knupfer M, Vogtmann C. Cardiac adaptation in small for gestational age neonates after prenatal hemodynamic disturbances. Early Hum. Dev 2003;72(2):123–129. DOI: 10.1016/s0378-3782(03)00045-8.
10. Heymann MA. Prostaglandins and leukotrienes in the perinatal period. Clin Perinatol 1987;14(4):857–880. PMID: 2827932.
11. Madeleneau D, Aubelle M.S, Pierron C, et al. Efficacy of a first course of ibuprofen for patent ductus arteriosus closure in extremely preterm newborns according to their gestational age-specific *Z*-score for birth weight. PLoS One 2015;10(4):e0124804. DOI: 10.1371/journal.pone.0124804.
12. Boghossian NS, Do BT, Bell EF, et al. Efficacy of pharmacologic closure of patent ductus arteriosus in small-for-gestational-age extremely preterm infants. Early Hum Dev 2017;113:10–17. DOI: 10.1016/j.earlhumdev.2017.07.011.
13. Sehgal A, McNamara PJ. Does echocardiography facilitate the determination of hemodynamic significance attributable to the ductus arteriosus? Eur J Pediatr 2009;168(8):907–914. DOI: 10.1007/s00431-009-0983-3.
14. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis: therapeutic decisions based upon clinical staging. Ann Surg 1978;187(1):1–7. DOI: 10.1097/00000658-197801000-00001.
15. Mohammad K, Scott JN, Leijser LM, et al. Consensus approach for standardizing the screening and classification of preterm brain injury diagnosed with cranial ultrasound: A Canadian perspective. Front Pediatr 2021;9; 618236. DOI: 10.3389/fped.2021.618236.
16. Olsen IE, Groveman SA, Lawson ML, et al. New intrauterine growth curves based on United States data. Pediatrics 2010;125(2):e124–e124. DOI: 10.1542/peds.2009-0913.
17. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: A Delphi procedure. Ultrasound Obstet Gynecol 2016;48(3):333–339. DOI: 10.1002/uog.15884.
18. Beune IM, Bloomfield FH, Ganzevoort W, et al. Consensus based definition of growth restriction in the newborn. J Pediatr 2018;196:71.e1–76.e1. DOI: 10.1016/j.jpeds.2017.12.059.
19. Villamor-Martinez E, Kilani MA, Degraeuwe PL, et al. Intrauterine growth restriction and patent ductus arteriosus in very and extremely preterm infants: A systematic review and meta-analysis. Front Endocrinol (Lausanne) 2019;10:58. DOI: 10.3389/fendo.2019.00058.
20. Guellec I, Lapillonne A, Renolleau S, et al. Neurologic outcomes at school age in very preterm infants born with severe or mild growth restriction. Pediatrics 2011;127(4):e883–e891. DOI: 10.1542/peds.2010-2442.
21. Zeitlin J, El Ayoubi M, Jarreau PH, et al. Impact of fetal growth restriction on mortality and morbidity in a very preterm birth cohort. J Pediatr 2010;157(5):733.e1–739.e1. DOI: 10.1016/j.jpeds.2010.05.002.
22. Waleh N, Kajino H, Marrache AM, et al. Prostaglandin E2-mediated relaxation of the ductus arteriosus: Effects of gestational age on G-protein-coupled receptor expression, signalling, and vasomotor control. Circulation. 2004;110(16):2326–2332. DOI: 10.1161/01.CIR.0000145159.16637.5D.
23. McElrath TF, Allred EN, Van Marter L, et al. ELGAN Study Investigators. Perinatal systemic inflammatory responses of growth-restricted preterm newborns. Acta Paediatr 2013;102(10):e439–e442. DOI: 10.1111/apa.12339.
24. Jaillard S, Houfflin-Debarge V, Riou Y, et al. Effects of catecholamines on the pulmonary circulation in the ovine fetus. Am J Physiol Regul Integr Comp Physiol 2001;281(2):R607–R614. DOI: 10.1152/ajpregu.2001.281.2.R607.
25. Magnenant E, Jaillard S, Deruelle P, et al. Role of the alpha2-adrenoceptors on the pulmonary circulation in the ovine fetus. Pediatr Res 2003;54:44–51. DOI: 10.1203/01.PDR.0000065726.43910.91.
26. Deruelle P, Houfflin-Debarge V, Magnenant E, et al. Effects of antenatal glucocorticoids on pulmonary vascular reactivity in the ovine fetus. Am J Obstet Gynecol 2003;189(1):208–215. DOI: 10.1067/mob.2003.444.
27. Goland RS, Jozak S, Warren WB, et al. Elevated levels of umbilical cord plasma corticotropin-releasing hormone in growth-retarded fetuses. J Clin Endocrinol Metab 1993;77(5):1174–1179. DOI: 10.1210/jcem.77.5.8077309.
28. Ibara S, Tokunaga M, Ikenoue T, et al. Histologic observation of the ductus arteriosus in premature infants with intrauterine growth retardation. J Perinatol 1994;14(5):411–416. PMID: 7830159.
29. Engbers AGJ, Flint RB, Völler S, et al. Enantiomer specific pharmacokinetics of ibuprofen in preterm neonates with patent ductus arteriosus. Br J Clin Pharmacol 2020;86(10):2028–2039. DOI: 10.1111/bcp.14298.
30. Qiu X, Lodha A, Shah PS, et al. Neonatal outcomes of small for gestational age preterm infants in Canada. Am J Perinatol 2012;29(2):87–94. DOI: 10.1055/s-0031-1295647.
31. Nobile S, Marchionni P, Carnielli. Neonatal outcome of small for gestational age preterm infants. Eur J Pediatr 2017;176(8):1083–1088. DOI: 10.1007/s00431-017-2957-1.