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Treatment of patent ductus arteriosus with bidirectional flow in neonates

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Abstract

Background—Patent ductus arteriosus is a common occurrence among prematurely born neonates and is believed to play a role in the development of other complications of prematurity including intraventricular hemorrhage, bronchopulmonary dysplasia, and necrotizing enterocolitis. The clinical decision to treat the patent ductus arteriosus is complicated by the lack of evidence available regarding clinical conditions under which closure should be attempted.

Study aims—To compare clinical outcomes for neonates who underwent treatment of patent ductus arteriosus exhibiting bidirectional blood flow versus those with flow that was left to right.

Study design—Cohort study of all neonates with patent ductus arteriosus in which medical closure was attempted at the Duke University between January 2002 and October 2007.

Outcome measures—Death and other important clinical conditions.

Results—We identified 20 neonates with bidirectional flow out of 317 cases in which medical closure of patent ductus arteriosus was attempted. There was no significant increase in overall complications due to closure of a bidirectional patent ductus arteriosus [40% (8/20)] versus ones with left to right shunting [38% (111/297) $p=0.82$]. Death occurred in 15% (3/20) with bidirectional PDA compared to 11% (34/297) in the left to right group, $p=0.72$.

Conclusion—The trend in mortality is worrisome but does not contraindicate an aggressive approach to the clinically significant PDA that has bidirectional flow at the time of the echocardiogram.

Keywords

Ductal closure; Preterm infant; Echocardiography; Bronchopulmonary dysplasia

1. Background

Patent ductus arteriosus (PDA) beyond the first 24 postnatal hours is a common occurrence among prematurely born neonates and is believed to play a role in the development of other complications of prematurity including intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), and necrotizing enterocolitis (NEC) [1,2]. The clinical

decision to treat the PDA is complicated by the lack of evidence available regarding clinical conditions under which closure should be attempted [3].

During echocardiography, a PDA is typically described by size and direction of blood flow across the PDA. Standard practice in the Duke University Medical Center Intensive Care Nursery (ICN) is to attempt closure of PDAs that are considered clinically significant by the attending neonatologist. A PDA may be considered clinically significant if the neonate is requiring increased ventilator support, increased FiO_2 , worsening metabolic acidosis, increased support with inotropic agents, or a chest x-ray showing pulmonary edema despite adequate fluid restriction. Treatment is often delayed if the PDA exhibits bidirectional flow for fear that closure may precipitate right-sided heart failure [4–9].

The purpose of this study was to compare clinical outcomes for neonates who underwent medical treatment of PDA exhibiting bidirectional blood flow to neonates exhibiting left to right flow across their PDA.

2. Methods

2.1. Study population

We identified all neonates with a medically treated PDA between January 2002 and October 2007 at Duke University Medical Center who did not have chromosomal or significant cardiac anomalies. The day of initiation of medical treatment for PDA, either with indomethacin or ibuprofen, was recorded. Echocardiography results were obtained, and blood flow across PDA was classified as bidirectional or left to right. Clinical outcomes evaluated included: IVH, medical NEC, surgical NEC, spontaneous ileal perforation (SIP), surgical ligation, and death.

During the study period, prophylactic indomethacin (0.1 mg/kg/day×3 doses) for the prevention of IVH was used in all neonates with a birth weight <750 g or gestational age <27 weeks. All neonates with clinical and echocardiographic evidence of PDA were treated with indomethacin prior to November 2006 and with ibuprofen L-lysine afterwards. Indomethacin was given at 12 h intervals and the dose varied by age: <48 h of life, 0.2 mg/kg, 0.1 mg/kg, and 0.1 mg/kg; 2–7 days of life 0.2 mg/kg; and >7 days of life, 0.2 mg/kg, 0.25 mg/kg, and 0.25 mg/kg. Ibuprofen was given in 3 doses of 10 mg/kg, 5 mg/kg, and 5 mg/kg at 24-hour intervals. Contraindications to either agent included serum creatinine >1.7 mg/dL or platelet count <70,000/mm³. Unless limited by poor renal function, 2 courses (6 total doses) of either agent were used if clinical and echocardiographic evidence of PDA persisted before surgical options were considered.

2.2. Statistical analysis

Outcomes were analyzed using Fisher's exact test. Survival curves were compared using Wilcoxon (Breslow) rank sum analysis. On noting the trend toward higher mortality among those treated with bidirectional flow, post hoc analyses were carried out to better understand factors that may correlate with bidirectional flow that also contribute to mortality. We conducted a multivariable logistic regression using a model that included both gestational age and direction of PDA flow at the time of medical treatment. Data were analyzed with STATA 10 (College Station, TX). The Duke University Medical Center Institutional Review Board granted permission for this study.

3. Results

We identified 317 neonates treated for PDA during the study time period (Table 1). At initiation of treatment, 20 neonates had bidirectional flow across the PDA and 297 neonates

had left to right flow across the PDA (Table 1). Median gestational age at birth was 26 weeks [interquartile range (IQR); 25, 28]. Median gestational age at birth was 26 weeks [25, 27.5] for neonates with bidirectional flow versus 26 weeks [25, 28] for neonates with left to right flow across the PDA, $p=0.04$. The majority of neonates identified (228/317, 72%) were extremely low birth weight (ELBW; <1000 g birth weight). Median birth weight was 850 g [676, 1030]. Neonates with bidirectional PDAs had a median birth weight of 783 g [635, 958] while the neonates with left to right flow through the PDA had a median birth weight of 855 g [695, 1035], $p=0.21$. Median age of initiation of treatment for the first course was day of life 3 [2, 4] with a range of 0 to 41 days. The median age of initiation of treatment for neonates with bidirectional PDA was 2 days [1, 2]. Neonates with left to right PDAs had a median age of 3 days [2, 5] at initiation of treatment, $p=0.003$. In our cohort of neonates, 13 out of 20 neonates received treatment on the same day their echo was performed, 3 initiated treatment the day after their echo, and 4 neonates had missing data regarding the day of initiation of treatment.

The proportion of successful medical closure was similar regardless of direction of flow across the PDA (bidirectional 13/19, 68% versus left to right 183/292, 63%), $p=0.81$. Overall mortality was 37/317 (12%) (Table 2). Death occurred in 3/20 (15%) of the neonates with a bidirectional PDA compared to 34/297 (11%) in the left to right group, $p=0.72$. Adjusting for gestational age, treatment of a bidirectional PDA was associated with an increased risk of death, $OR=1.43$ [0.39, 5.28], $p=0.59$.

IVH (Grade 3 or 4) was observed in 48/313 (15%) of our population; 5/19 (26%) of these neonates had a bidirectional PDA at treatment and 43/294 (15%) were left to right, $p=0.19$. Incidence of medical NEC, surgical NEC and SIP were similar in both study groups. Surgical ligation was performed on 98/317 (31%) neonates. The PDA was ultimately surgically ligated in 6/20 (30%) of the neonates with bidirectional PDA versus 92/297 (31%) of the left to right PDAs, $p=0.99$. Overall complications (death, medical and surgical NEC, and SIP) were observed in 119/317 (38%) of the study population. IVH was not included in this total because most neonates developed IVH prior to PDA closure. Overall complications were similar between the two groups of neonates investigated: 8/20 (40%) bidirectional cohort versus 111/297 (38%) left to right cohort, $p=0.82$.

4. Discussion

Previous researchers have shown that left to right shunting across the PDA may increase the risk of IVH, NEC, BPD, and death [2,10,11]. Controversy exists among neonatologists regarding when to initiate therapy. Our data suggest that neonates treated for PDA in our center had similar outcomes regardless of the direction of flow across their PDA.

Clinicians are often hesitant to close a PDA that is bidirectional because of the theoretical risk of right-sided heart failure [12]; however, no information is available reporting outcomes after attempted closure of a bidirectional PDA by echocardiograph in neonates with signs consistent with compromised systemic circulation attributable to a PDA. In a multicenter trial, early prophylactic ligation was performed in ELBW neonates within 24 h of birth regardless of the presence or absence of signs or symptoms of PDA and outcomes were compared with neonates who were not ligated early [13,14]. Although not verified by echocardiography, a subset of these neonates likely had bidirectional or even right to left flow across the PDA at the time of surgery, yet survival through 1 year after birth in the study group was similar to the control group (18/44, 41% control, versus 15/40, 38%, prophylactic ligation, $p=ns$). In this study, in the days prior to widespread use of antenatal steroids and surfactant replacement, neonates who underwent prophylactic ligation, having never been exposed to a symptomatic PDA, had significantly less NEC than the control

group, although they were more likely to require supplemental oxygen at 36 weeks postmenstrual age.

We observed a higher mortality in neonates with bidirectional PDA (3/20 [15%]) compared to neonates with left to right PDA (34/297 [11%]), $p=0.72$. Adjusting for gestational age, treatment of a bidirectional PDA was associated with increased risk of death, $OR=1.43$ (0.39, 5.28), however this test failed to reach statistical significance, $p=0.59$. Although our study was not powered to make this comparison, this trend was troubling. Survival analysis was performed to compare the times that death occurred in these two groups of neonates (Fig. 1). The majority of deaths in both groups occurred soon after ductal closure. Cause of death in neonates who had bidirectional PDA at treatment was investigated further to see if these neonates appeared to die from pathology directly related to closure of their PDAs (Table 3). While it is troubling that we observed a higher mortality in neonates with bidirectional PDA, no clear mechanism was apparent.

Previously published rates of ductal closure are higher than what we observed in this study. Van Overmeire et al. reported ductal closure in 49/74 (66%) neonates given indomethacin and 52/74 (70%) given ibuprofen. Neonates in this trial had higher mean birth weight (1230 g) and gestational ages (29 weeks) than our cohort of neonates. Our closure rates are consistent with those reported by Koch et al. who demonstrated <half of the neonates <27 weeks gestation were successfully treated medically for their PDA [15].

We analyzed data obtained from the charts of the patients in this study, specifically the echocardiography reports, and chose to classify our results categorically. These categories came directly from the text of the dictated echocardiogram reports. For example, a PDA described as “bidirectional, predominantly left to right” was classified as left to right. Similarly, we chose to analyze any PDA identified as “mostly left to right” in the left to right category. We did this to avoid underestimating differences in important clinical outcomes by including PDAs that are predominantly exhibiting left to right physiology as bidirectional in our analysis. In order to classify a PDA as bidirectional, the echo report had to specifically state “bidirectional” without any mention of predominance to the left to right component of flow. We analyzed data using three groups including “mostly left to right” as a category. There was no significant difference in any of the outcomes investigated; therefore we chose to present only the two categories (bidirectional versus left to right).

Neonates <750 g or <27 weeks gestational age at birth, are given prophylactic indomethacin upon admission to the intensive care nursery at our center. Although echocardiography is not routinely performed on the first day of life, flow across the ductus is likely bidirectional in many of these neonates. The effect of prophylactic indomethacin on the hemodynamics of PDA is not well understood, however, these neonates do not appear to suffer complications related to early closure of the ductus before their pulmonary vascular resistance has fallen to physiologic levels expected in transition. Researchers demonstrated pulmonary hypertension in 3 neonates in a randomized, double blind placebo-controlled trial comparing prophylactic ibuprofen versus placebo in very preterm infants [12]. However this effect was not observed in any of the nine studies included in a meta-analysis of ibuprofen versus indomethacin for closure of PDA. While pulmonary hypertension has been seen with ibuprofen — tris-hydroxyamino-methane, as noted by Gournay et al., there is no apparent association with ibuprofen L-lysine and pulmonary hypertension [16].

The average age at treatment was less for neonates with a bidirectional PDA. We speculate that neonates that were treated medically for a bidirectional PDA may have been more critically ill, requiring higher levels of ventilatory and inotropic support, and therefore were treated more aggressively. In addition, clinicians uncomfortable treating a PDA

demonstrating bidirectional flow in a neonate that was less critically ill may have delayed treatment until the flow across the ductus was purely left to right. Neonates with elevated pulmonary vascular resistance from pathology such as BPD may exhibit bidirectional flow across their PDA later in life, presenting a clinical scenario where closure of the PDA may carry increased risk. However, the oldest neonate in our cohort with bidirectional PDA was only 5 days old at initiation of treatment.

Limitations to this study include its retrospective, single center design. We obtained data on 317 patients, however the power of this study to detect statistically significant outcomes between groups is limited because only 20 neonates had bidirectional PDAs. Based on our sample size, we would have 80% power to detect a difference in outcomes with an alpha $p < 0.05$ if the prevalence of important clinical outcomes in the bidirectional group was 45% and the prevalence in the left to right group was 16%.

We did not directly view the echocardiography of neonates in this study with a cardiologist. We felt this was unnecessary because staff cardiologists performed interpretation of the images and the dictated reports. These reports contained the pertinent information, including size and direction of flow across the PDA that physicians used to guide their therapy.

In summary, this study illustrates the need for better understanding of the hemodynamics of PDA and how typical interventions such as prophylactic indomethacin, influence the physiology during transition. Our data suggest that outcomes may not reflect the theoretical complications of closing bidirectional PDA. The natural history of PDA is not completely understood and there is no literature to guide clinicians on whether or not to treat a neonate with clinical signs consistent with decreased systemic flow and excessive pulmonary flow and an anatomically open, bidirectional PDA at the moment when the diagnostic echocardiogram was performed. The current data does not contraindicate an aggressive approach to the clinically significant PDA that has bidirectional flow at the time of the echocardiogram, but the trend in mortality is worrisome. A prospective randomized clinical trial is needed to better inform clinicians facing this dilemma.

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Fig. 1.
Survival curve — bidirectional versus left to right.

Table 1

Demographics.

	Bidirectional (n=20)	Left to right (n=297)	p
Gender			
Male	60%	54%	0.65
Race			
Caucasian	30%	36%	0.89
African American	60%	53%	
Other	10%	11%	
Gestational age (weeks)			
<27	55%	55%	0.99
27–29	40%	39%	
≥30	5%	6%	
Birth Weight (g)			
<750	40%	33%	0.83
751–1000	40%	38%	
1001–1500	20%	27%	
≥1500	0%	2%	
Day of life	2 [1,2]	3 [2,5]	0.003
IVH prophylaxis	62%	54%	0.77

IVH — intraventricular hemorrhage.

Day of life — reported as median [interquartile range].

Table 2

Outcomes.

	Bidirectional (n=20)	Left to right (N=297)	p
Medical necrotizing enterocolitis	15%	16%	0.99
Surgical necrotizing enterocolitis	15%	11%	0.49
Spontaneous intestinal	11%	8%	0.66
Perforation			
Death	15%	11%	0.72
Surgical ligation	30%	31%	0.99
Intraventricular hemorrhage	26%	15%	0.19
Overall complications	40%	37%	0.82

Overall complications — death, medical necrotizing enterocolitis and surgical necrotizing.

Enterocolitis, or spontaneous intestinal perforation.

Table 3

Cause of death for neonates with bidirectional PDA.

Birth weight (g)	Gestational age (weeks)	DOL at treatment	Days after treatment	Cause of death
510	27	3	7	Necrotizing enterocolitis
660	24	2	8	Respiratory failure, sepsis
770	28	1	14	Code, unclear etiology

DOL — day of life.

Days after treatment — the number of days after treatment that death occurred.