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RESEARCH ARTICLE

Maternal and Neonatal Factors Associated with Indomethacin-Induced Ductal Closure in Extremely-Low-Birth-Weight Infants

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Abstract

Background: Ductal response to indomethacin in extremely-low-birth-weight (ELBW) infants is not well studied.

Objective: The purpose of this study was to identify predictors of ductal closure in ELBW infants treated with indomethacin.

Methods: A single-center, retrospective cohort of ELBW infants treated with indomethacin for patent ductus arteriosus (PDA) were included. Predictors of PDA closure were identified using multivariable adjusted logistic regression.

Results: One hundred and five infants with a PDA were treated with indomethacin. Primary PDA closure with one course of indomethacin occurred in 61.9%. The rate of primary PDA closure was lower in infants with gestational age (GA) < 28 weeks compared to infants ≥ 28 weeks (58.1% vs 91.7%, p =0.03). Multivariable logistic regression model identified PDA size (OR 0.29, 95% CI 0.11-0.74, p =0.009) and exposure to antenatal indomethacin (OR 0.28, 95% CI 0.08–0.99, p =0.048) and magnesium (OR 0.31, 95% CI 0.12–0.82, p =0.019) as significant predictors for failure of ductal closure in infants treated with indomethacin. Infants with failed PDA closure were more likely to have moderate/severe bronchopulmonary dysplasia, severe intraventricular hemorrhage, and longer duration of hospitalization (p <0.05).

Conclusions: Large PDA and antenatal indomethacin and magnesium were predictors for failure of ductal closure with indomethacin. The negative association between antenatal indomethacin and magnesium on ductal closure with postnatal indomethacin warrants further investigation regarding routine use in mothers at risk for preterm delivery. Future studies focusing on developing predictive models to identify ideal candidates for indomethacin within the ELBW population could reduce the burden of the disease and improve overall outcomes.

Abbreviations: BPD: bronchopulmonary dysplasia, BW: birth weight, CI: confidence intervals, COX: cyclooxygenase, DA: ductus arteriosus, ELBW: extremely-low-birth weight, GA: gestational age, GI: gastrointestinal, hsPDA: hemodynamically significant PDA, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis; OR: odds ratios, RDS: respiratory distress syndrome, PDA: patent ductus arteriosus, VLBW: very-low-birth weight

Keywords: Non-steroidal anti-inflammatory drugs, pediatric cardiology, neonatology, prostaglandin inhibitors, critical care

Introduction

Failure of spontaneous closure of ductus arteriosus (DA) also known as patent ductus arteriosus (PDA) is a common problem with serious implications in extremely preterm infants. In preterm infants, especially in extremely-low-birth weight (ELBW, <1000 gm) infants, there is higher risk for prolonged patency of the DA resulting in hemodynamic instability and complications related to shunting of blood between the systemic and pulmonary circulations [1]. Failure of spontaneous ductal closure has been attributed to several risk factors such as low gestational age (GA) and birth weight (BW), increased fluid intake during the first week of life, postnatal infection, presence of severe respiratory distress syndrome (RDS), exposure to antenatal magnesium, and intrauterine growth restriction [2,3]. Non-selective cyclooxygenase (COX) inhibitors, indomethacin and ibuprofen, have been the mainstay medical management of PDA in preterm infants. However, not all infants respond equally to COX inhibitors. Approximately 10% to 30% of preterm infants treated with COX inhibitors fail to respond [4]. Male gender, older GA, and higher platelet count at the time of indomethacin have been found to be associated with successful ductal closure with indomethacin while larger ductal size and delayed indomethac in treatment were associated with failed ductal closure [3, 5-7].

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Additionally, the lack of antenatal steroid exposure, Caucasian race, and severity of RDS were independently associated with failed indomethacin therapy [8]. However, these studies were mostly evaluated in very-low-birth-weight (VLBW) infants (<1500 gm) as a whole; thereby, not clearly defining ductal responses to indomethacin in subgroups, especially ELBW infants, who are considered the most vulnerable cohort among preterm infants. The purpose of this study was to identify maternal and neonatal factors associated with successful ductal closure with indomethacin in ELBW infants, and to compare subsequent neonatal outcomes. We hypothesize that response to indomethacin in ELBW infants is poorer and less predictable and risk factors associated with ductal closure are different compared to larger preterm infants.

Methods: This is a single-center, retrospective, cohort study of ELBW (birth weight ≤ 1000 gm) infants admitted to a level III tertiary care neonatal intensive care unit at the University of Illinois Hospital & Health Sciences System from January 2008 to December 2016 and have a PDA. Infants who were out born and/or transferred out to another hospital were excluded. This study was approved by the University of Illinois at Chicago Institutional Review Board.

Data Collection: Data was retrieved from electronic medical records and included the presence of pre-eclampsia, prolonged rupture of membrane, chorioamnionitis use of antenatal magnesium and steroids mode of delivery GA, BW, gender, race, 5-minute Apgar score, date/time of birth, indomethacin regimen (prophylaxis and treatment), and the PDA size per echocardiogram. The use of inotropes, fluid intake, serum creatinine, urine output, and platelet counts were collected during the first week of life. An echocardiogram is performed in infants with a hemodynamically significant PDA (hsPDA), defined as those that cause clinical signs of inappropriate shunting such as widened pulse pressure, murmur, need for increased respiratory support, renal dysfunction, and systemic hypotension. Moderate-to-large PDA is defined as ductal size >1.5mm. Neonates born prior to September 2010 did not receive prophylactic indomethacin. From September 2010 to 2014, infants born with birth weights ≤ 1000 gm were eligible to receive prophylactic indomethacin. In 2015, with the change in criteria, only those born with birth weights ≤ 750 gm were eligible to receive prophylactic indomethacin for the prevention of intraventricular hemorrhage. The dosing regimen for prophylactic indomethacin is 0.1 mg/kg/dose Q24 hour for 3 doses given intravenously, administered within 12 hours of life. Infants with a hsPDA were treated with at least one course of indomethacin, which consists of 3 doses (0.2 mg/kg/dose given intravenously over 30 minutes followed by two subsequent doses of 0.1-0.2 mg/kg/dose every 12-24 hours). After completion of a course of indomethacin, a repeat echocardiogram is performed within 12-24 hours from the last dose. Infants with hsPDA may receive up to 2-3 courses of indomethacin, if the ductus remains patent or reopened after initial closure. During the study period, ibuprofen lysine or acetaminophen was not prescribed for PDA treatment. Surgical ligation is generally reserved for those with contraindications to or have failed two courses of indomethacin. Contraindications to indomethacin include necrotizing enterocolitis (NEC), any active bleeding (gastrointestinal [GI], severe intraventricular hemorrhage [IVH] grade 3-4), renal dysfunction (serum creatinine >1.6 mg/dl and/or urine output <1 mL/kg/hr), severe thrombocytopenia (<100,000 cells/μL), and congenital heart disease.

Outcomes: Infants with PDA were stratified according to three treatment groups:

a) Received no treatment,

b) Treated with indomethacin, and

c) Underwent primary surgical ligation.

Patients who were treated with indomethacin may or may not have received prophylactic indomethacin. Primary surgical ligation is defined as those who never received indomethacin due to contraindications whereas surgical ligation is defined as those whose ductus failed to close with indomethacin. Primary outcome was the identification of maternal and neonatal factors that are associated with successful ductal closure, defined as complete closure following one course of indomethacin therapy (primary closure). Secondary outcomes included *overall closure* rates (after two to three courses of indomethacin), improvement in oxygen requirement, ventilator days, bronchopulmonary dysplasia (BPD) at 28 days and 36 weeks' postmenstrual age, pulmonary hemorrhage, IVH, NEC stage ≥ 2, renal dysfunction, GI bleed, length of hospitalization, and mortality between infants who respond to one course of indomethacin to those who did not respond. Head ultrasounds were performed at various intervals, including within the first 3 days of life, at 7th day of life, and at 1 month of life, unless indicated earlier.

Statistical Analyses: Neonatal and maternal characteristics of ELBW infants and their outcomes for PDA were compared between those receiving no treatment, indomethacin treatment, or primary surgical ligation. These characteristics and outcomes were summarized using descriptive statistics. Chi-square and Fisher's exact tests were used to compare categorical variables, and one-way ANOVA or the Kruskal-Wallis test was used to compare parametric or nonparametric continuous variables, respectively. Using bivariate analyses, neonatal and maternal characteristics and outcomes were compared among ELBW infants with PDA who had initial closure to those who did not have closure. Unadjusted and multivariable adjusted logistic regression with backward selection was used to identify risk factors associated with initial ductal closure. Potential confounders, defined as variables with p-value <0.05 on bivariate analysis with the outcome, as well as other variable determined a priori as conceptual confounders (i.e., GA, gender, antenatal magnesium and indomethacin, Apgar score, postnatal age at treatment, receipt of prophylactic indomethacin, fluid intake, platelet count, PDA size) were assessed in the multivariable logistic regression model. Results were described as odds ratios (OR) and 95% confidence intervals (CI). Statistical tests were two-sided and

p <0.05 defined statistical significance. All analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina).

Results

A total of 170 ELBW infants had a PDA, of which 32% (n =54) received no treatment for PDA, 62% (n =105) received indomethacin, and 6.4% (n =11) required primary surgical ligation (Table 1). Infants who underwent primary surgical ligation had lower mean BW compared to those receiving no treatment or indomethacin (579 vs 775 vs 773 gm, respectively). A higher proportion of infants in the no treatment group had small PDA (< 1.5mm) and received prophylactic indomethacin compared to infants who underwent primary ligation or received indomethacin. No significant differences in maternal characteristics were observed across groups, except only a smaller percentage of infants who underwent primary surgical ligation were exposed to antenatal magnesium (18.2% primary ligation vs 59.3% no treatment vs 62.9% indomethacin, p =0.017). Infants in the two treatment groups had a higher incidence of RDS and BPD, and longer ventilation days compared to infants who did not require any treatment for PDA (Table 1).Among the 105 ELBW infants who were treated with indomethacin, 61.9% (n =65) had primary PDA closure (after one course of indomethacin) with an overall closure rate of 73.3%. The rate of primary PDA closure with indomethacin was significantly lower in infants with GA < 28 weeks compared to infants with GA ≥ 28 weeks (58.1% vs 91.7%, respectively, p =0.03). However, there was no significant difference in closure rates among BW subgroups (< 500gm, 500-750 gm, > 750 gm; 60% vs 64% vs 60%, respectively). No significant differences were noted on the timing of indomethacin initiation between groups (median 3 vs 3.5 days, respectively, p =0.52).

On univariate analysis, infants who did not respond to indomethacin were more likely to have a larger PDA, received prophylactic indomethacin, and were exposed to

Table 1: Characteristics of ELBW Infants with PDA by Treatment Groups.

Neonatal Factors	**No Treatment** (n=54; 31.8%)	**Indomethacin** (n=105; 61.8%)	**Primary Ligation** (n=11; 6.4%)	**P value**[a]
Male, n (%)	27 (50.0)	51 (48.6)	4 (36.4)	0.71
Race, n (%) African American Caucasian Hispanic/Latino Other	 33 (61.1) 3 (5.5) 9 (16.7) 9 (16.7)	 74 (70.5) 5 (4.8) 20 (19.0) 6 (5.7)	 7 (63.6) 1 (9.1) 0 (0.0) 3 (27.3)	0.07
GA (weeks), mean (SD)	26.3 (1.8)	25.9 (1.5)	25.5 (2.3)	0.19
Birthweight (grams), mean (SD)	775.0 (166.9)	773.3 (166.4)	579.1 (100.9)	<0.001
SGA, n (%)	13 (24.1)	15 (14.3)	4 (36.4)	0.10
5-min Apgar Score, mean (SD) n (%) ≤ 3 4 to 6 ≥ 7	6.6 (1.7) 5 (9.3) 18 (33.3) 31 (57.4)	6.6 (1.7) 7 (6.7) 37 (35.2) 61 (58.1)	6.6 (1.0) 0 (0.0) 3 (27.3) 8 (72.7)	 0.98 0.89
PDA Size, n (%) Small Moderate Large	 27 (50.0) 18 (33.3) 9 (16.7)	 8 (7.6) 40 (38.1) 57 (54.3)	 2 (18.2) 5 (45.4) 4 (36.4)	<0.001
Use of Inotropes, n (%)	27 (50.0)	52 (49.5)	7 (63.6)	0.67
Prophylactic Indomethacin, n (%)	24 (44.4)	30 (28.6)	1 (9.1)	0.03
Fluids Intake Over First 3 Days of Life (mL/kg/day), mean (SD)	100.0 (12.2)	102.1 (12.2)	105.6 (17.2)	0.34
RDS, n (%)	45 (83.3)	100 (95.2)	10 (90.9)	0.04
BPD, n (%)	48 (88.9)	105 (100)	11 (100)	0.01
Ventilator Days, median (IQR)	7 (3 – 23)	18 (5 – 54)	22 (6 – 49)	0.02
Maternal Factors				
Mode of Delivery, n (%) Vaginal delivery Caesarean section	 17 (31.5) 37 (68.5)	 28 (26.7) 77 (73.3)	 4 (36.4) 7 (63.6)	0.70
Pre-eclampsia, n (%)	12 (22.2)	28 (26.7)	4 (36.4)	0.59
Antenatal Steroids, n (%)	42 (77.8)	93 (88.6)	9 (81.8)	0.19
Antenatal Magnesium, n (%)	32 (59.3)	66 (62.9)	2 (18.2)	0.02
Antenatal Indomethacin, n (%)	5 (9.3)	15 (14.3)	3 (27.3)	0.26
Chorioamnionitis, n (%)	8 (14.8)	21 (20.0)	2 (18.2)	0.72
pPROM, n (%)	14 (25.9)	34 (32.4)	3 (27.3)	0.69

ELBW: extremely-low-birthweight, PDA: patent ductus arteriosus, SD: standard deviation, GA: gestational age, SGA: small for GA, pPROM: preterm premature rupture of membranes, RDS: respiratory distress syndrome; BPD: bronchopulmonary dysplasia; IQR: interquartile range

[a]Chi-square test used for categorical variables, Fisher's exact test used for categorical variables when ≥ 20% of cells have expected value < 5, one-way ANOVA used for parametric continuous variables, and Kruskal-Wallis test used for nonparametric continuous variables.

antenatal magnesium compared to infants who had primary closure (Table 2). The multivariable logistic regression model, adjusted for GA and other variables, showed that PDA size and exposure to antenatal indomethacin and magnesium remained as significant risk factors for failure of ductal closure among ELBW infants who were treated with indomethacin. The odds of primary PDA closure with indomethacin is lower in those with a large PDA (OR 0.29, 95% CI 0.11–0.74, p =0.009). Similarly, infants exposed to antenatal magnesium and indomethacin were less likely to have PDA closure (OR 0.31, 95% CI 0.12 – 0.82, p =0.019 and OR 0.28, 95% CI 0.08–0.99, p =0.048 respectively) (Table 3). ELBW infants who had primary PDA closure were less likely to have moderate/severe BPD, severe IVH, and have shorter hospitalizations (p <0.05). No strong differences in the incidence of NEC or renal dysfunction was found among the groups, however, the absolute number of infants experiencing these events was very small. The median ventilator days were 13 and 26.5, respectively, p =0.269, for infants with primary and failed primary PDA closure. Overall and 28-day mortality were not significantly different between the groups. (Table 4).

Table 2: Unadjusted Odds Ratio of Association between Characteristics of Infants Who Received Indomethacin for PDA Treatment and Primary PDA Closure.

Neonatal Factors	Primary PDA Closure[a]		Odds Ratio	95% CI	P value[b]
	Yes (61.9%, n=65)	No (38.1%, n=40)			
Male, n (%)	34 (52.3)	17 (42.5)	1.48	0.67 – 3.28	0.33
African American, n (%)	42 (64.6)	32 (80.0)	0.46	0.18 – 1.15	0.10
GA (weeks), mean (SD) < 28 weeks; n (%) ≥ 28 weeks; n (%)	26.1 (1.5) 54 (83.1) 11 (16.9)	25.7 (1.4) 39 (97.5) 1 (2.5)	1.23 -- 7.94	0.93 – 1.63 reference 0.98 – 64.11	0.15 0.05
Birthweight (grams), mean (SD)	780.4 (166.7)	761.8 (167.4)	1.00	1.00 – 1.00	0.58
SGA, n (%)	10 (15.4)	5 (12.5)	1.27	0.40 – 4.04	0.68
5-min Apgar Score, mean (SD) ≤ 3; n (%) 4 to 6; n (%) ≥ 7; n (%)	6.8 (1.6) 3 (4.6) 21 (32.3) 41 (63.1)	6.2 (1.8) 4 (10.0) 16 (40.0) 20 (50.0)	1.24 -- 1.75 2.73	0.97 – 1.58 reference 0.34 – 8.95 0.56 – 13.40	0.08 -- 0.50 0.21
Large PDA size, n (%)	29 (44.6)	28 (70.0)	0.35	0.15 – 0.80	0.01
Serum Creatinine (mg/dL), mean (SD)	1.1 (0.2)	1.1 (0.3)	0.56	0.12 – 2.53	0.45
Urine Output (mL/kg/hr), mean (SD)[c]	3.3 (1.1)	3.5 (0.8)	0.87	0.59 – 1.28	0.47
Platelet Count (x10^3μL^{-1}), mean (SD)[d] ≥ 150 x 10^3 μL^{-1}; n (%)	199.2 (81.6) 48 (73.9)	196.0 (97.3) 24 (60.0)	1.02 1.88	0.81 – 1.28 0.81 – 4.36	0.86 0.14
Fluid Intake Over First 3 Days of Life (mL/kg/day), mean (SD)[e]	101.6 (12.0)	103.1 (12.7)	0.90	0.65 – 1.25	0.54
Prophylactic Indomethacin n (%) 0 doses 1-2 doses 3 doses	14 (21.5) 51 (78.5) 4 (6.1) 10 (15.4)	16 (40.0) 24 (60.0) 9 (22.5) 7 (17.5)	0.41 -- 0.21 0.67	0.17 – 0.98 reference 0.06 – 0.75 0.23 – 1.98	0.04 -- 0.02 0.47
Postnatal Age at Initiation of INDO (days), median (IQR)	3 (2 – 5)	3.5 (2 – 8.5)	0.97	0.88 – 1.07	0.52
Number of INDO Doses for First Course, mean (SD)[a]	2.8 (0.6)	2.9 (0.6)	0.66	0.32 – 1.35	0.25
Total Number of INDO Doses for Treatment, mean (SD)	2.9 (0.8)	4.8 (2.0)	0.39	0.26 – 0.58	<0.001
Maternal Factors					
Mode of Delivery, n (%) Vaginal delivery Caesarean section	 16 (24.6) 49 (75.4)	 12 (30.0) 28 (70.0)	 -- 1.31	 reference 0.54 – 3.17	 -- 0.54
Pre-eclampsia, n (%)	20 (30.8)	8 (20.0)	1.78	0.70 – 4.54	0.23
Antenatal Steroids, n (%)	57 (87.7)	36 (90.0)	0.79	0.22 – 2.82	0.72
Antenatal Magnesium, n (%)	36 (55.4)	30 (75.0)	0.41	0.17 – 0.99	0.04
Antenatal Indomethacin, n (%)	7 (10.8)	8 (20.0)	0.48	0.16 – 1.45	0.19
Chorioamnionitis, n (%)	14 (21.5)	7 (17.5)	1.29	0.47 – 3.54	0.62
pPROM, n (%)	22 (33.9)	12 (30.0)	1.19	0.51 – 2.79	0.68

ELBW: extremely-low-birthweight, PDA: patent ductus arteriosus, CI: confidence interval, GA: gestational age, SD: standard deviation, SGA: small for GA, INDO: indomethacin, pPROM preterm premature rupture of membranes

[a]Initial closure defined as closure of PDA per echocardiogram after one course of indomethacin

[b]P value for odds ratio of association between neonatal or maternal factors and initial PDA closure, estimated using bivariate logistic regression

[c]Urine output during the first week of life

[d]Odds ratio for every 50 unit increase in platelet count (x 10^3 μL^{-1})

[e]Odds ratio for every 10 mL/kg/day increase in fluids

Among infants who failed indomethacin for PDA closure (n =40), 52.5% (n =21) received two courses of indomethacin and 10% (n=4) received three courses. Forty percent (16/40) of these infants received prophylactic indomethacin. Surgical ligation was subsequently performed on 55% (22/40) of these infants who failed indomethacin. Of those who underwent ligation, over 90% (20/22) of these infants received three indomethacin courses, 77.3% had a large PDA, and 50% required inotropic support. Ninety-one percent of infants who underwent ligation had moderate/ or severe BPD, 31.8% had NEC, and 36.4% had severe IVH. Among infants with primary PDA closure, the PDA re-opened in 4 of the 65 cases (6.2%), and ligation was subsequently performed in two of the four cases.

Discussion

The overall incidence of PDA among ELBW infants ranged between 23.5% to 67% over a 10-year period (2008-2018) at our institution. This rate is higher than other studies, which reported rates of 40% in infants weighing 751-1000gm [9]. However, our rate is similar to Yang and colleagues, who reported an incidence of 60.3% in ELBW infants [10]. The incidence among VLBW infants at our institution is lower, ranging between 12.8% to 42.9%. About 55% of ELBW infants required pharmacological closure of the ductus, while only 30% of VLBW infants were considered candidates for treatment [11]. This highlights the increased risk for hsPDA and the need for intervention among ELBW infants. It can be speculated that ELBW infants are at an increased risk for PDA due to the profound lack of response to constricting factors and susceptibility to dilatory factors [12]. The use of indomethacin in this population is only based on extrapolated data from larger infants, and the response and efficacy to indomethacin in this group remains largely unknown and may vary significantly. In our study, primary PDA closure, defined as closure after one course of indomethacin, was 61.9% with an overall closure rate of 73.3%. Eleven out of 170 (6.4%) infants underwent primary ligation, while 22 out of 40 (55%) who failed indomethacin subsequently underwent ligation. Yang and colleagues reported a similar primary ductal closure rate of 63.3% after one course of indomethacin with an overall closure rate of 77.7%. They also found a significantly higher primary and overall closure rates in infants with BW >800 gm compared to infants of lower BW (75% and 85.5% versus 49.2% and 68.3% respectively). This finding was comparable with results of our study. Large PDA size was associated with lower primary closure rates following indomethacin in our population. This mechanism could be attributed to potentially large blood flow through the ductus impeding the constrictive effects of indomethacin. We evaluated other predictors for indomethacin response such as fluid intake and timing of indomethacin initiation and found no significant associations with indomethacin response. Both

Table 3: Multivariable Adjusted Odds Ratio of the Association between Characteristics of Infants Who Received Indomethacin for PDA Treatment and Primary PDA Closure.

Neonatal Factors	Odds Ratio	95% CI	P value[a]
Gestational Age ≥ 28 weeks	8.90	0.94 – 83.95	0.056
Apgar Score	1.26	0.96 - 1.66	0.093
Large PDA Size	0.29	0.11 - 0.74	0.009
Antenatal Magnesium	0.31	0.12 – 0.82	0.019
Antenatal Indomethacin	0.28	0.08 – 0.99	0.048

ELBW: extremely-low-birthweight, PDA: patent ductus arteriosus, CI confidence interval,
[a]P value for odds ratio of association between neonatal or maternal factors and initial PDA closure, estimated using bivariate logistic regression.

Table 4: Outcomes of Infants Who Received Indomethacin for PDA Treatment and Primary PDA Closure.

Neonatal Comorbidities	Initial PDA Closure[a]		Odds Ratio	95% CI	P value[b]
	Yes (61.9%, n=65)	No (38.1%, n=40)			
RDS, n (%)	61 (93.9)	39 (97.5)	0.39	0.04 – 3.63	0.41
Moderate or Severe BPD, n (%)	46 (70.8)	37 (92.5)	0.21	0.06 – 0.76	0.02
Severe BPD, n (%)	29 (44.6)	22 (55.0)	0.68	0.31 – 1.50	0.34
NEC Stage ≥ 2, n (%)	9 (13.9)	11 (27.5)	0.42	0.16 – 1.14	0.09
IVH All Grades, n (%)	20 (30.8)	21 (52.5)	0.40	0.18 – 0.91	0.03
Severe IVH Grades 3 or 4, n (%)	8 (12.3)	13 (32.5)	0.29	0.11 – 0.79	0.01
Renal Dysfunction, n (%)	6 (9.2)	4 (10.0)	0.92	0.24 – 3.47	0.90
Ventilator Days, median (IQR)	13 (4 - 38)	26.5 (6.5 - 63)	0.99	0.98 – 1.01	0.27
Length of Stay (days), mean (SD)	101.8 (52.5)	123.9 (54.9)	0.99	0.99 – 1.00	0.04
Death at 28 Days of Life, n (%)	4 (6.2)	1 (2.5)	2.56	0.28 – 23.7	0.41
Overall Mortality, n (%)	8 (12.3)	3 (7.5)	1.73	0.43 – 6.95	0.44

ELBW: extremely-low-birthweight, PDA: patent ductus arteriosus, RDS: respiratory distress syndrome, CI confidence interval, BPD: bronchopulmonary dysplasia, NEC: necrotizing enterocolitis, IVH: intraventricular hemorrhage, IQR: interquartile range, SD: standard deviation
[a]Initial closure defined as closure of PDA per echocardiogram after one course of indomethacin
[b]P value for odds ratio of association between neonatal or maternal factors and initial PDA closure, estimated using bivariate logistic regression.

groups had similar fluid intake in the first three days of life. Although the median postnatal age at time of indomethacin initiation was also similar, infants who failed treatment were slightly older ([interquartile ranges] IQR 2–8.5 vs 2–5 days).

PDA in premature infants is frequently influenced by maternal and perinatal factors. We found a poorer response to indomethacin in infants who were exposed to antenatal magnesium (75% vs 55.4%, p=0.046). This significance continued to persist after adjusting for confounding factors on multivariate analysis (p =0.019). The underlying mechanism behind the role of antenatal magnesium is unclear. Current hypothesis is that the extracellular magnesium hampers intracellular calcium movement in vascular muscle cells and endothelial cells, causing delayed closure [13]. We did not collect serum magnesium levels to assess its association with ductal closure; however, magnesium levels in infants have been recorded to be high after antenatal exposure. Katayama and colleagues reported magnesium levels in infants to be 70-100% higher than maternal levels due to passive or facilitated transport and concentration can remain high for the first 72 hours of life [14]. Our findings of antenatal magnesium exposure and failure of ductal closure in response to indomethacin, in addition to the lack of neuroprotective effects of magnesium based on emerging studies, raises questions about the risk versus benefit of antenatal magnesium as routine use in mothers at risk for preterm delivery [15]. Similarly, antenatal indomethacin has been shown to adversely impact ductal closure in response to postnatal indomethacin. The underlying mechanism for this may be attributable to the loss of sensitivity to prostaglandin inhibition [16]. We found significant associations between antenatal indomethacin and primary closure rates. Infants exposed to antenatal indomethacin were less likely to have primary PDA closure with indomethacin (p =0.048); although only a small number of infants in our study were exposed to antenatal indomethacin. On the contrary recent studies have reported beneficial effects of antenatal indomethacin on early PDA closure. However, its influence on indomethacin treatment for PDA is unclear and requires further investigation [17, 18].

We observed PDA closure rates after one indomethacin course changes at 28 weeks' gestation. Infants born ≥ 28 weeks had a PDA closure rate of 91.7% following indomethacin, compared to 58.1% in infants born < 28 weeks (p <0.03). On multivariate analysis, infants born ≥ 28 weeks had higher PDA closure rates; however, the difference was not statistically significant (p =0.056). Due to the small sample size, it is difficult to estimate the true magnitude of this effect. Interestingly, infants born at 23 weeks only had a closure rate of 20%, pointing towards an inverse relationship between GA and response to indomethacin. Elfhoff and colleagues also reported differential treatment response to indomethacin at the 28 weeks' mark. Infants with median of 25 weeks' gestation were associated with a higher treatment failure rate compared to infants with median of 28 weeks (p <0.0001) [19]. Similarly, Madan and colleagues reported a linear correlation between GA and ductal closure with indomethacin in infant's ≤ 27 weeks. With each additional week of gestation, an increase in PDA closure was noted (OR 1.51 per week gestation, 95% CI 1.14–2.01, p =0.004). However, this correlation was not observed in infants above 27 weeks. Multiple factors play a role on the change of prostaglandin sensitivity to indomethacin at 28 weeks. Anatomically, neointimal mound formation in infants born < 28 weeks' gestation is less well developed affecting the luminal closure [20]. In infants born < 28 weeks, intrinsic tone of ductus is lower along with increased sensitivity to vasodilators due to absence of normal weaning of prostaglandin E_2 receptors with advancing age, affecting the DA closure [21]. When evaluating closure rates based on BW subgroups (<500 gm, 500–750 gm, >750 gm), we did not find a difference in closure rates among the subgroups (60%, 64%, and 60%, respectively). Thus, we speculate GA is a better predictor of PDA closure compared to BW.

Although an inverse relationship between GA and response to indomethacin was observed in our study, mean GA and BW were similar among infants who had a favorable response to one indomethacin course, compared to those who required repeat courses (26.2 vs 25.7 weeks and 780.4 vs 761.8 gm, respectively). This finding suggests that response to indomethacin in the extremely preterm population (< 28 weeks) may also depend on factors other than GA or BW. Therefore, we evaluated the impact of some of these predictive factors previously studied such as male gender, African American race, platelet counts and clinical chorioamnionitis. However, we did not establish any significant correlations between these factors and ductal response to indomethacin. The role of prophylactic indomethacin spontaneous ductal closure seemed evident in our population. Forty-four percent (24/54) of infants who had spontaneous ductal closure had received indomethacin prophylaxis compared to 28% (30/105) in the treatment group (p =0.03). This finding is in accordance with results of a meta-analysis [22]. On the contrary, infants who received prophylactic indomethacin had a lower odd of responding to indomethacin treatment (OR 0.41 CI 0.17-0.98 p =0.045). Based on our results and from studies correlating poor postnatal response to indomethacin following antenatal exposure, we speculate that response to indomethacin declines after repeated exposure. The underlying mechanism although unclear, could be related to desensitization of the ductal musculature to prostaglandin effects with repeated exposure to indomethacin, a prostaglandin inhibitor. However, with additional confounding factors such as large PDA size and exposure to antenatal magnesium that may impact response to indomethacin, it might be challenging to derive conclusions from this cohort.

Infants who underwent primary ligation, less frequently received prophylactic indomethacin suggesting that these

infants might have had contraindications to indomethacin. They were notably ventilator dependent for a longer period compared to infants who closed spontaneously or with indomethacin (22 vs 7 vs 18 days, respectively, p =0.024). However, the incidence of BPD was significantly higher in the treatment groups irrespective of the method of closure (spontaneous closure 88% vs indomethacin or primary ligation 100%, p =0.003) highlighting the negative impact of a hsPDA on lung function and development. Additionally, we also found that infants who responded to one course of indomethacin were at a lower risk for severe IVH compared to those who did not (OR 0.40 95% CI 0.18-0.91, p=0.028). This finding emphasizes the negative hemodynamic effects of persistent PDA in these extremely premature infants. Although findings from our study have provided a better understanding on factors influencing ductal closure and its response to indomethacin in ELBW infants, confirmation of these findings through larger prospective studies is necessary. Our study was limited due to its retrospective nature and inadequacy of power to study some of the associations. In the future, we plan to continue to monitor this population and develop strategies using clinical, laboratory, and echocardiographic data to predict risks for hsPDA. Additionally, we plan to follow these infants long-term to evaluate the benefits and perils for our treatment strategies.

Conclusion

Our study adds to current literature where gestational age remains as the biggest predictor for primary ductal closure with indomethacin. Response to indomethacin in infants born < 28 weeks, although considerably lower compared to older infants, was rather variable. Infants at the lowest gestational age of 23 weeks had the worst response to indomethacin emphasizing the significance of gestational age as a modifying factor. Additionally, the negative association between both antenatal indomethacin and magnesium on ductal closure with postnatal indomethacin warrants further investigation regarding routine use of these medications in mothers at risk for preterm delivery. Future studies focusing on developing predictive models to identify ideal candidates for indomethacin treatment within the ELBW population could reduce the burden of the disease and improve overall outcomes.

Disclosure Statements

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