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Efficacy of pharmacologic closure of patent ductus arteriosus in small-for-gestational-age extremely preterm infants

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Abstract

Background—Optimal management of the patent ductus arteriosus (PDA) in preterm infants remains controversial. Therefore, studies identifying infants who are most likely to benefit from PDA treatment are needed.

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CONFLICT OF INTEREST

None declared.

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Aim—We sought to examine if significant intrauterine growth restriction, defined by birth weight z-score, reduces the efficacy of PDA closure with indomethacin or ibuprofen and thereby increases the need for surgical closure of PDA after pharmacologic treatment.

Study design, subjects, and outcome measures—We studied infants 23–28 weeks' gestation born 2006–2013 at NICHD Neonatal Research Network centers. We examined the responses to PDA treatment with indomethacin and/or ibuprofen and whether the PDA was subsequently closed surgically. Logistic regression generated adjusted odds ratios (ORs) for the associations between the z-score groups (<-2 , -2 to -0.5 , and >-0.5) and PDA surgery following pharmacologic treatment.

Results—5,606 infants were diagnosed with PDA; 3,587 (64.0%) received indomethacin or ibuprofen or both, and 909 (25.3%) underwent PDA surgery. Mothers of infants with PDA non-closure were less likely to have hypertension (19% vs. 28%). Infants with non-closure were more likely to be female (53% vs. 49%), have lower gestational age and birth weight and to develop sepsis (42% vs. 31%). Compared to infants with z-score >-0.5 , PDA surgery was increased among infants with z-score -2 to -0.5 (OR=1.23; 95% CI 1.02–1.47) but not among infants with z-score <-2 .

Conclusion—Infants with birth weight z-score -2 to -0.5 are more likely than normally grown infants to require PDA surgery following pharmacologic treatment.

Keywords

Ibuprofen; indomethacin; mortality; morbidity; premature infants

INTRODUCTION

The short and long-term consequences of patent ductus arteriosus (PDA) for extremely preterm infants are controversial [1–3]. Nevertheless, many infants are treated with medications in an attempt to close the PDA, and many others undergo surgical closure, usually after failed pharmacologic treatment [4]. Any treatment strategy should maximize efficacy and minimize toxicity. Therefore, studies identifying infants most likely to benefit from PDA treatment are needed. The majority of previous studies have examined infants based mainly on their birth weight⁵ and gestational age [5,6]. Only one study has examined the success of pharmacologic PDA closure among infants based on their degree of intrauterine growth restriction [7].

Compared to preterm infants who are appropriately sized for gestational age, preterm infants who are small for gestational age (SGA) are at increased risk of neonatal mortality and morbidities [8–10]. SGA preterm infants have a higher incidence of significant PDA but also more frequent and earlier hemodynamic consequences of PDA [11,12]. Consequently, SGA infants could potentially experience less benefit and more side effects from pharmacologic PDA treatment [7].

Using data from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) Generic Database, an extremely preterm infant registry, we examined the association between degree of growth restriction,

defined by birth weight z-score, and need for surgical closure following indomethacin or ibuprofen treatment, as well as other important morbidities. We hypothesized that infants with a higher degree of growth restriction are more likely to fail pharmacologic treatment and therefore be referred for surgical PDA closure.

MATERIALS AND METHODS

Study population

We analyzed data from the NICHD Neonatal Research Network (NRN) registry for extremely preterm infants born January 1, 2006 through December 31, 2013 at 24 NRN centers. For this registry, trained research nurses enter prospectively collected data on maternal demographic, pregnancy, and delivery information and infant data from birth to discharge, transfer, death, or 120 days. The institutional review board at each center approved the registry.

We excluded infants if they were born with a major congenital malformation, died within 12 hours of birth, or had missing sex status. To maintain consistency over the study period, we included only inborn infants born between 23 and 28 weeks' gestation. Infants born prior to 23 weeks were excluded, as the Olsen norms [13], used to calculate the standard z-scores, are only available for infants born at 23–41 weeks. As we were interested in infants who had a PDA treated with medication, we further excluded those without a PDA and those who had a PDA but did not receive medication for closing the PDA.

Definitions

Standard z-scores calculated using the Olsen norms [13] and used to define the degree of growth restriction, were classified according to these cutoff points: z-score <-2 , z-score -2 to -0.5 , and z-score >-0.5 . Infants with z-score >-0.5 constituted the reference group.

Significant PDA was defined as PDA diagnosed clinically with evidence of left-to-right shunt or diagnosed echocardiographically with left-to-right ductal shunting. Surgical PDA closure was defined as surgical closure following at least 1 course of indomethacin and/or ibuprofen for the purpose of PDA closure. Acetaminophen was not used for PDA closure during the period of study. We assumed that surgical PDA closure was not required if indomethacin and/or ibuprofen was given and no ductal surgery followed. As ductal closure with medication might have been unsuccessful and the infant might have died prior to receiving PDA surgery, we also examined the composite outcome of surgical PDA closure following pharmacologic treatment or death, coded as 'yes' if the infant had pharmacologic treatment for PDA followed by surgical closure or died before PDA surgery and 'no' if the infant survived and did not have ductal surgery after receiving pharmacologic treatment for PDA. Prophylactic indomethacin was not considered to be pharmacologic treatment for PDA.

Other morbidities diagnosed during the hospital stay and recorded for infants surviving >12 hours included necrotizing enterocolitis (NEC), defined as a modified Bell's Stage 2A or greater [14,15]; severe intracranial hemorrhage (ICH), defined as grade 3–4 according to Papile's classification [16]; severe retinopathy of prematurity (ROP), defined as stage 3 or

plus disease; and bronchopulmonary dysplasia (BPD), defined as continuous use of supplemental oxygen at 36 weeks' postmenstrual age.

Certified examiners conducted the neurodevelopmental assessment for infants surviving at 18–22 months' corrected age if they weighed 401–1000 grams at birth (those whose follow-up window opened before January 1, 2008) or were born at ≥26 weeks' gestational age (GA). Neurodevelopmental impairment (NDI) was defined as ≥1 of bilateral blindness, hearing impairment (permanent bilateral hearing loss requiring amplification), moderate to severe cerebral palsy, Gross Motor Function Classification System level ≥2, or Bayley-III cognitive composite score <70. Beginning January 1, 2010, the Bayley-III motor score was also collected, and a motor composite score <70 was added to the NDI definition. The composite outcome of NDI or death was coded as 'yes' if an infant had NDI or died before NDI was evaluated at 18–22 months' corrected age and 'no' if the infant survived without NDI.

Data analysis

We compared baseline maternal and neonatal characteristics between infants by PDA treatment group (≥1 course of indomethacin and/or ibuprofen without surgery vs. ≥1 course of indomethacin and/or ibuprofen followed by surgical closure). Continuous variables were described using means and standard deviations and compared using the Student's t-test. Categorical variables were compared using the chi-square test. The Cochran-Armitage trend test was used to test for changes over time in the percentage of infants in each z-score group with PDA who were treated with indomethacin and/or ibuprofen and the percentage of infants who required surgery.

Outcomes were analyzed by birth weight z-score group. For the analysis of the primary outcome, surgical PDA closure following pharmacologic treatment, we fitted two logistic regression models; the reduced model adjusted for GA, sex, multiple gestation, maternal race, hypertension before pregnancy, and chorioamnionitis, whereas the full model additionally adjusted for other predictors of PDA treatment including prophylactic indomethacin use within the first 24 hours of life, Apgar score at 5 minutes, exposure to antenatal corticosteroids, and culture-proven sepsis.

Secondary outcomes were decided a priori and included the composite outcome of need for surgical PDA closure following pharmacologic treatment or death, NEC, severe ROP, severe ICH, BPD, and the composite of NDI or death. For secondary outcomes, we adjusted for the same maternal and neonatal variables mentioned above and additionally assessed the significance of the interaction term between the z-score and need for PDA surgery following pharmacologic treatment. A significant interaction term implies that the association between PDA treatment and the examined outcome differs by z-score group. The models were adjusted for study center.

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Adjusted odds ratios (OR) and 95% confidence intervals (CI) are reported.

RESULTS

A total of 5,606 infants were diagnosed with PDA. Of these, 3,587 (64.0%) received at least one course of indomethacin and/or ibuprofen (Fig. 1) (75% received only indomethacin, 21% only ibuprofen, and 4% received both indomethacin and ibuprofen); 909 out of 3,587 (25.3%) infants also underwent surgical PDA closure. There were no significant differences ($p=0.09$) in the distribution of pharmacologic treatment modes among the three z-score groups (data not shown). The z-score distribution of our study population ($n=3,587$) included: 141 (3.9%) infants with z-scores <-2 , 1,039 (29.0%) with z-scores between -2 and -0.5 , and 2,407 (67.1%) with z-scores >-0.5 . While the percentage of infants receiving indomethacin and/or ibuprofen decreased over the study period, the decrease reached statistical significance only for infants with z-score >-0.5 ($p<0.01$); it was borderline for infants with z-scores between -2 and -0.5 ($p=0.06$) (Fig. 2A). There was no significant trend in the percentage of infants requiring surgery after pharmacologic treatment (Fig. 2B). Infants with z-scores <-2 had higher mortality ($n=53$, 38%) than infants with z-scores between -2 and -0.5 ($n=184$, 18%) and infants with z-scores >-0.5 ($n=273$, 11%) ($p<0.01$). Infants who had only pharmacologic treatment for PDA without surgery were more likely to be males and to have higher GA, birth weight, and 5-minute Apgar score, but they were less likely to have z-scores between -2 and -0.5 , to have had prophylactic indomethacin within the first 24 hours of life, and to have had culture-proven late onset sepsis compared to those who had pharmacologic treatment for PDA with surgery (Table 1). Infants who had pharmacologic PDA treatment followed by surgery received more courses of indomethacin and/or ibuprofen than those who had pharmacologic PDA treatment without surgery. The rates of BPD and severe ROP were higher among infants who had PDA surgery following pharmacologic treatment than among those who did not have surgery.

In the reduced model with the primary outcome of surgical PDA closure following pharmacologic treatment, compared to infants with z-scores >-0.5 , infants who had z-scores between -2 and -0.5 were 28% more likely to have PDA surgery (OR=1.28; 95% CI 1.07–1.53), while the association was not significant for infants with z-scores <-2 (Table 2). In the full model adjusting for maternal and neonatal variables, this association was also found (OR=1.23; 95% CI 1.02–1.47). When we examined the composite of PDA surgery following pharmacologic treatment or death, the association was significant for infants with z-scores <-2 (OR=3.40; 95% CI 2.33–4.97) and for infants with z-scores between -2 and -0.5 (OR=1.52; 95% CI 1.28–1.79) (Table 2). Restricting the data to only infants who received indomethacin did not alter the results of the primary outcome for the reduced model but rendered the results nonsignificant for the full model (OR=1.19; 95% CI: 0.96–1.47); and it did not affect the composite outcome of PDA surgery following pharmacologic treatment or death in either model (not shown).

When examining the other secondary outcomes including NEC, severe ROP, severe ICH, BPD, and the composite of NDI or death, none of the interaction terms was significant, and so these were subsequently excluded from the final models (Table 3). This indicates that there were no differences in the association of PDA treatment and the examined outcomes by z-score group.

DISCUSSION

In this large multicenter study of extremely preterm infants, we found that after accounting for several maternal and neonatal factors, 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. Infants with z-scores <-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. The association between PDA treatment and the other examined morbidities including NEC, severe ROP, severe ICH, BPD, and the composite of NDI or death did not differ by degree of growth restriction (z-score group).

Several mechanisms are implicated in the delayed closure of the ductus arteriosus in preterm infants [17]. Prostaglandins seem to be the most critical factor responsible for ductus patency, as inhibition of prostaglandin synthesis results in ductus closure in the majority of infants [17,18]. However, approximately 30–40% of preterm infants fail to respond to prostaglandin inhibition requiring retreatment or surgical closure of the ductus arteriosus [5,19,20]. Gestational age [5,6,21,22], birth weight [5,23], and postnatal age at first treatment [20,23,24] have been examined previously as factors associated with medication failure. Similar to previous studies, at the bivariate level we found that several neonatal variables were significantly associated with successful pharmacologic treatment including male sex [25], higher GA [22,24] and higher birth weight [26], and we confirmed earlier work showing that infection seems to reduce the chance of successful pharmacologic closure [27]. Contrary to other studies, however, lack of antenatal corticosteroid exposure [22] and chorioamnionitis [28] did not seem to affect the success of pharmacologic treatment.

The majority of previous studies have examined SGA mainly as a risk factor for PDA, adjusting for it in analyses rather than examining it as a predictor of the need for surgery following pharmacologic treatment. Only one recent small French study ($n=185$) examined the efficacy of a first course of ibuprofen in newborns and identified a linear relationship between the degree of growth restriction and the need for surgical closure following pharmacologic treatment [7]. Compared to infants with z-scores >-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 <-1.5 had more than 12-fold ($OR=12.8$; 95% CI: 2.3–70.5) increased odds of undergoing surgical closure following a first course of ibuprofen [7]. Our study includes data on 5,606 infants born at 23–28 week' gestation with PDA; 3,587 (64%) of these infants were treated with at least one course of indomethacin or ibuprofen, and 909 (25%) underwent surgical closure of the PDA after pharmacologic treatment. Intrauterine growth restriction has been previously associated with persistent ductus patency [12,29]. Higher rates of significant patent ductus arteriosus within 48 hours of birth have been observed among growth-restricted preterm infants of 26–32 weeks in comparison to non-growth-restricted infants (65% vs 40%) [11]. In addition, growth restricted infants have higher concentrations of some inflammation-related proteins, which might affect their response to pharmacologic PDA treatment [30].

Given the potential complications associated with indomethacin use, including renal and electrolyte abnormalities [31–33], intestinal perforation [34,35], gastrointestinal bleeding [31], and alterations in organ perfusion including the brain [36], it is important to identify which infants are less likely to respond to treatment. In such infants, surgery might be the treatment of choice for hemodynamically significant PDA.

Our results should be interpreted with caution given the limitations inherent in a retrospective observational study. Treatment approaches were determined by physician preference rather than a predetermined treatment protocol. We assumed that there was no need for PDA surgery if only medications were used and that the ductus did not close with medications if surgery was performed. However, early mortality and contraindications to pharmacologic therapy might have impacted the likelihood of ductal surgery. Examining the composite outcome of failure of PDA treatment or death, in fact, strengthened our effect estimates. We did not have data to examine whether some of the important outcomes of treatment such as renal side effects differed by growth restriction level. We also recognize the difficulty in classifying NEC and ICH as outcomes potentially related to PDA treatment, as these may have predated the treatment, and in classifying sepsis as a covariate in the model, as this may have occurred after PDA treatment. We did not have data on the size or hemodynamic significance of the PDA, the duration of ductus patency before treatment, postnatal age at the time of treatment, or clinical status at the time of the decision to treat medically or surgically.

Despite these limitations, we believe our conclusion that SGA infants are more likely to experience failed pharmacologic treatment of PDA is valid, as there is no reason to think that surgery decisions would have been systematically different for SGA infants compared with their normally grown peers.

In conclusion, SGA infants in our extremely preterm cohort were more likely than their appropriately grown counterparts to receive PDA surgery following pharmacologic treatment. Given the adverse outcomes associated with PDA medications, particularly indomethacin, our study may help inform which infants are less likely to respond to pharmacologic treatment. Future studies are needed to confirm our findings and to examine the impact of intrauterine growth restriction on the renal side effects associated with PDA and its pharmacologic treatment.

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Abbreviations

BPD bronchopulmonary dysplasia

BW	birth weight
GA	gestational age
ICH	intracranial hemorrhage
NDI	neurodevelopmental impairment
NEC	necrotizing enterocolitis
NRN	Neonatal Research Network
OR	adjusted odds ratio
PDA	patent ductus arteriosus
ROP	retinopathy of prematurity
RDS	respiratory distress syndrome
SGA	small for gestational age

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APPENDIX

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University of Iowa and Mercy Medical Center (U10 HD53109, M01 RR59) – Tarah T. Colaizy, MD MPH; Michael J. Acarregui, MD; Dan L. Ellsbury, MD; John A. Widness, MD; Karen J. Johnson, RN BSN; Donia B. Campbell, RNC-NC; Diane L. Eastman, RN CPNP MA; Jacky R. Walker, RN.

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University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997) – Kristi L. Watterberg, MD; Jean R. Lowe, PhD; Janell F. Fuller, MD; Robin K. Ohls, MD; Conra Backstrom Lacy, RN; Andrea F. Duncan, MD MSc; Rebecca Montman, BSN.

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Highlights

- Optimal management of the patent ductus arteriosus (PDA) in preterm infants is controversial. Therefore, studies identifying the infants most likely to benefit from PDA treatment are needed.
- We examined the management and outcomes of 5606 infants of 23–28 weeks' gestation diagnosed with PDA who were treated with indomethacin and/or ibuprofen. Among these infants, small-for-gestational-age infants with birth weight z-score -2 to -0.5 were more likely than normally grown infants to subsequently require PDA surgery (odds ratio 1.23; 95% confidence interval 1.02–1.47).

Figure 1.
CONSORT diagram for study cohort

Figure 2A

Figure 2B

Figure 2. Percent of infants from receiving: A. 1 course of indomethacin and/or ibuprofen; B. surgical closure after 1 course of indomethacin and/or ibuprofen

Table 1

Baseline neonatal and maternal characteristics comparing PDA treatment groups

	1 course of indomethacin or ibuprofen without surgical closure (N=2678)	1 course of indomethacin or ibuprofen followed by surgical closure (N=909)	P-Value
Neonatal characteristics and outcomes			
Male, n (%)	1376/2678 (51)	430/909 (47)	0.03
Gestational age, mean (SD)	26.2 (1.5)	25.5 (1.4)	<0.01
Birth weight, mean (SD)	842 (218)	756 (175)	<0.01
Mode of delivery, n (%)	N=2678	N=909	
Vaginal	834 (31)	318 (35)	0.03
Cesarean Section	1844 (69)	591 (65)	0.03
Apgar score at 5 minutes, mean (SD)	6.5 (2.1)	6.1 (2.1)	<0.01
z-score, n (%)	N=2678	N=909	
z-score < -2.0	116 (4)	25 (3)	0.03
-2.0 < z-score < -0.5	743 (28)	296 (32)	0.01
z-score > -0.5	1819 (68)	588 (65)	0.07
Prophylactic indomethacin, n (%)	565/2678 (21)	225/909 (25)	0.02
Late-onset sepsis, n (%)	827/2678 (31)	384/909 (42)	<0.01
Respiratory distress syndrome, n (%)	2664/2678 (99)	908/909 (100)	0.14
Death	464/2678 (17)	83/909 (9)	<0.01
# Indomethacin courses, n (%)	N=2087	N=743	
1	1429 (68)	288 (39)	<0.01
2	509 (24)	330 (44)	<0.01
3	136 (7)	108 (15)	<0.01
4	13 (1)	17 (2)	<0.01
# Ibuprofen courses, n (%)	N=688	N=220	
1	536 (78)	105 (48)	<0.01
2	120 (17)	93 (42)	<0.01
3	31 (5)	18 (8)	0.04
4	1 (0)	4 (2)	<0.01
Necrotizing enterocolitis, n (%)	296/2678 (11)	90/909 (10)	0.33
Severe ROP, n (%)	392/2678 (15)	285/909 (31)	<0.01
Severe ICH, n (%)	424/2644 (16)	144/907 (16)	0.91
BPD, n (%)	1173/2259 (52)	654/856 (76)	<0.01

	1 course of indomethacin or ibuprofen without surgical closure (N=2678)	1 course of indomethacin or ibuprofen followed by surgical closure (N=909)	P-Value
Neurodevelopmental impairment *, n (%)	553/1490 (37)	218/654 (33)	0.10
Maternal characteristics			
Receipt of antenatal steroids, n (%)	2340/2668 (88)	805/907 (89)	0.40
Maternal race, n (%)	N=2627	N=887	
African American or black	885 (34)	320 (36)	0.23
Caucasian	1540 (59)	509 (57)	0.43
Other	202 (8)	58 (7)	0.24
Multiple gestations, n (%)	806/2678 (30)	271/909 (30)	0.87
Hypertension, n (%)	737/2672 (28)	174/909 (19)	<0.01
Hypertension before pregnancy, n (%)	302/2676 (11)	72/909 (8)	0.01
Chorioamnionitis, n (%)	387/2673 (14)	150/909 (16)	0.14

* Children eligible for 18–22 month follow-up

Logistic modeling of use of PDA surgery following pharmacologic treatment and use of PDA surgery following pharmacologic treatment or death adjusted for center variability

Table 2

Variable	PDA surgery following pharmacologic treatment				PDA surgery following pharmacologic treatment or death			
	Reduced model	Full model	Reduced model	Full model	Reduced model	Full model	Reduced model	Full model
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Gestational age (weeks)	0.70 (0.66–0.74)	<0.01	0.73 (0.69–0.78)	<0.01	0.60 (0.57–0.63)	<0.01	0.64 (0.60–0.67)	<0.01
Male	0.86 (0.73–1.02)	0.08	0.85 (0.72–1.00)	0.05	1.03 (0.89–1.20)	0.66	1.01 (0.87–1.17)	0.92
Prophylactic indomethacin	-----	---	1.44 (1.10–1.91)	0.01	-----	---	1.42 (1.12–1.81)	<0.01
Apgar score at 5 minutes	-----	---	0.97 (0.93–1.01)	0.16	-----	---	0.93 (0.90–0.97)	<0.01
Receipt of antenatal steroids	-----	---	1.09 (0.83–1.43)	0.56	-----	---	0.94 (0.73–1.20)	0.60
Late-onset sepsis	-----	---	1.32 (1.11–1.58)	<0.01	-----	---	1.54 (1.31–1.81)	<0.01
Maternal race								
African American or black	1.34 (0.92–1.95)	0.12	1.35 (0.93–1.97)	0.12	1.15 (0.82–1.61)	0.42	1.17 (0.83–1.65)	0.37
Caucasian	1.43 (1.01–2.02)	0.04	1.46 (1.03–2.06)	0.03	1.17 (0.85–1.60)	0.33	1.21 (0.88–1.66)	0.24
Other	REF	---	REF	---	REF	---	REF	---
Multiple gestation	1.16 (0.97–1.38)	0.11	1.14 (0.95–1.37)	0.15	1.14 (0.96–1.34)	0.13	1.14 (0.96–1.34)	0.13
Hypertension before pregnancy	0.81 (0.60–1.08)	0.15	0.79 (0.59–1.06)	0.12	0.93 (0.72–1.20)	0.59	0.91 (0.70–1.17)	0.45
Chorioamnionitis	1.06 (0.84–1.33)	0.63	1.04 (0.83–1.31)	0.71	1.01 (0.82–1.24)	0.93	1.00 (0.80–1.23)	0.96
z-score								
z-score < -2.0	0.88 (0.56–1.40)	0.60	0.83 (0.52–1.33)	0.44	3.65 (2.51–5.32)	<0.01	3.40 (2.33–4.97)	<0.01
-2.0 < z-score < -0.5	1.28 (1.07–1.53)	0.01	1.23 (1.02–1.47)	0.03	1.60 (1.36–1.89)	<0.01	1.52 (1.28–1.79)	<0.01
z-score > -0.5	REF	---	REF	---	REF	---	REF	---

Table 3

Logistic modeling* of necrotizing enterocolitis, severe retinopathy of prematurity, severe intracerebral hemorrhage, bronchopulmonary dysplasia, and NDI/death

Variable	NEC		Severe ROP		Severe ICH		BPD		NDI or Death	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Gestational age (week)	0.88 (0.80–0.95)	<0.01	0.59 (0.54–0.63)	<0.01	0.73 (0.68–0.78)	<0.01	0.67 (0.62–0.71)	<0.01	0.70 (0.64–0.77)	<0.01
Male	1.22 (0.98–1.52)	0.08	1.01 (0.84–1.22)	0.89	1.15 (0.95–1.40)	0.14	1.31 (1.10–1.55)	<0.01	1.50 (1.23–1.82)	<0.01
Prophylactic indomethacin	1.22 (0.87–1.71)	0.26	1.43 (1.06–1.92)	0.02	1.06 (0.79–1.42)	0.71	0.79 (0.60–1.05)	0.11	1.15 (0.85–1.55)	0.37
Apgar score at 5 minutes	1.02 (0.97–1.08)	0.40	0.99 (0.95–1.04)	0.80	0.90 (0.86–0.94)	<0.01	0.90 (0.86–0.94)	<0.01	0.91 (0.87–0.95)	<0.01
Receipt of antenatal steroids	0.81 (0.58–1.14)	0.22	0.88 (0.65–1.20)	0.42	0.59 (0.44–0.78)	<0.01	1.13 (0.86–1.48)	0.38	0.93 (0.68–1.28)	0.66
Postnatal infection	2.09 (1.66–2.63)	<0.01	1.55 (1.28–1.89)	<0.01	1.19 (0.97–1.46)	0.09	1.37 (1.13–1.67)	<0.01	1.50 (1.23–1.84)	<0.01
Maternal race										
African American or black	0.80 (0.50–1.29)	0.36	0.45 (0.29–0.69)	<0.01	1.14 (0.74–1.74)	0.56	0.89 (0.60–1.31)	0.55	0.71 (0.44–1.14)	0.16
Caucasian	0.73 (0.47–1.13)	0.16	0.80 (0.54–1.19)	0.27	1.18 (0.79–1.74)	0.42	0.97 (0.68–1.38)	0.87	0.81 (0.52–1.26)	0.35
Other	REF	---	REF	---	REF	---	REF	---	REF	---
Multiple gestations	0.87 (0.68–1.13)	0.30	1.18 (0.96–1.46)	0.12	1.14 (0.93–1.41)	0.22	0.95 (0.79–1.14)	0.58	0.98 (0.79–1.22)	0.86
Hypertension before pregnancy	1.06 (0.74–1.50)	0.76	0.97 (0.70–1.35)	0.87	0.99 (0.71–1.37)	0.93	1.29 (0.96–1.73)	0.09	1.46 (1.03–2.08)	0.03
Chorioamnionitis	0.93 (0.68–1.28)	0.66	0.94 (0.7–1.23)	0.66	1.30 (1.01–1.68)	0.04	0.82 (0.64–1.05)	0.12	1.09 (0.84–1.41)	0.52
z-score										
z-score < -2.0	2.68 (1.70–4.22)	<0.01	3.66 (2.38–5.63)	<0.01	1.08 (0.66–1.78)	0.76	7.18 (3.85–13.39)	<0.01	5.66 (3.40–9.45)	<0.01
-2.0 z-score -0.5	1.20 (0.94–1.54)	0.15	1.48 (1.20–1.83)	<0.01	0.87 (0.69–1.08)	0.20	2.25 (1.84–2.75)	<0.01	1.33 (1.07–1.65)	0.01
z-score > -0.5	REF	---	REF	---	REF	---	REF	---	REF	---
PDA surgery following pharmacologic treatment	0.90 (0.69–1.18)	0.44	1.99 (1.62–2.44)	<0.01	0.78 (0.62–0.99)	0.04	2.45 (1.98–3.02)	<0.01	0.83 (0.66–1.03)	0.09

* Interaction term z-score $\times$ PDA surgery following pharmacologic treatment was not significant and was not included in any of the models.