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Prophylactic Indomethacin in Extremely Preterm Infants: Association with Death or BPD and Observed Early Serum Creatinine Levels

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Abstract

OBJECTIVES: To identify the relationship between prophylactic indomethacin (PI) administration and 1) mortality and bronchopulmonary dysplasia (BPD) at 36-weeks postmenstrual age (PMA) (primary outcome), and 2) to evaluate for PI-associated acute kidney injury.

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AUTHOR CONTRIBUTIONS

HHA and JLS designed, analyzed, interpreted, drafted, revised, and approved the final version of the manuscript. CHB, MKB, MMT, MAK, SRJ, and THM interpreted, revised, and approved the final version.

Supplementary information is available on JPER's website.

STUDY DESIGN: Retrospective cohort investigation of 22–28 weeks gestation infants (N=1,167) who were admitted to Nationwide Children’s Hospital on postnatal days 0–1 between May 2009–September 2017 and survived 24-hours postnatal. The associations of PI treatment with mortality or BPD, and other secondary outcomes, was evaluated via multivariable robust-error-variance Poisson regression.

RESULTS: The adjusted risks of death or BPD (1.02, 95% CI: 0.83, 1.25), BPD (0.97, 95% CI: 0.77, 1.21), and death 1.33 (95% CI: 0.84, 2.10) by 36-weeks PMA were unchanged following PI treatment after multivariable adjustment. No changes in mean creatinine levels were detected in exposed versus unexposed infants to suggest PI-induced AKI.

CONCLUSION: Prophylactic indomethacin treatment was unrelated to mortality or BPD outcomes.

Keywords

Acute Kidney Injury; Bronchopulmonary dysplasia; Indomethacin prophylaxis; Mortality

Introduction

Prophylactic indomethacin (PI) administration within the first 24-hours postnatal is often prescribed in neonatal intensive care units (NICUs) to reduce the risks of intraventricular hemorrhage (IVH) and patent ductus arteriosus (PDA) in very low birth weight (<1500 gram birth weight) (VLBW) infants [1,2]. However, there is little evidence of its effectiveness in improving mortality and longer-term neonatal morbidities including neurodevelopmental delay and bronchopulmonary dysplasia (BPD) [3–6]. Up-to-date systematic reviews of RCTs conducted primarily in the period from 1985–2001 have consistently concluded little to no improvement in long-term respiratory outcomes and mortality following PI treatment [3,4,7,8]. However, as some neonatologists have questioned the relevancy of decades-old trial data in the modern neonatal era, more recent observational studies have reported improvements in both BPD and death [9,10].

Moreover, concerns exist regarding the short and long term effects of the indomethacin treatment itself [3]. Left untreated, the vast majority of VLBW infants will not develop severe (Grades 3 or 4) IVH [4,11] and their PDAs will spontaneously close [1]. And given the medication’s mechanism of action, renal impairment may also be a risk associated with the introduction of prophylactic indomethacin. A Cochrane meta-analysis ($n= 618$ total patients) of trials that randomly assigned VLBW neonates to prophylactic indomethacin or placebo and studied serum creatinine as a secondary outcome did not find a difference in the proportion of patients with serum creatinine levels greater than a 1.8 mg/dL [12,13] threshold [3]. However, multiple studies examining the use of treatment dosing of indomethacin in premature infants have reported post-treatment signs of acute kidney injury including serum creatinine elevation (relative to pre-treatment levels) [14–16], decreased glomerular filtration rate [14], and decreased urinary potassium excretion [15]. Recent studies have reported that 15% of treated infants experienced renal toxicity and 24% developed acute renal failure following indomethacin [14,17].

Our primary objective was to evaluate, using local electronic medical records, the association between prophylactic indomethacin treatment during the first 24-hours following birth and a composite outcome of death or BPD. As a secondary outcome, we also evaluated median serum creatinine concentration in treated versus untreated infants during the first postnatal week. Additional secondary outcomes included BPD, death, severe IVH, and necrotizing enterocolitis (NEC). We hypothesized that we would observe no differences in BPD, IVH, and mortality between treated and untreated groups and that PI administration would be associated with an increase in serum creatinine levels.

METHODS

Study Population

We analyzed a cohort of infants with a gestational age between 22–28 completed weeks, who survived the first 24 hours after birth (thus, eligible to receive prophylactic indomethacin during that entire period), and were admitted on postnatal day 0 or 1 to a neonatal intensive care unit (NICU) within the Nationwide Children's Hospital (NCH) Neonatal Network (Columbus, OH) from May 2009 to September 2017. Services were distributed among four level III birth-hospital NICUs, two level II birth-hospital NICUs, and a single level IV referral-only NICU. The data were derived from electronic medical records and included demographic data, diagnoses, Apgar scores, daily respiratory modality (e.g. oxygen, continuous positive airway pressure, mechanical ventilation), and serum creatinine results. The study was approved by the Nationwide Children's Hospital Institutional Review Board.

Exposure and Outcome Determination

Prophylactic indomethacin exposure was defined as intravenous administration of indomethacin within the first 24-hour postnatal day, to capture an initial intention to treat with prophylactic indomethacin. If administered, the prescribed dose of prophylactic indomethacin at our institution is 0.1 mg/kg/dose beginning in the first postnatal day and continuing every 24-hours for three total doses. Prophylactic indomethacin is featured on our admission order set to ensure treatment shortly after NICU admission. Our primary outcome was a composite outcome of death or BPD at 36-weeks postmenstrual age (PMA). We chose this primary outcome since death and BPD are competing risks. BPD was defined as a need for oxygen or positive pressure ventilation (invasive or non-invasive) at 36-weeks PMA. Secondary outcomes included BPD among survivors at 36-weeks PMA, death by 36-weeks PMA, acute renal failure, severe intraventricular hemorrhage (IVH) (classified as grades 3 or 4), and necrotizing enterocolitis (NEC) (grades 2 or 3) [11,18]. We also assessed serum creatinine concentration during the first seven days postnatal.

Statistical Analysis

Analyses were performed using Stata 15.0 (StataCorp, College Station, Texas, USA). Our sample-size was determined by the number of subjects in the available dataset meeting our pre-specified inclusion criteria. Binary comparisons were calculated between exposure groups using Pearson chi-square and Wilcoxon rank-sum testing. Multivariable adjusted relative risks (aRR) were measured using robust-error-variance Poisson regressions

including gestational age (GA), small for gestational age (<10th percentile of birthweight) [19], sex, race, ethnicity, birth year, and 5-minute Apgar scores as covariates. We also examined median serum creatinine concentrations collected during the first week of postnatal age (percentage of infants in total cohort for which creatinine was measured: postnatal day 0= 3.4%; day 1=13.4%; day 2=14.9%; day 3=14.3%; day 4=14.4%; day 5=15.2%; day 6=15.7%; day 7=14.5%) since this data did not follow a normal distribution. Serum creatinine values were compared in treated and untreated infants after stratification into 22–25 6/7 weeks and 26–28 weeks gestational age groups.

RESULTS

Patient characteristics

Our 8-year study population included a total of 1,167 infants; 200 were treated with prophylactic indomethacin within the first postnatal day and 967 were untreated. Treated infants significantly had a lower mean birth weight, lower mean gestational age, and were more likely to be female (Table 1). Of the 200 treated infants, 155 (77.5%) received all three doses, 30 (15.0%) received two doses, and 15 (7.5%) received one dose.

Unadjusted Binary Outcomes

The prevalence of the primary composite outcome, death or BPD among survivors at 36-weeks PMA, was significantly higher among those exposed to prophylactic indomethacin than those with no exposure ($P<0.0001$, Table 2). When assessed as individual outcomes, BPD and death before 36-weeks PMA were also both more common in the treated group ($P<0.0001$, Table 2). IVH was more frequent in treated infants (Table 2). There was no difference in NEC development between exposure groups.

Multivariable Outcomes

BPD or Death—Neither the adjusted risk of developing the primary composite outcome, BPD or death (adjusted relative risk [aRR] 1.02, 95% CI: 0.83, 1.25), nor the adjusted risk of developing BPD, were different (aRR 0.97, 95% CI: 0.77, 1.21) following prophylactic indomethacin treatment after adjustment for measured covariates (Table 3). The adjusted risk of mortality by 36-weeks PMA was 1.33 (95% CI: 0.84, 2.10) following prophylactic indomethacin treatment. Small for gestational age infants and those born at 22–24 weeks had significantly higher risks for death, BPD, and the primary composite outcome. As an exploratory analysis, we tested for subgroup interactions which denote the adjusted relative risk for our primary and secondary outcomes among only those patients within each demographic subgroup who were treated with indomethacin (Appendix Table 1). Caution should be used in interpretation of these exploratory findings given small sample sizes for most groups (wide confidence intervals) and multiple comparisons.

IVH and NEC—Infants with severe (grades 3 and 4) IVH were not significantly more or less likely to be exposed to prophylactic indomethacin compared to infants without IVH after adjustment (aRR: 1.15, 95% CI: 0.76, 1.73) (Table 3). There were also no differences in NEC outcome (grades 2 or 3) between treated and untreated infants (aRR 0.75, 95% CI: 0.35, 1.59).

Serum Creatinine

After stratification by <26 and ≥26-week gestational age categories, median serum creatinine concentrations during the first postnatal week were similar in treated and untreated infants, with the exception of two time points, (Figure 1). Serum creatinine levels were significantly increased in the prophylactic indomethacin group (n=22; median = 0.95 mg/dl) on day 2 postnatal relative to the untreated group (n=58; median = 0.65 mg/d) ($p<0.0001$) for infants less than 26-weeks GA. Median creatinine among the untreated group, however, was significantly greater on day 7 postnatal ($p=0.0002$) for smaller preterm infants and day 2 for babies ≥26-weeks GA ($p=0.0297$).

DISCUSSION

We demonstrated no associations between prophylactic indomethacin administration within 24-hours postnatal and mortality or BPD, or any of our secondary clinical outcomes including mortality, following adjustment for measured clinical and demographic risk factors that were present at the time of neonatal intensive care unit (NICU) admission.

Randomized control trials have not demonstrated an improvement in mortality following prophylactic indomethacin treatment [3], [4,13]. In contrast, recent observational studies have provided conflicting results. No reduction in mortality was found in two large studies that each followed a complete cohort of <29-weeks birth gestation infants from birth to determination of mortality and BPD at 36-weeks corrected age. However, a meta-analysis of both found a slight reduction in mortality risk (adjusted odds ratio [aOR] 0.81, 95% CI: 0.66, 0.98), but not in the composite risk of death or BPD (aOR 0.93, 95% CI: 0.76, 1.13), following prophylactic indomethacin [8]. Other studies that evaluated select cohorts of referred and transferred survivors found a marked improvement in mortality following prophylactic indomethacin administration [10,20], but may have been at increased risk for bias since transferred infants might have been transferred due to increased severity of illness or comorbidities and because both treated and untreated infants that died prior to transfer were necessarily omitted from the analyses [21]. Another recent study evaluated the effect of prophylactic indomethacin by comparing outcomes during an initial 6-year period, when prophylactic indomethacin was given per local standard of care, with a subsequent 5-year period when indomethacin was never administered. Mortality or BPD (risk ratio [RR] 0.78, 95% CI: 0.62–0.95) and BPD (RR 0.68, 95% CI: 0.46–0.89) were lowered during the era of routine prophylactic indomethacin administration [9]. The authors acknowledged it was difficult to control for other changes in neonatal care at their institution within the study time frame [9].

Our finding of no change in the risk of mortality following prophylactic indomethacin administration within 24-hours of birth (aRR 1.33, 95% CI: 0.84–2.10) is consistent with both the Trial of Indomethacin Prophylaxis in Preterms (TIPP) (Risk Ratio [RR] 1.13, 95% CI: 0.9–1.42), the largest multicenter randomized control trial (RCT) examining prophylactic indomethacin treatment for extremely preterm infants, and a meta-analysis of prophylactic indomethacin RCTs conducted between 1985–2001 (RR 0.96, 95% CI: 0.81–1.12) [3,4,6,22,23]. Similarly, our finding of no change in the risk of BPD at 36-weeks

following prophylactic indomethacin treatment (aRR 0.97, 95% CI: 0.77–1.21) is also consistent with the TIPP trial's reported results (RR 1.06, 95% CI: 0.92–1.22) [23].

Indomethacin, whether administered prophylactically, early for symptomatic PDA, and late for symptomatic PDA, has been associated with elevated serum creatinine [24]. Since the last randomized trials for prophylactic indomethacin that measured elevated creatinine level as a secondary outcome were conducted >20-years ago (using a binary >1.8 mg/dl serum creatinine cutoff) [12,13], the evaluation of acute kidney injury (AKI) in neonates has rapidly evolved [25]. Indomethacin treatment post-birth is a risk factor for acute kidney injury (AKI) and may further increase the susceptibility of infants <29-weeks GA to chronic kidney disease [26,27]. Serum creatinine has several limitations as a marker of kidney injury in the neonatal period. First, it is a functional rather than an injury marker. Levels do not rise following a renal insult until 25–50% of renal function has been lost. It crosses the placenta. Therefore, it reflects maternal levels in the first few postnatal days and could take up to two weeks to reach true infantile steady-state levels in <26-weeks GA preterm infants due to the physiologic immaturity of filtration. In fact, it has been reported that serum creatinine levels are expected to rise in the first 3–4 postnatal days in infants born less than 26-weeks GA [28]. The differences in serum creatinine observed in our study could reflect gestational and chronologic age-related physiologic influences in a setting of immature renal function. Each infant's daily fluid balance or receipt of other nephrotoxic medications might also have played a role and might be better modeled in future prospective cohorts. However, given the inherent limitations of serum creatinine as a biomarker, kidney injury in the treated group of <26-weeks GA infants on day two postnatal cannot be completely ruled out. Due to the known nephrotoxicity of indomethacin in preterm neonates, clinicians should remain sensitive to the risk for AKI and renal function should be closely monitored.

As in previous RCTs, we found no change in NEC risk following prophylactic indomethacin administration [3]. Indomethacin has been shown in previous large RCTs to reduce the incidence of IVH [4,13]. However, we did not observe a protective benefit of prophylactic indomethacin treatment for severe IVH. Other recent observational studies and some of the smaller RCTs [3] also failed to detect a reduction in severe IVH following prophylactic indomethacin treatment [29,30]. Interestingly, in our study 11.2% of the infants (131 of 1167 total) developed severe IVH. This is the same overall proportion of infants within the TIPP trial (11.2%; 127 of 1136 total patients) that developed severe IVH. In the TIPP trial, 9% of treated infants developed IVH compared to 13% of untreated infants (Risk Difference=4%; Number Needed to Treat= 25 patients) [4]. Our need to adjust for measured confounders potentially reduced our power to detect a meaningful difference in severe IVH. Additionally, unmeasured confounders including antenatal corticosteroids and antenatal insults may have impacted our adjusted outcome estimates.

Strengths and Limitations

Our study has several limitations. Given our study's observational nature and reliance on data originally recorded for routine medical care, there is always a risk of residual confounding and an inability to completely adjust for patient severity of illness just prior to treatment. Therefore it may be impossible to completely adjust for a clinician's decision to

provide or withhold indomethacin prophylaxis based on early severity of illness. We were unable to adjust for illness severity scores in the first postnatal day prior to treatment as is possible in prospective investigations. However, we were able to adjust for 5-minute Apgar scores, which were demonstrated in the Canadian Neonatal Network (CNN) study [22] to be closely correlated with Score of Neonatal Acute Physiology version II [SNAP-II] scores. We also had no maternal data or data on prenatal treatments. Our single-centered data, although a very large sample, may limit the generalizability of our result.

Our evaluation for AKI was based on serum creatinine, which is often measured clinically in routine practice and available to us, but a late marker for AKI/renal injury and a biomarker that crosses the placenta and contributes to neonatal serum creatinine levels at the time of PI administration. Larger targeted investigations are needed to prospectively evaluate more sensitive novel biomarkers for AKI both after indomethacin prophylaxis and treatment dosing for PDA. In routine practice, serum creatinine may have been measured more frequently in infants with early severe illness and creatinine measures were only available for a given subset of our cohort on any given postnatal day. In addition, other AKI risk factors including nephrotoxic medications administered in the early postnatal days and early fluid balance should be prospectively measured and modeled in future studies.

We purposely did not attempt to measure the presence or timing of PDA-closure following indomethacin treatment. Any indirect effect of PDA-closure on our outcomes following indomethacin exposure would be as a mediating (intermediary) (process measure) variable, not as a confounder which by definition must influence both the exposure and the outcome. Therefore, the exclusion of PDA-closure data from our analyses is proper and would in no way lead to bias in our results.

Our large cohort study had multiple strengths. We did include infants hospitalized at multiple Level II and Level III birth hospital NICUs in addition to a Level IV NICU at a large freestanding children's hospital and we were able to follow each surviving infant within our NICU Network from postnatal day one until the 36-weeks mortality or BPD primary outcome event. Although patients in 2 of the 7 hospitals that contributed patients to this ~8-years study may have also been included in the NICHD Neonatal Research Network (NRN) study [6] during the April 2011-December 2012 time period, the vast majority of patients included in this large cohort study and their prophylactic indomethacin-associated outcomes have not previously been reported. Another very small subset of infants within our study may have been included in two investigations that studied infants within our local, level IV all-referral NICU who had previously been treated with prophylactic indomethacin [10,20]. Only infants who had an indication for transfer for Level IV NICU care and who survived to be transferred were included in those studies. We were fortunate to obtain data from all seven NICUs within our Nationwide Children's Neonatal Network which allowed us to continuously follow all eligible babies from the date of birth when prophylactic indomethacin treatment would occur, if administered, until outcome assessment at 36-weeks PMA. At our institution, PDA is not treated via indomethacin within the first postnatal week per our PDA guideline so we are reassured that all indomethacin administration within the first 24-hours postnatal was prophylactic rather than treatment for a diagnosed PDA. Although we transparently report binary associations between prophylactic indomethacin

treatment and our primary and secondary outcomes, we have solely focused our conclusions on our multivariable adjusted models given the known impact of variables including gestational age on both the probability of prophylactic indomethacin treatment and important neonatal outcomes. We only adjusted for measured risk factors present at the time of neonatal intensive care unit (NICU) admission, prior to the time when an infant might potentially receive prophylactic indomethacin, and we required all infants to survive 24-hours and thus be eligible for treatment throughout the entire 24-hour postnatal prophylactic indomethacin treatment window. This is important since neonatal mortality in <29-weeks gestation infants is highest in the first days postnatal and survivor treatment selection bias (immortal time bias) can lead to a false association between early treatment and decreased mortality. Since an infant must by default survive to be treated [5,31], a clinician may be less likely to treat an infant if they are thought to be near death.

Finally, our results for our primary mortality or 36-weeks BPD outcome, and our secondary 36-weeks BPD in survivors and mortality outcomes, closely align with reported RCT outcomes and with the two other large, recent observational studies that followed complete <29-weeks GA infant cohorts from birth until 36-weeks outcomes ascertainment. Although the meta-analysis of the two cohorts (but neither cohort investigation independently) found a very slight reduction in mortality risk (aOR 0.81, 95% CI: 0.66, 0.98), the addition of our new findings to those pooled results would move the adjusted mortality risk further towards the null of no effect [8].

CONCLUSION

Our investigation detected no protective benefit of prophylactic indomethacin treatment for improving the risk of death or BPD at 36-weeks PMA in preterm infants born at <29-weeks gestation. We also found no significant change in the adjusted post-treatment risk of BPD among survivors at 36-weeks PMA, death by 36-weeks, or NEC. The risks of treating all eligible infants with prophylactic indomethacin may exceed potential benefits. When taken in the context of previous meta-analyses of RCTs and large observational investigations, there remains no clear evidence that prophylactic indomethacin treatment improves the long-term outcomes of most extremely preterm infants. Given the demonstrated nephrotoxicity of indomethacin and our study finding of higher creatinine levels on postnatal day 2 among treated patients, prospective investigations utilizing sensitive biomarkers of acute kidney injury are needed to more fully evaluate the risks of indomethacin treatment on developing neonatal kidneys.

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Appendix

Appendix Table 1:

Stratified Adjusted Relative Risks of Clinical Outcomes Among Prophylactic Indomethacin Treated vs Untreated Infants.

	Adjusted Risk Ratio [95% CI]				
	BPD or Death	Death	BPD ^I	Severe IVH	NEC
Prophylactic Indomethacin Treatment	1.02 [0.83, 1.25]	0.97 [0.77, 1.21]	1.33 [0.84, 2.10]	1.15 [0.76, 1.73]	0.75 [0.35, 1.59]
Stratified adjusted relative risks by subgroup:					
Gestational age					
22–24	1.03 [0.74, 1.44]	1.23 [0.60, 2.51]	1.04 [0.71, 1.52]	1.06 [0.60, 1.88]	0.88 [0.32, 2.37]
25–26	1.00 [0.74, 1.35]	1.70 [0.40, 7.17]	0.99 [0.73, 1.35]	2.03 [0.86, 4.76]	1.28 [0.20, 8.13]
27–28	0.87 [0.42, 1.77]	4.40 [0.38, 51.56]	0.85 [0.40, 1.82]	1.14 [0.15, 8.68]	2.59 [0.31, 21.82]
Small for gestational age					
<10 th percentile	1.05 [0.52, 2.14]	3.17 [0.36, 27.80]	1.09 [0.46, 2.57]	2.90 [0.18, 46.33]	1.79 [0.12, 27.51]
10 th percentile	0.99 [0.80, 1.23]	1.41 [0.73, 2.72]	0.98 [0.78, 1.24]	1.32 [0.82, 2.11]	0.89 [0.39, 2.04]
Sex					
Female	0.92 [0.69, 1.24]	0.77 [0.28, 2.08]	0.92 [0.67, 1.26]	0.86 [0.44, 1.67]	0.67 [0.19, 2.35]
Male	1.04 [0.77, 1.40]	2.51 [1.14, 5.57]	1.01 [0.73, 1.40]	1.99 [1.05, 3.76]	1.13 [0.40, 3.21]
Race					
White	0.94 [0.71, 1.24]	1.35 [0.60, 3.05]	0.92 [0.68, 1.24]	1.22 [0.64, 2.29]	0.52 [0.14, 1.95]
Black	1.05 [0.72, 1.54]	1.41 [0.42, 4.74]	1.05 [0.70, 1.58]	1.41 [0.64, 3.09]	1.46 [0.40, 5.37]
Multiracial	1.10 [0.44, 2.74]	*	1.07 [0.42, 2.72]	5.57 [0.22, 141.09]	2.23 [0.19, 25.58]
Other [†]	1.20 [0.33, 4.32]	*	1.17 [0.32, 4.26]	*	*
Ethnicity					
Hispanic/Latino	47.87 [0.00, 601763]	*	47.87 [0.00, 601763]	*	*
Non-Hispanic/Latino	0.99 [0.81, 1.22]	*	0.98 [0.78, 1.23]	1.31 [0.83, 2.06]	0.97 [0.44, 2.13]
Birth Year					
2009–2013	1.10 [0.76, 1.60]	1.71 [0.64, 4.59]	1.12 [0.74, 1.68]	1.27 [0.50, 3.21]	0.38 [0.04, 3.49]
2014–2015	0.93 [0.68, 1.27]	1.27 [0.45, 3.59]	0.91 [0.65, 1.27]	1.29 [0.64, 2.59]	0.94 [0.27, 3.22]
2016–2017	0.97 [0.60, 1.54]	0.60 [0.11, 3.29]	0.98 [0.60, 1.60]	0.98 [0.41, 2.35]	1.49 [0.36, 6.20]

* omitted due to insufficient data.

^I among those that survived to 36-weeks PMA.

Note: wide confidence intervals due to very limited sample sizes within some strata.

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FIGURE 1:
Median Serum Creatinine Values by Gestational Age Group Over Time.

Table 1:

Cohort Demographic Characteristics.

	Prophylactic indomethacin N=200	No prophylactic indomethacin N=967	P value
Gestational age (weeks) - mean (SD)	24.9 (1.3)	26.4 (1.6)	<0.0001
22–24	75 (37.5)	161 (16.6)	<0.0001
25–26	107 (53.5)	257 (26.9)	<0.0001
27–28	18 (9.0)	549 (56.8)	<0.0001
Birth weight (grams) - mean (SD)	757 (175)	940 (257)	<0.0001
Small for gestational age			
<10 th percentile	17 (8.5)	65 (6.8)	0.3854
10 th percentile	183 (91.5)	895 (93.2)	
Sex			
Female	111 (55.5)	445 (46.1)	0.0156
Male	89 (44.5)	520 (53.9)	
Race			
White	94 (47.0)	530 (54.8)	0.0439
Black	64 (36.0)	267 (27.6)	0.2101
Multiracial	14 (7.0)	58 (6.0)	0.5919
Other ^I	5 (2.5)	34 (3.5)	0.4668
Missing	13 (6.5)	78 (8.1)	0.1159
Ethnicity			
Hispanic/Latino	5 (2.5)	18 (2.0)	0.5239
Non-Hispanic/Latino	176 (97.2)	877 (98.0)	
Birth Year			
2009–2012	66 (33.0)	370 (38.3)	0.1616
2013–2015	92 (46.0)	280 (29.0)	<0.0001
2016–2017	42 (21.0)	317 (32.8)	0.0010

Column values are n (%) unless otherwise noted. P-values <0.05 cutoff are in bold.

^I Babies identified as American Indian or Alaskan Native, Asian, or other.

Table 2:

Binary (Unadjusted) Clinical Outcomes by Treatment Status.

	Prophylactic indomethacin N=200 (%)	No prophylactic indomethacin N=967 (%)	<i>P</i> value
BPD ^{<i>I</i>}	124 (74.3)	513 (57.3)	<0.0001
Death	33 (16.5)	71 (7.3)	<0.0001
BPD or death	157 (78.5)	584 (60.4)	<0.0001
Severe IVH	38 (19.0)	93 (9.6)	0.0001
NEC	11 (5.5)	44 (4.55)	0.5639

P-value <0.05 cutoffs are in bold.

^{*I*} among those that survived to 36-weeks PM. N=167 and 896 for treated and untreated groups, respectively.

Table 3:

Multivariable Adjusted Relative Risk of Clinical Outcomes by Treatment and by Other Demographic Factors.

	Adjusted Risk Ratio [95% CI]				
	BPD or Death	BPD ^I	Death	Severe IVH	NEC
Prophylactic Indomethacin Treatment	1.02 [0.83, 1.25]	0.97 [0.77, 1.21]	1.33 [0.84, 2.10]	1.15 [0.76, 1.73]	0.75 [0.35, 1.59]
Adjusted risk ratios of clinical outcomes for other measured variables:					
Gestational age					
22–24	1.79 [1.44, 2.23]	1.78 [1.41, 2.24]	12.78 [5.36, 30.50]	3.52 [2.13, 5.80]	3.08 [1.51, 6.29]
25–26	1.59 [1.32, 1.92]	1.60 [1.32, 1.93]	2.02 [0.74, 5.53]	1.06 [0.60, 1.86]	0.55 [0.21, 1.41]
27–28			Reference		
Small for gestational age					
<10 th percentile	1.36 [1.03, 1.79]	1.36 [1.01, 1.84]	2.95 [1.37, 6.32]	0.68 [0.28, 1.67]	1.44 [0.51, 4.08]
10 th percentile			Reference		
Sex					
Male	1.10 [0.94, 1.28]	1.10 [0.93, 1.29]	1.47 [0.83, 2.60]	0.94 [0.64, 1.38]	1.81 [0.97, 3.39]
Female			Reference		
Race					
White	1.28 [1.07, 1.54]	1.29 [1.07, 1.56]	1.39 [0.75, 2.56]	1.15 [0.75, 1.75]	0.93 [0.47, 1.85]
Black			Reference		
Multiracial	1.11 [0.78, 1.57]	1.12 [0.78, 1.61]	0.49 [0.06, 3.77]	0.89 [0.35, 2.29]	2.24 [0.79, 6.36]
Other ⁺	1.25 [0.82, 1.92]	1.27 [0.81, 1.99]	1.18 [0.27, 5.16]	0.77 [0.24, 2.50]	2.32 [0.76, 7.08]
Ethnicity					
Hispanic/Latino	0.81 [0.36, 1.81]	0.82 [0.37, 1.84]	*	2.42 [0.75, 7.74]	*
Non-Hispanic/Latino	Reference	Reference	*	Reference	*
Birth Year					
2009–2012	0.81 [0.63, 1.06]	0.80 [0.61, 1.05]	1.60 [0.67, 3.86]	0.57 [0.30, 1.07]	1.43 [0.52, 3.94]
2013–2015	0.98 [0.79, 1.22]	0.99 [0.79, 1.24]	0.82 [0.37, 1.80]	0.72 [0.44, 1.16]	1.23 [0.50, 3.01]
2016–2017			Reference		

Data are shown as adjusted relative risk (95% confidence interval).

P-value <0.05 cutoffs are in bold.

^I among those that survived to 36-weeks PMA.

* omitted due to insufficient data.