Indomethacin Prophylaxis in Preterm Infants: Changes over Time

Samantha F. Curtis, MD[1] C. Michael Cotten, MD MHS[1] Matthew Laughon, MD, MPH[2] Noelle Younge, MD MHS[1] Jennifer Peterson, MD[1] Reese H. Clark, MD[3] Rachel G. Greenberg, MD, MB MHS[1,4]

[1] Department of Pediatrics, Duke University School of Medicine, Durham, North Carolina
[2] Department of Pediatrics, The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, North Carolina
[3] MEDNAX, Inc., Sunrise, Florida
[4] Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina

Address for correspondence Rachel G. Greenberg, MD, MB, MHS, 300 West Morgan Street, Durham, NC 27705 (e-mail: rachel.greenberg@duke.edu).

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Abstract

Objective Our objective was to examine changes in the use of indomethacin prophylaxis in the neonatal intensive care unit (NICU) between 2008 and 2018.

Study Design The design of the study included cohort of 19,715 infants born between $22^{0/7}$ and $26^{6/7}$ weeks' gestation from 213 NICUs. A nonparametric trend test evaluated indomethacin prophylaxis and the percentage of sites using any prophylaxis over time. We evaluated the prevalence of indomethacin prophylaxis by the center and the correlation between indomethacin prophylaxis and severe intraventricular hemorrhage prevalence among 12 centers with the largest relative change in indomethacin prophylaxis prevalence.

Results In total, 16% of infants received indomethacin prophylaxis. The use of indomethacin prophylaxis did not significantly decrease between 2008 and 2018 but it significantly decreased between 2014 and 2018 ($p = 0.046$). Among 74 centers with $\geq$10 infants included, 20% increased the use of indomethacin prophylaxis, while 57% decreased the use over the study period. Of the 12 centers with the largest relative change in indomethacin prophylaxis prevalence, 50% showed an inverse correlation between indomethacin prophylaxis prevalence and severe intraventricular hemorrhage, while 50% showed a positive correlation.

Conclusion Receipt of indomethacin prophylaxis remained similar until 2014, decreased from 2014 to 2018, and varied by the center.

Keywords
- indomethacin
- neonates
- intraventricular hemorrhage
- prophylaxis

Key Points

- The receipt of indomethacin prophylaxis decreased over time.
- Center change in the use of indomethacin prophylaxis does not correlate with the center prevalence of IVH.
- Variability in the use of indomethacin prophylaxis across centers persists.

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Severe intraventricular hemorrhage (IVH) occurs in 18% of extremely preterm infants less than 28 weeks gestation, a group that is at high risk for neurodevelopmental impairment.[1] IVH places stress on the brain by causing primary brain injury, due to its immediate mass effect and secondary brain injury due at least in part to its inflammatory cell infiltrates.[2] The combination of primary and secondary injury increases the risk for posthemorrhagic hydrocephalus, cerebral palsy, and developmental impairment.[3]

A prostaglandin H2 inhibitor, indomethacin, inhibits cerebral prostacyclin synthesis in the brain leading to vasoconstriction, which decreases cerebral blood flow and decreases the risk of germinal matrix hemorrhage.[4–12] However, indomethacin's short-term vasoconstrictive effects also decrease gastrointestinal and renal blood perfusion, leading to decreased glomerular filtration rates, decreased urine output, and electrolyte disturbances.[13–15] Results of multicenter, double-blind randomized clinical trials completed over two decades ago demonstrate a reduction in risk of IVH with prophylactic indomethacin, but with no clear-cut benefits in longer term neurodevelopmental outcomes.[5,16]

Subsequent cohort studies indicate that clinicians at many centers have continued to use prophylactic indomethacin for extremely preterm infants.[17–19] The use of prophylactic indomethacin in extremely preterm infants is highly variable due to its potential benefits and risks.[4–19] To better understand evolving utilization of prophylactic indomethacin, our study objective was to examine changes in indomethacin prophylaxis over time and across centers in U.S. neonatal intensive care units (NICUs) in extremely preterm infants between 2008 and 2018.

Materials and Methods

Study Population

This study was approved by the Institutional Review Board with a waiver of consent. We identified infants who died during hospitalization or were discharged from Pediatrix Medical Group NICUs from 2008 to 2018. We chose this study period because there has not been recent literature examining the trend of prophylactic indomethacin exposure in extremely premature infants since 2010, and resuscitation and active treatment of infants with gestational age ≤23 weeks are increasing.[14,20,21] We included only inborn infants $22^{0/7}$ and $26^{6/7}$ weeks' gestation. We excluded infants with major congenital anomalies, infants who died on postnatal day 0 or 1 due to the inability to track secondary outcomes, and infants transferred to another hospital prior to discharge (►Fig. 1).

Data and Variables

The Pediatrix Medical Group Clinical Data Warehouse prospectively captures clinical information into an electronic health record by clinicians at 213 NICUs in the United States. Clinicians in these NICUs generate infant data daily including admission history and physicals, daily progress notes, and discharge summaries with administered medications, limited dosing information, and diagnoses available. From the daily notes, data are extracted and consolidated into the Pediatrix BabySteps Clinical Data Warehouse.[22] We had a total of 74 of the total 213 with greater than 10 infants in each year category included in the overall analysis.

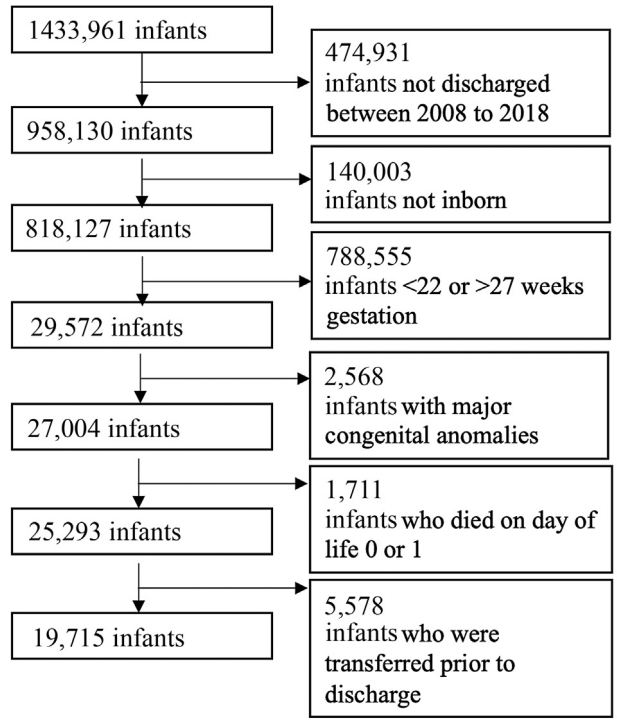

Fig. 1 Study population included in the study analysis.

Definitions

Prophylactic indomethacin was defined as any exposure to a dose of indomethacin in the first 2 postnatal days (postnatal day 0 or 1). Severe IVH was defined as grade III and grade IV.[23] Mild IVH was defined as grade I and grade II.[24] Hemodynamically significant patent ductus arteriosus (hsPDA) was defined as PDAs that received the medical intervention (indomethacin or ibuprofen, except for prophylactic use) or surgical intervention (PDA ligation or catheter closure).[25] The day of diagnosis of a hsPDA was the first day of either medical or surgical intervention. Surgical intervention for PDA was defined as either surgical occlusion or ligation. Bronchopulmonary dysplasia (BPD) was defined as infants <32 weeks' gestation who received supplemental oxygen or respiratory support (nasal cannula, continuous positive airway pressure or mechanical ventilation) continuously from a corrected gestational age of 36 to 37 weeks' gestation. Infants in room air without any respiratory support or those who only required oxygen transiently were classified as not having BPD.[26] The outcome of BPD was left as missing if the infant was discharged prior to the test period while receiving supplemental oxygen or respiratory support.[26] Spontaneous intestinal perforation (SIP) was defined as intestinal perforation within the first 28 days of age without the diagnosis of necrotizing enterocolitis (NEC). We defined antenatal steroid use as a mother who received at least one dose of betamethasone or dexamethasone prior to

delivery.[27] We defined small for gestational age (SGA) as birth weight <10th percentile for age.[28]

Statistical Analysis

We divided infants into two groups: those who received indomethacin prophylaxis and those who did not receive indomethacin prophylaxis. For each group, we summarized demographics and clinical characteristics of interest including gestational age, birth weight, sex assigned at birth, race/ethnicity, prenatal steroid exposure, and indomethacin administration year. Categorical variables were reported as counts with percentages and continuous variables as medians with 25th and 75th percentiles. Variables evaluated by categories included gestational age (22, 23, 24, 25, and 26 weeks), birth weight (<500, 500–749, 750–1,000, and >1,000 g), race/ethnicity (White, Black, Hispanic, other), and administration year (2008–2010, 2011–2013, 2014–2016, 2017–2018). Only centers that had greater than 10 infants in each year category were included in the analysis.

We investigated the association between indomethacin exposure and secondary variables of interest (antenatal steroid use, mild IVH, BPD, NEC, hsPDA, PDA receiving surgical intervention, SIP, severe retinopathy of prematurity [ROP], duration of stay, and death during hospitalization) and stratified results by gestational age. We used a nonparametric trend test to evaluate the change in indomethacin prophylaxis over time and the percentage of sites using any indomethacin prophylaxis between 2008 and 2018, and 2014 and 2018. We then compared infant demographics and the prevalence of grade-III and -IV IVH in infants who did and did not receive indomethacin prophylaxis using Chi-square tests and stratified our analysis by gestational age.

Among centers with ≥10 included infants from 2008 to 2018, we identified the 12 centers with the greatest absolute change in indomethacin prophylaxis between the earliest and most recent year categories. We did this to study centers with the greatest change in indomethacin use and to determine if all centers with the greatest change had similar changes in indomethacin prophylaxis over time. We evaluated trends over these time periods in indomethacin prophylaxis, incidence of grade-III and -IV IVH, and mean gestational age. A p-values of <0.05 was considered statistically significant. Analyses were conducted using Stata version 16.1 (College Station, TX).

Results

Patients and Characteristics

During the study period, 19,715 infants from 213 centers met the inclusion criteria. The median (25th and 75th percentile) gestational age and birth weight were 25 weeks (24, 26) and 726 g (610, 850), respectively. Of these, 3,246 (16%) from 117 centers received indomethacin prophylaxis (►Table 1). Most infants who received indomethacin prophylaxis were male (53%) and white (46%); the median gestational age was 25 weeks (24, 26) and the median birth weight was 700 g (598, 820). Most infants who did not receive indomethacin prophylaxis were male (51%) and white (38%); the median gestational age was 25 weeks (24, 26) and the median birth weight was 730 g (613, 850). Prevalence of prophylaxis was highest for 22 weeks' infants (19%) and lowest for 26 weeks' infants (14%).

Table 1 Characteristics of study populations

Demographic characteristic	Indomethacin prophylaxis ($n = 3,246$)	No indomethacin prophylaxis ($n = 16,469$)	p-Value
Gestational age (wk)			<0.001
• 22	49 (2)	215 (1)	
• 23	424 (13)	1,911 (12)	
• 24	827 (25)	3,800 (23)	
• 25	989 (30)	4,632 (28)	
• 26	957 (29)	5,911 (36)	
Birth weight (g)			<0.001
• < 500	259 (8)	1,164 (7)	
• 500–749	1,686 (52)	7,661 (47)	
• 750–999	1,179 (36)	6,519 (40)	
• 1,000+	122 (4)	1,125 (7)	
Male	1,724 (53)	8,451 (51)	0.06
Race/ethnicity			<0.001
• White	1,447 (46)	6,069 (38)	
• Black	1,142 (36)	5,315 (34)	
• Hispanic	425 (13)	3,371 (21)	
• Other	149 (5)	1,073 (7)	
Prenatal steroid exposure	2,716 (84)	14,058 (85)	0.01
Administration year			<0.001
• 2008–2010	968 (30)	4,496 (27)	
• 2011–2013	875 (27)	4,470 (27)	
• 2014–2016	994 (31)	4,385 (27)	
• 2017–2018	409 (13)	3,118 (19)	

Secondary Variables of Interest

There was no significant difference in BPD, NEC (medical or surgical), or death during hospitalization between the groups (►Table 2). Indomethacin-exposed infants were more likely to have hsPDA ($p \leq 0.005$ for all gestational ages). Surgical intervention for hsPDAs was significantly more common in infants who did not receive indomethacin compared to infants who received indomethacin (14 vs. 11%, $p < 0.001$). There was a significantly lower percentage of mild IVH and severe IVH in infants who received indomethacin prophylaxis compared to those who were not exposed to indomethacin prophylaxis at 26 weeks' gestation (19 vs. 23%, respectively, $p = 0.03$; 7 vs. 9%, respectively, $p = 0.009$), respectively. Infants who received indomethacin prophylaxis had a significantly lower percentage of severe ROP compared to infants who were unexposed to indomethacin overall ($p = 0.01$), but when stratified by gestational age, no significant difference was found. Infants who received indomethacin prophylaxis were slightly less likely to receive antenatal corticosteroids compared to infants who did not receive indomethacin prophylaxis overall ($p = 0.01$). When stratified by gestational age, this difference only remained significant in infants at 26 weeks' gestation ($p = 0.02$). In our cohort, 36%

Table 2 Secondary variables of interest in infants exposed and unexposed to indomethacin prophylaxis

	Indomethacin prophylaxis ($n = 3,246$)	No indomethacin prophylaxis ($n = 16,469$)	*p*-Value
Antenatal steroid exposure (wk)	2,716 (84)	14,058 (85)	0.01
• 22	24 (49)	121 (56)	0.35
• 23	322 (76)	1,416 (74)	0.43
• 24	700 (85)	3,289 (87)	0.15
• 25	851 (86)	4,020 (87)	0.53
• 26	819 (86)	5,212 (88)	0.02
Mild IVH (wk)	779 (24)	4,310 (26)	0.01
• 22	9 (18)	56 (26)	0.26
• 23	104 (25)	548 (29)	0.09
• 24	219 (26)	1,100 (29)	0.16
• 25	261 (26)	1,267 (27)	0.54
• 26	186 (19)	1,339 (23)	0.03
Severe IVH (wk)	534 (16)	2 561 (16)	0.20
• 22	23 (47)	74 (34)	0.10
• 23	149 (35)	596 (31)	0.11
• 24	163 (20)	752 (20)	0.96
• 25	136 (14)	597 (13)	0.47
• 26	63 (7)	542 (9)	0.009
BPD (wk)	1,661 (72)	8,395 (70)	0.23
• 22	18 (90)	61 (87)	0.73
• 23	175 (83)	866 (88)	0.05
• 24	448 (81)	2,099 (81)	0.80
• 25	550 (72)	2,575 (72)	0.79
• 26	470 (62)	2,794 (59)	0.26
NEC (medical or surgical; wk)	290 (9)	1,351 (8)	0.17
• 22	3 (6)	14 (7)	0.92
• 23	44 (10)	181 (9)	0.57
• 24	79 (10)	345 (9)	0.67
• 25	95 (10)	387 (8)	0.20
• 26	69 (7)	424 (7)	0.97
SIP (wk)	191 (6)	618 (4)	<0.001
• 22	4 (8)	25 (12)	0.48
• 23	41 (10)	146 (8)	0.16
• 24	78 (9)	207 (5)	<0.001
• 25	49 (5)	143 (3)	0.003
• 26	19 (2)	97 (2)	0.44
Severe ROP	293 (9)	1,269 (8)	0.01
• 22	9 (18)	21 (10)	0.09
• 23	40 (9)	234 (12)	0.10
• 24	115 (14)	449 (12)	0.10
• 25	90 (9)	356 (8)	0.14
• 26	39 (4)	209 (4)	0.41
HsPDA (wk)	1 690 (52)	5 462 (33)	<0.001
• 22	22 (45)	53 (25)	0.005
• 23	215 (51)	694 (36)	<0.001
• 24	486 (59)	1,518 (40)	<0.001
• 25	528 (53)	1,637 (35)	<0.001
• 26	439 (46)	1,560 (26)	<0.001
PDAsurg (wk)	344 (11)	2,278 (14)	<0.001
• 22	6 (12)	27 (13)	0.95
• 23	53 (13)	385 (20)	<0.001
• 24	114 (14)	724 (19)	<0.001
• 25	107 (11)	665 (14)	0.003
• 26	64 (7)	477 (8)	0.14
Death during hospitalization (wk)	738 (23)	3,534 (21)	0.11
• 22	28 (57)	140 (65)	0.30
• 23	208 (49)	920 (48)	0.73
• 24	258 (31)	1,134 (30)	0.44
• 25	149 (15)	774 (17)	0.21
• 26	95 (10)	566 (10)	0.73

Abbreviations: BPH, bronchopulmonary dysplasia; HsPDA, hemodynamically significant PDA; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDAsurg, patent ductus arteriosus requiring surgical intervention; SIP, spontaneous intestinal perforation; ROP, retinopathy of prematurity.
Note: Data presented as count (%).

of SGA infants died, and 19% of non-SGA infants died. There were no significant differences between indomethacin prophylaxis use and death within SGA and non-SGA infants overall or when stratified by gestational age (data not shown).

Prevalence of Indomethacin Prophylaxis over Time and across Centers

The highest prevalence of indomethacin prophylaxis occurred between 2014 and 2016 (18%), while the lowest prevalence occurred between 2017 and 2018 (12%). Overall, there was no significant change in indomethacin prophylaxis between 2008 and 2018 ($p = 0.23$; ►Fig. 2). From 2014 to 2018, indomethacin prophylaxis significantly decreased ($p = 0.046$). The percentage of centers using indomethacin prophylaxis was 39% in 2008 and 20% in 2018, representing a significant decrease over this time period ($p = 0.005$).

Of the 74 centers with infants exposed to indomethacin from 2008 to 2018, 15 (20%) increased use, 42 (57%) decreased use, and 17 (23%) had no change. Overall, there was

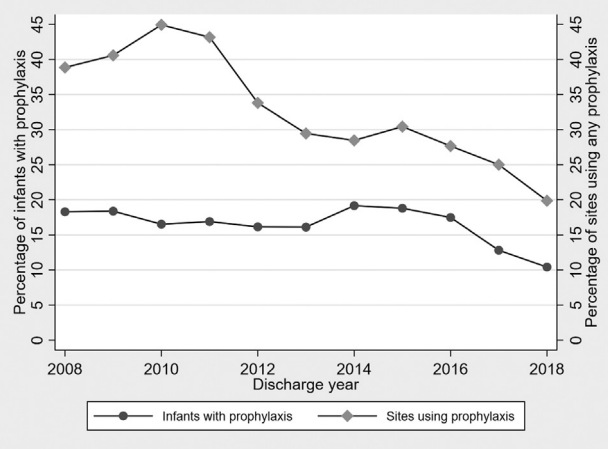

Fig. 2 Indomethacin exposure on postnatal day 0 or 1 in infants <27 weeks' gestation and percentage of sites using indomethacin prophylaxis from 2008 to 2018.

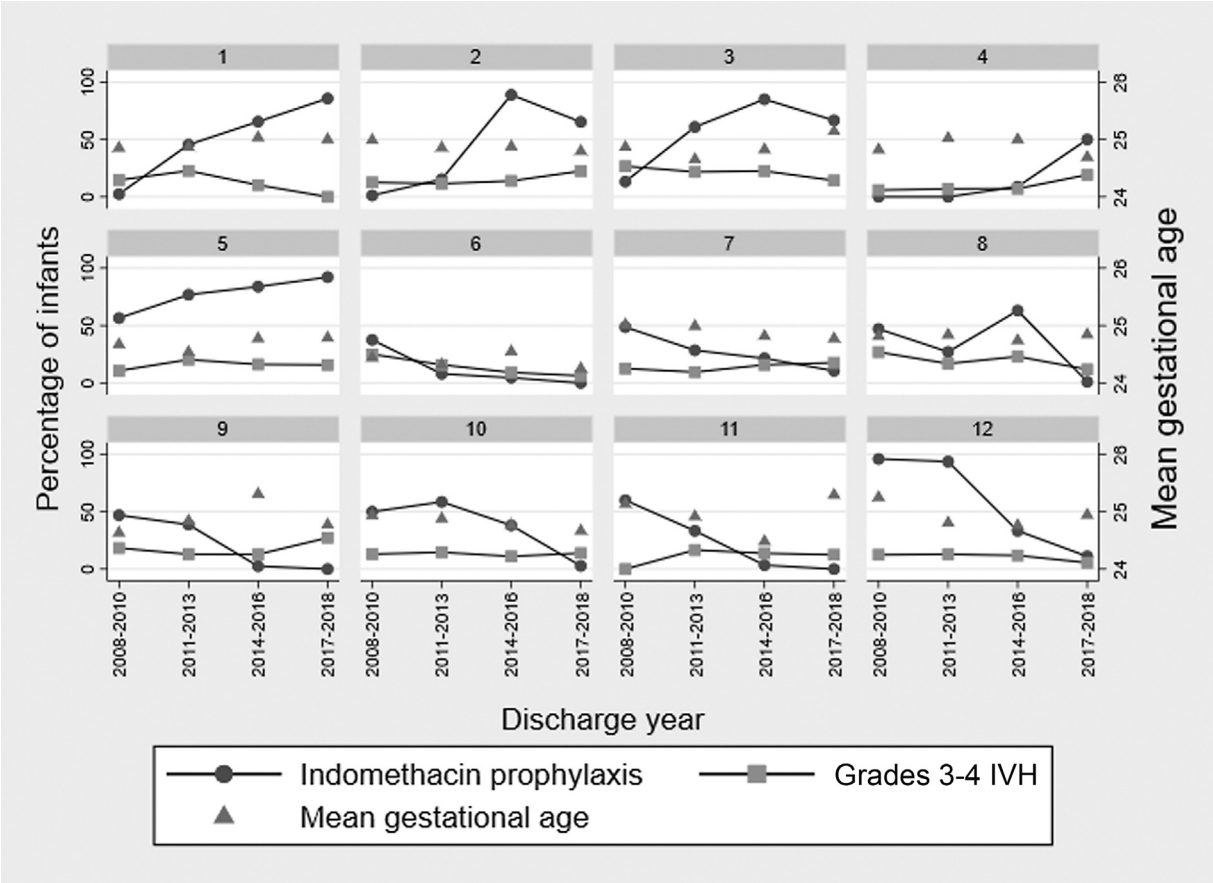

Fig. 3 Indomethacin prophylaxis prevalence, grades III and IV IVH and mean gestational age in 12 different NICUs stratified by discharge year. 50% of the centers (1–6) show an inverse correlation between indomethacin and grade III and IV IVH and 50% of centers (7–12) show a positive correlation between indomethacin and grade III and IV IVH. Centers orders by decreasing change in indomethacin prophylaxis. IVH, interventricular hemorrhage; NICU, neonatal intensive care unit.

no universal trend in indomethacin prophylaxis over time. Among the 12 centers with the greatest absolute change in prevalence of indomethacin prophylaxis, 5 (42%) increased use and 7 (58.3%) decreased use (►**Fig. 3**; ►**Supplementary Table S1** [available in the online version]). Among these 12 centers, 50% showed an inverse relationship between indomethacin prophylaxis prevalence and IVH, while 50% showed a positive relationship. Mean gestational age did not appear to be associated with whether centers administered indomethacin prophylaxis.

Discussion

Our study revealed that indomethacin prophylaxis decreased, although not significantly, from 2008 to 2018, but decreased significantly between 2014 and 2018. The decrease in indomethacin prophylaxis correlated with the decrease in the percentage of sites using any prophylaxis from 2014 to 2018. Furthermore, indomethacin prophylaxis among centers is highly variable and the trend in prevalence over time from our data set did not correlate with recommendations from the published literature. However, we do not know the specific reasons for the decline in indomethacin prophylaxis as these are likely center specific.

In 2008, indomethacin prophylaxis was not used routinely in our overall cohort; however, 39% of centers had highly prevalent use. In 2007, a multicenter registry from the Eunice Kennedy Shriver National Institute of Child Health and Development's Neonatal Research Network was used to determine the association between the use of indomethacin prophylaxis and the publication of the first large randomized control trial published in 1994 and the TIPP trial in 2001.[6] Prophylactic indomethacin significantly increased after the publication of the former trial (odds ratio [OR]: 50, 95% confidence interval [CI]: 38–63, $p < 0.0001$) and then significantly decreased after the publication of the later trial (OR: 0.84; 95% CI: 0.73–0.97, $p < 0.015$).[6]

In 2008, a retrospective cohort study examined neurodevelopmental outcomes of premature infants after indomethacin prophylaxis.[23] This study did not find an association between exposure to indomethacin within 48 hours of birth and poor neurodevelopmental outcomes (OR: 0.2, 95% CI: 0.03,1.02). The average gestational age was 26.2 weeks, which was similar to our median gestational age of 25 weeks (24, 26) and 64% received indomethacin exposure within the first 3 postnatal days. This study supported a positive correlation between indomethacin-exposed infants and improved mental developmental index in infants <29

weeks' gestation ($p < 0.01$).[23] Despite these results, our data showed little change in indomethacin prophylaxis prevalence following this publication between 2008 and 2013 even though the percentage of sites using indomethacin prophylaxis declined significantly.

From 2008 to 2014, certain studies both supported and discouraged indomethacin prophylaxis. A large meta-analysis of 19 randomized or quasi-randomized controlled trials (including 2,872 infants) examined prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants.[20] It was found that indomethacin prophylaxis within the first postnatal day significantly reduced the risk of developing PDAs (relative risk [RR]: 0.44, 95% CI: 0.38, 0.50) and IVH (RR: 0.66, 95% CI: 0.53, 0.82) but showed no evidence of mortality (RR: 0.96, 95% CI: 0.81, 1.12) or neurodevelopmental benefits (RR 1.02, 95% CI: 0.90, 1.15) at 18 to 26 months.[20] We hypothesize that these results, led to the minimal change in prevalence from 2008 to 2013, and possibly influenced the larger shift toward the lower prevalence of use in the 2014 to 2018 period.

Interestingly, indomethacin prophylaxis and percentage of sites using any prophylaxis declined between 2014 and 2018 without further strong signals of benefits or risks from prophylactic indomethacin in the accumulating literature. During this time period, data from randomized control trials and cohort studies reexamined the short-term impact of indomethacin prophylaxis which supported earlier findings of the first large, randomized control trial.[7,11,13,29] In 2014, a literature review studied different interventions for closing PDAs and found that indomethacin prophylaxis decreased the rate of surgical ligations of PDAs and pulmonary hemorrhage events with little adverse effects.[6] This result was then followed by a prospective structured survey in three tertiary perinatal centers in Saudi Arabia, which found that after discussion with high-risk pregnant women at 23 to 28 weeks' gestation, 82% wanted their infants to have indomethacin prophylaxis versus delaying treatment interventions.[13] Indomethacin use in very low birth weight infants (VLBW) was then supported by a prospective study which showed that prophylactic indomethacin was associated with a lower risk-adjusted incidence of severe IVH.[30] There were no new studies or articles suggesting alternative neuroprotective strategies or guidelines following 2014 to explain the sharp decline in the use of indomethacin prophylaxis at that time.

Our data demonstrate that indomethacin prophylaxis varied substantially among centers. Our results were similar to survey results of NSAID (nonsteroidal anti-inflammatory drug) administration and PDA ligations in U.S. Children's Hospitals.[31] This survey revealed intrainstitutional practice variations in NSAIDs for the treatment of PDAs among large medical centers, with only 28% of centers administering indomethacin prophylaxis from 2006 to 2014.[31] This survey found that indomethacin's side effects including nephrotoxicity, acute renal failure, decreased cerebral, and intestinal blood flow deterred many centers from administering this medication.

Our data suggest that hsPDA was significantly more common in infants who received indomethacin prophylaxis compared to infants who did not receive indomethacin prophylaxis across all age groups. These findings are in contrast to previous reports. A retrospective cohort study of extremely low birth weight infants suggested an association between infants who received indomethacin prophylaxis at any age and lower need for PDA ligation.[11] Furthermore, a retrospective cohort study of infants at a gestational age <29 weeks and birth weight <1,000 g found that the odds of developing PDAs are lower in those who received indomethacin prophylaxis compared to those who did not receive indomethacin prophylaxis (OR: 0.83, 95% CI: 0.71 to 0.98).[8] The known physiologic effect of indomethacin as a prostaglandin-H2 inhibitor does not support the higher percentage of infants in the indomethacin-exposed group with hsPDA. We hypothesize that centers that are more likely to use indomethacin for prophylaxis are also more likely to treat PDA with medication. Since our definition of hsPDA relied on treatment, this limits the interpretation of the finding that infants treated with indomethacin were more likely to have hsPDA.

Additionally, our data suggest that surgical intervention (ligation or occlusion) was significantly more common in infants who did not receive indomethacin compared to infants who received indomethacin. This supports our previous hypothesis that centers that are more likely to use indomethacin for prophylaxis are also more likely to treat PDA with medication over surgical intervention. A retrospective cohort study showed PDAs were less common in infants who were treated with indomethacin after the first day of life, compared to infants who were not treated with indomethacin (21 vs. 36.1%, $p < 0.001$).[8] Similarly, in a large retrospective study, pharmacological closure (with either indomethacin or ibuprofen) was the method of choice prior to surgical ligation.[32] This suggests that infants who received indomethacin may have experienced pharmacologic benefits for hsPDA, with a correspondingly lower rate of surgical intervention.

There was no significant difference in BPD prevalence between infants who were exposed to indomethacin prophylaxis and infants who were not exposed to indomethacin prophylaxis, a finding which is consistent with previous studies.[15] Additionally, we found that severe ROP was significantly lower in infants who received indomethacin prophylaxis compared to infants who did not receive indomethacin prophylaxis, which is consistent with the findings of a retrospective case-control analysis of 47 neonates.[33] Continued monitoring of the use of prophylactic indomethacin is warranted given recent recommendations from ACOG regarding the dosing of antenatal steroids for infants <24 weeks' gestation.[18,19,34,35] Retrospective cohort studies of interactions between antenatal steroid dosing and use of postnatal indomethacin in the first postnatal days show a perplexing mix of risk and benefit which warrants ongoing study.[18,19] In our cohort, a significantly higher percentage of infants received antenatal corticosteroids in the indomethacin prophylaxis group compared to the group who did not receive indomethacin prophylaxis overall and at 26 weeks' gestation.

Fifty percent of centers with the greatest change in indomethacin prophylaxis had an inverse correlation between indomethacin prophylaxis prevalence and IVH. A recent study in 2017, reported the reappearance of indomethacin prophylaxis in the clinical setting due to indomethacin's efficacy in lowering the incidence of IVH, symptomatic PDAs, and surgical ligation of PDAs and BPD.[9] Some centers may choose to not use prophylactic treatment based on research supporting the lack of improvement in long-term neurodevelopmental outcomes.

Recent studies have addressed other methods to decrease IVH in preterm infants. A recent multicenter cohort study examined the impact of neonatal care bundles, which consisted of maintaining the head midline, tilting the head of the incubator, and avoiding flushing/rapid withdrawal of blood and sudden elevation of legs.[36] They found that bundling nursing interventions was associated with a reduced risk of developing new or progressive severe IVH, cystic periventricular leukomalacia, and mortality (OR: 0.42, 95% CI: 0.27 to 0.65).[36] An additional retrospective cohort study found that the number of intubation attempts was significantly greater in infants with a birth weight <750 g who had severe IVH compared with those with mild or no IVH (OR: 1.395, $p = 0.008$) and suggested that minimizing the number of intubation attempts may reduce severe IVH.[37] Interventions such as care bundles and minimizing the number of intubation attempts may thus represent alternative, low-risk strategies to reduce IVH.

SIP is another morbidity that has been associated with indomethacin use in previous studies.[18,19] In our study, there was a significant difference in SIP between infants who were exposed to indomethacin and infants who were not exposed to indomethacin ($p < 0.001$). This result is consistent with two recent articles published by the Canadian Neonatal Network which evaluated the prevalence of SIP and indomethacin prophylaxis.[18,19] The first, a multicenter, retrospective cohort study suggested that infants ≥25 weeks' gestation who received indomethacin did not have neurological benefit and experienced an increased risk of SIP.[19] The second, a retrospective cohort study, found that infants who received prophylactic indomethacin and antenatal corticosteroids within 7 days of birth had an increased risk for SIP compared to infants who received antenatal corticosteroids >7 days prior to birth. In our study population, infants at 24 to 25 weeks' gestation and who received indomethacin were significantly more likely to have SIP than infants who did not receive indomethacin, which is consistent with previous research.

Finally, previous studies have suggested that infants who are considered SGA have an increased risk of death compared to infants who are normal or large for gestational age. A retrospective cohort study subgroup analysis that evaluated the association between indomethacin prophylaxis and death found that infants with birth weights ≥10th percentile who received prophylactic indomethacin had a lower odds of death compared to infants in that group who did not receive indomethacin ($p = 0.007$).[8] This apparently protective effect from the retrospective cohort study was not observed in this cohort of infants with birth weight <10th percentile. In our study, there were no significant associations between indomethacin exposure and death in subgroups of SGA and non-SGA infants.

Strengths and Limitations

Our study was strengthened by the use of data from a large sample size of infants across many NICUs across the United States. There are limitations to this study. First, we did not include infants who were not inborn because outborn infants could have received indomethacin prophylaxis prior to transfer. Because we focused on extremely preterm neonates due to evidence for benefit in this age group, we excluded infants born at later gestational ages who received indomethacin prophylaxis and cannot make conclusions on this group. While we reported the prevalence of IVH in addition to indomethacin prophylaxis at 12 centers with the greatest change in indomethacin prophylaxis prevalence, there are other unmeasured factors that could have affected the prevalence of IVH. For this reason, and the fact that randomized controlled trial data are available to show the association between indomethacin prophylaxis and prevalence of IVH, we elected not to perform an adjusted analysis of our data. Additionally, we defined the presence of PDA by medical or surgical treatment, since we lacked quantitative data from echocardiograms; some PDAs that were medically or surgically treated may not have been hemodynamically significant, while some significant PDAs may not have been treated. In addition, our definition of indomethacin prophylaxis is imperfect since our database did not contain indications for administration. Some infants may have been treated on day 0 or day 1 for PDA rather than prophylaxis. We did not include acetaminophen in our definition of treatment because we could not differentiate between use for PDA treatment and use for pain. The dose of indomethacin was also unknown, so we were not able to determine whether the dosing followed recommended guidelines.[10] Finally, we did not have access to indomethacin prophylaxis guidelines at each center or other changes in practice that could affect IVH.

Conclusion

In conclusion, indomethacin prophylaxis in our cohort decreased from 2008 to 2018, but not significantly over time, and varied substantially by the center. Centers with large changes in the prevalence of indomethacin prophylaxis were equally likely to have an increase or decrease in IVH prevalence. Future studies should evaluate factors associated with changes in practice at different centers, and whether such changes are associated with infant outcomes.

Authors' Contributions

S.F.C. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. S.F.C. contributed to the conception and design of the study, the data interpretation, the

manuscript drafting, and the critical revision of the manuscript.

C.M.C. contributed to the data interpretation, the manuscript drafting, and the critical revision of the manuscript.

M.L. contributed to the data interpretation, the manuscript drafting, and the critical revision of the manuscript.

N.Y. contributed to the data interpretation, the manuscript drafting, and the critical revision of the manuscript.

J.P. contributed to the data interpretation, the manuscript drafting, and the critical revision of the manuscript.

R.H.C. contributed to the data interpretation, the manuscript drafting, and the critical revision of the manuscript.

R.G.G. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. R.G.G. contributed to the conception and design of the study, the data interpretation, the manuscript drafting, and the critical revision of the manuscript.

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Conflict of Interest

R.G.G. reports consulting services for Tellus Therapeutics. The other authors have no conflicts of interest to disclose.

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