Prophylactic Indomethacin and Intestinal Perforation in Extremely Low Birth Weight Infants

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KEY WORDS

indomethacin, intestinal perforation, necrotizing enterocolitis, neonate

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WHAT'S KNOWN ON THIS SUBJECT: Prophylactic indomethacin in extremely low birth weight infants decreases severe intraventricular hemorrhage and patent ductus arteriosus but it is unknown whether concurrent enteral feeding and prophylactic indomethacin is associated with increased risk of spontaneous intestinal perforation.

WHAT THIS STUDY ADDS: The combination of prophylactic indomethacin and enteral feeding during the first 3 days after birth does not increase the risk of spontaneous intestinal perforation.

abstract

OBJECTIVE: Prophylactic indomethacin reduces severe intraventricular hemorrhage but may increase spontaneous intestinal perforation (SIP) in extremely low birth weight (ELBW) infants. Early feedings improve nutritional outcomes but may increase the risk of SIP. Despite their benefits, use of these therapies varies largely by physician preferences in part because of the concern for SIP.

METHODS: This was a cohort study of 15 751 ELBW infants in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network from 1999 to 2010 who survived beyond 12 hours after birth. The risk of SIP was compared between groups of infants with and without exposure to prophylactic indomethacin and early feeding in unadjusted analyses and in analyses adjusted for center and for risks of SIP.

RESULTS: Among infants exposed to prophylactic indomethacin, the risk of SIP did not differ between the indomethacin/early-feeding group compared with the indomethacin/no-early-feeding group (adjusted relative risk [RR] 0.74, 95% confidence interval [CI] 0.49–1.11). The risk of SIP was lower in the indomethacin/early-feeding group compared with the no indomethacin/no-early-feeding group (adjusted RR 0.58, 95% CI 0.37–0.90, $P = .0159$). Among infants not exposed to indomethacin, early feeding was associated with a lower risk of SIP compared with the no early feeding group (adjusted RR 0.53, 95% CI 0.36–0.777, $P = .0011$).

CONCLUSIONS: The combined or individual use of prophylactic indomethacin and early feeding was not associated with an increased risk of SIP in ELBW infants. *Pediatrics* 2014;134:e1369–e1377

Prophylactic indomethacin during the first 3 days after birth in extremely low birth weight (ELBW) infants (birth weight ≤ 1000 g) decreases the incidence of severe intraventricular hemorrhage and patent ductus arteriosus (PDA).^{1,2,3} However, administration of indomethacin soon after birth in preterm infants may be associated with an increased risk for spontaneous intestinal perforation (SIP)^{4–8} or necrotizing enterocolitis (NEC) with intestinal perforation.¹⁰ The incidence of SIP in ELBW infants is 6%.^{2,9} A large case-control study that compared 633 infants with SIP with 581 control infants matched by gestational age, birth weight, and gender showed that exposure to indomethacin during the first 3 days after birth was associated with a higher risk for SIP compared with control infants (odds ratio [OR] 1.86, 95% confidence interval [CI] 1.4–2.5, $P < .0001$).⁵ A retrospective study of ELBW infants in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN) showed that indomethacin treatment of a PDA but not the prophylactic use of indomethacin was associated with a higher risk for SIP (adjusted OR 1.61, 95% CI 1.25–2.08, $P < .05$).⁷ However, 3 randomized controlled trials^{2,3,11} and a retrospective cohort study of premature infants treated with indomethacin¹² showed that neither SIP nor NEC was associated with the indomethacin exposure.

Although the presence of enteral nutrition has been studied as a risk factor for development of NEC,^{13,14} studies have not shown an association between enteral nutrition and SIP.^{15–17} A case-control study⁸ and a randomized controlled trial¹¹ have shown that enteral feeding concurrent with treatment of a PDA with indomethacin results in fewer days to reach full enteral feeds without evidence of increased feeding intolerance or increased SIP or necrotizing enterocolitis. The question of whether ELBW infants who receive prophylactic indomethacin should concurrently

receive enteral nutrition or have their feeds withheld temporarily because of the risk of SIP remains unanswered. In the absence of a randomized controlled trial to test the safety and efficacy of prophylactic indomethacin treatment concurrent with enteral feedings and to determine if a trial is feasible, we undertook this retrospective study. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development NRN Generic Database (GDB; NCT00063063)¹⁸ provides prospective longitudinal data pertaining to both indomethacin treatment within the first 24 hours after birth for any indication and the occurrence and timing of SIP. The primary hypothesis was that in ELBW infants, concomitant prophylactic intravenous indomethacin within the first 24 hours after birth, and any enteral feeding within the first 3 days after birth would be associated with a $\geq 20\%$ increased relative risk of SIP during the first 14 days after birth compared with those who received prophylactic indomethacin but no feeding within the first 3 days after birth.

METHODS

Study Design

This was a retrospective 2-by-2 factorial cohort study of 2 neonatal exposures: (1) prophylactic intravenous indomethacin initiated during the first 24 hours after birth and (2) early enteral nutrition defined as any feeding administered during the first 3 days after birth. Data pertaining to indomethacin treatment, feeding during the first 3 days after birth, and other demographic and perinatal variables were collected prospectively as previously described.¹⁹

Population and Exposures

The study population included 15 751 ELBW (birth weight 401–1000 g) infants who survived to at least 12 hours after birth within the member NICUs of the NRN during the study period 1999–2010. This study period was selected to represent a period when the practice of

prophylactic indomethacin was increasingly prevalent based on the results of 2 trials in ELBW infants during the 1990s.^{2,3} The primary exposures examined within the GDB cohort included prophylactic intravenous indomethacin during the first 24 hours after birth (yes/no, I+/I–) and any enteral nutrition during the first 3 days after birth (yes/no, E+/E–). The GDB includes data on the administration of indomethacin for any prophylaxis purposes within the first 24 hours after birth.¹⁸ Indomethacin for the purpose of closing a PDA (ie, treatment) is recorded separately within the database. There were 4 study cohorts based on prophylactic indomethacin and early enteral feeding status: (1) group I+E+, infants who received prophylactic indomethacin (I+) during the first 24 hours and any enteral feeding (E+) during the first 3 days after birth; (2) group I+E–, infants who received prophylactic indomethacin (I+) during the first 24 hours and did not receive enteral feeding (E–) during the first 3 days after birth; (3) group I–E+, infants who did not receive prophylactic indomethacin (I–) during the first 24 hours but received enteral feeding (E+) during the first 3 days after birth; and (4) group I–E–, infants who did not receive prophylactic indomethacin (I–) during the first 24 hours and did not receive enteral feeding (E–) during the first 3 days after birth. The I–E– group was the nonexposed referent group for comparisons unless otherwise specified to examine the interaction of feeding and indomethacin.

Outcome Measures

The primary outcome of this study was SIP without NEC occurring within the first 14 days after birth. SIP was defined as a clinical diagnosis of spontaneous gastrointestinal perforation without signs suggestive of NEC. The secondary outcomes included death before discharge, NEC with intestinal perforation during the first 14 days after birth, death or survival with severe neurodevelopmental impairment (NDI) at 18- to 22-month

follow-up, severe NDI in surviving infants at 18- to 22-month follow-up, indomethacin or ibuprofen treatment of PDA, and the need for surgical PDA treatment. NEC was defined according to the modified Bell staging criteria.²⁰ Secondary nutritional outcomes included number of days to reach full enteral feeds, days of parenteral nutrition, and days to regain birth weight. Additional secondary outcomes included proven NEC with or without surgical treatment occurring anytime beyond day 14 after birth and SIP without NEC occurring anytime beyond day 14 after birth. The study had missing outcome data for some infants. There were 13 infants with SIP for whom the specific date of documentation of SIP was missing. In addition, there were 61 infants for whom the cause of death between 12 hours and 14 days after birth was missing. These missing outcome data resulted in slight differences in population denominators for the clinical outcomes shown in Table 2.

Survivors were evaluated at 18 to 22 months' corrected age and received a comprehensive neurodevelopmental examination that included a neurologic examination and the administration of the Bayley Scales of Infant and Toddler Development, Second Edition (Bayley II) for children born from 1999 to 2005 and the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley III) for children born from 2006 to 2010. For infants born from 1999 to 2005, severe NDI at 18 to 22 months' corrected age was defined as having any of the following: Bayley II Mental Developmental Index <70 (≥ 2 SD below the mean), Bayley II Psychomotor Developmental Index <70, moderate to severe cerebral palsy, deafness (presence of hearing aids in both ears), and/or blindness (no useful vision in either eye).²¹ For infants born from 2006 to 2010, severe NDI was defined as having any of the following: Bayley III cognitive composite score <70,²² Modified Gross Motor Function Classification

level ≥ 2 ,²³ deafness (hearing impairment), and/or blindness (no or some functional vision in either eye).

Statistical Analyses

The NRN enrollment includes ~1500 ELBW infants per year in the GDB. Over the 12-year study period, it was estimated that there would be a total population of 18 000 infants. A previous NRN publication has shown that 29% of these patients receive prophylactic indomethacin.¹¹ It was estimated that ~14% of ELBW infants may have died before receiving any prophylactic indomethacin. This resulted in an expected study population of 16 500 infants who were eligible to receive prophylactic indomethacin and any enteral feeding within the first 3 days after birth. The α was predefined as .05. The incidence of SIP was 6% and 5% in both the indomethacin ($n = 601$) and placebo control groups ($n = 601$), respectively, in the Trial of Indomethacin Prophylaxis in Preterms.² It was estimated that for the comparison of I+E+ versus I+E- to detect an absolute increase in the incidence of SIP from 5% to 7.2% there would be a power of 80%. The study hypothesis was that the combined exposure to prophylactic indomethacin and early feeding (any feeds ≤ 3 days after birth) increases the risk for SIP within 14 days after birth in ELBW infants from 5% to $\geq 6\%$ absolute risk (ie, by $\geq 20\%$ relative risk [RR] increase).

Baseline demographic and perinatal characteristics of the 4 groups of newborns (I+E+, I+E-, I-E+, and I-E-) were analyzed by χ^2 for categorical variables (surfactant, antepartum hemorrhage, Apgar scores, race, etc) and by Wilcoxon test for continuous variables (birth weight, gestational age). Both unadjusted and adjusted analyses were performed to ascertain the effect of the 4 groups (I+E+, I+E-, I-E+, and I-E-) on the primary outcome of SIP within 14 days and all the secondary outcomes. Unadjusted analysis was performed by

using χ^2 tests for categorical outcomes and Wilcoxon test for continuous outcomes. Adjusted analysis was performed using multivariate logistic regression analysis and Poisson regression models with robust variance estimators.²⁴ The model was adjusted for covariates including gestational age, birth weight, male gender, race, antenatal corticosteroid administration, surfactant administration, small for gestational age (birth weight <10th percentile for gender and gestational age as determined from growth curves by Alexander et al²⁵), and 5-minute Apgar score. The analyses were also adjusted for site.

Unadjusted and adjusted risk ratios comparing the risk of each of the exposure groups (I+E+, I+E-, I-E+) with nonexposure group (I-E-) for the primary outcome of SIP within 14 days and all the secondary outcomes were estimated. In addition, the adjusted risk ratio comparing early feeding and no early feeding groups among infants exposed to indomethacin (I+E+ vs I+E-) was estimated. SAS Version 9.2 (Cary, NC) was used for all statistical analyses. Denominators reported reflect missing values.

RESULTS

During the period of 1999–2010, 20 655 ELBW infants were enrolled in the NRN GDB registry (Fig 1). Among these infants, 15 751 ELBW infants survived >12 hours after birth and received enteral nutrition. Baseline demographic and clinical characteristics are shown in Table 1. Among infants exposed to prophylactic indomethacin, the risk of SIP did not differ between the I+E+ and I+E- groups (RR 0.74, 95% CI 0.49–1.11, $P = .1467$). The rate of SIP was lower in the I+E+ relative to the I-E- referent group (RR 0.58, 95% CI 0.37–0.90, $P = .0159$, Table 2). The unadjusted rate of SIP was increased in the I+E- group relative to the I-E- referent group (RR 1.31, 95% CI 1.08–1.57, $P = .0051$), but this was not significant in the adjusted

FIGURE 1
Selection of the study cohorts.

analysis (RR 0.79, 95% CI 0.60–1.04, $P = .0960$). However, early enteral feeding in the absence of prophylactic indomethacin (I–E+) was associated with a significantly lower risk of SIP when compared with the I–E– referent group (RR 0.53, 95% CI 0.36–0.777, $P = .0011$). Prophylactic indomethacin with early feeding was associated with lower death or severe NDI at 18- to 22-month follow-up (I+E+: RR 0.86, 95% CI 0.77–0.95, $P = .0046$) when compared with the group that did not receive indomethacin or early feeding. Early enteral feeding regardless of prophylactic indomethacin was associated with lower risk of death or severe NDI at 18- to 22-month follow-up (I+E+ and I–E+, $P = .0046$ and ≤ 0.0001 , respectively) when compared with the group that did not receive prophylactic indomethacin

or early feedings. Prophylactic indomethacin with early feeding was associated with less death or severe NDI at 18- to 22-month follow-up (I+E+: RR 0.82, 95% CI 0.76–0.89, $P \leq .0001$) when compared with those infants who received prophylactic indomethacin but not early feeding. Early enteral feeding regardless of prophylactic indomethacin was associated with significantly fewer days to reach full enteral feed and fewer total numbers of days of parenteral nutrition (both $P < .001$, Table 3).

DISCUSSION

This study provides observational data that the combined administration of prophylactic indomethacin during the first 24 hours after birth and any enteral nutrition during the first 3 days was not associated with increased SIP when

compared with infants who did not receive prophylactic indomethacin and early feeding. Infants who received any enteral feeding during the first 3 days after birth in the absence of prophylactic indomethacin had a lower risk of SIP compared with infants in the no prophylactic indomethacin/no-early-feeding group. Among infants exposed to indomethacin, the adjusted risk of SIP did not differ significantly between those who received enteral nutrition during the first 3 days compared with those who did not receive early feeding. Early enteral feeding regardless of use of prophylactic indomethacin was associated with lower rates of death or severe NDI at 18- to 22-month follow-up (I+E+ and I–E+, both $P < .001$) when compared with those ELBW infants who never received either prophylactic indomethacin and any early enteral nutrition (I–E–).

SIP occurs predominantly in ELBW infants, with the diagnosis often based on clinical findings. Among SIP infants who undergo surgery, histopathologic features are distinct from NEC and are characterized by focal intestinal perforations, typically in the ileum, without evidence of mucosal ischemic injury or intestinal inflammation.²⁶ Numerous risk factors have been associated with SIP including prematurity, low birth weight,²⁷ early indomethacin treatment with^{4,13,28,29} or without concurrent early postnatal corticosteroid administration,^{4,7,13} indomethacin treatment of a PDA later than 24 hours after birth,⁷ being outborn from a tertiary-level NICU, treatment with pressors, presence of a PDA,⁴ fetal inflammatory response, antenatal maternal antibiotic use,²⁶ infectious agents, and intrauterine growth restriction.²⁷ A meta-analysis showed that antenatal corticosteroids are not associated with SIP.⁶ A case-control study of 2105 infants identified the following risk factors for SIP: being outborn from a tertiary level NICU (mother less likely to have received antenatal corticosteroids), treatment with

TABLE 1 Baseline Characteristics of Study Cohorts

Characteristic	I+E+ <i>n</i> = 1186	I+E− <i>n</i> = 4688	I−E+ <i>n</i> = 3128	I−E− <i>n</i> = 6749	<i>P</i>
Gestation, wk, median (p25, p75)	26 (25, 27)	25 (24, 26)	27 (26, 29)	26 (25, 27)	<.001
Birth wt, g, median (p25, p75)	820 (700, 910)	750 (641, 865)	870 (760, 945)	766 (650, 876)	<.001
Race					
White, <i>n</i> /total <i>n</i> (%)	603/1182 (51)	2645/4651 (57)	1629/3099 (53)	3507/6714 (52)	<.001
Black, <i>n</i> /total <i>n</i> (%)	547/1182 (46)	1839/4651 (39)	1327/3099 (43)	2839/6714 (42)	<.001
Male gender, <i>n</i> /total <i>n</i> (%)	550/1186 (46)	2312/4688 (49)	1397/3128 (45)	3301/6749 (49)	<.001
Vaginal delivery, <i>n</i> /total <i>n</i> (%)	429/1186 (36)	1547/4682 (33)	981/3127 (31)	2194/6744 (32)	.025
5 min Apgar, median (p25, p75)	7 (6, 8)	7 (5, 8)	8 (7, 8)	7 (5, 8)	<.001
Antenatal corticosteroid, <i>n</i> /total <i>n</i> (%)	1031/1183 (87)	3974/4670 (85)	2700/3121 (86)	5306/6711 (79)	<.001
Singleton pregnancy, <i>n</i> /total <i>n</i> (%)	926/1186 (78)	3507/4688 (75)	2498/3128 (80)	5251/6749 (78)	<.001
Small for gestational age, <i>n</i> /total <i>n</i> (%)	184/1186 (15)	586/4688 (12)	853/3128 (27)	1175/6748 (17)	<.001
Surfactant, <i>n</i> /total <i>n</i> (%)	925/1186 (78)	4287/4683 (91)	1854/3127 (59)	5797/6733 (86)	<.001
Congenital anomalies, <i>n</i> /total <i>n</i> (%)	22/1186 (2)	109/4688 (2)	112/3128 (4)	283/6749 (4)	<.001

Denominators vary to reflect missing values. p25, 25th percentile, p75, 75th percentile. I−E− is the baseline referent group for all comparisons.

either dopamine or dobutamine within 14 days before SIP, the diagnosis of a PDA and treatment with hydrocortisone during the first 3 days after birth.⁴ Another case-control study showed that infants with SIP were more likely than control infants

matched for birth weight and gestational age to have evidence of fetal inflammatory response defined as acute vasculitis of the fetal placental surface or umbilical perivascularitis (funisitis).²⁶ Mothers of infants with SIP were more likely than

controls to have received antibiotics before or at the time of delivery. There is, however, a lack of strong evidence to establish a definitive infectious mechanism for the etiology of SIP. There is a lack of strong evidence to support the theory

TABLE 2 Clinical Outcomes*

Outcome	I+E+ <i>n</i> = 1186		I+E− <i>n</i> = 4688		I−E+ <i>n</i> = 3128		I−E− <i>n</i> = 6749	
	<i>n</i> /Total <i>n</i> (%)	RR (95% CI)	<i>n</i> /Total <i>n</i> (%)	RR (95% CI)	<i>n</i> /Total <i>n</i> (%)	aRR (95% CI)	<i>n</i> /Total <i>n</i> (%)	RR (95% CI)
SIP during first 14 d after birth ^a	32/1182 (3)	0.58 (0.37–0.90)*	177/4673 (4)	0.79 (0.60–1.04)	35/3117 (1)	0.53 (0.36–0.77)***	207/6705 (3)	Referent
SIP after day 14 after birth ^{a,b}	8/1185 (0.7)	0.48* (0.23–0.98)	52/4684 (1)	0.56 (0.40–0.79)****	25/3127 (0.8)	0.83 (0.53–1.31)	116/6742 (2)	Referent
Deaths: 12 h–14 d ^a	43/1184 (4)	1.53 (1.03–2.28)*	148/4674 (3)	1.37 (1.03–1.82)*	74/3119 (2)	1.57 (1.17–2.12)***	175/6713 (3)	
Death before discharge ^a	146/1185 (12)	0.96 (0.81–1.14)	742/4674 (16)	1.16 (1.03–1.29)*	287/3119 (9)	0.94 (0.83–1.07)	1037/6714 (16)	Referent
NEC with intestinal perforation during first 14 d after birth ^b	2/1185 (0.2)	0.40 (0.10–1.69)	15/4684 (0.3)	0.60 (0.32–1.12)	11/3127 (0.4)	1.14 (0.56–2.33)	32/6742 (0.5)	Referent
Death or severe NDI at 18- to 22-mo follow-up	335/902 (37)	0.83 (0.75–0.91)**	1754/3608 (49)	1.02 (0.96–1.08)	620/2036 (31)	0.82 (0.76–0.89)****	2476/5202 (48)	Referent
Severe NDI in survivors at 18- to 22-mo follow-up	184/751 (25)	0.71 (0.61–0.83)****	995/2849 (35)	0.98 (0.89–1.08)	342/1758 (20)	0.76 (0.68–0.84)****	1399/4125 (34)	Referent
Indomethacin or ibuprofen treatment of PDA	236/1184 (20)	1.15 (1.13–1.20)****	1332/4655 (29)	1.11 (1.10–1.13)****	813/3128 (26)	1.08 (1.07–1.10)****	3403/6747 (50)	Referent
Surgery for PDA	72/1185 (6)	0.42 (0.32–0.55)****	566/4687 (12)	0.68 (0.60–0.77)****	235/3127 (8)	0.58 (0.51–0.67)****	1438/6746 (21)	Referent
Proven NEC with or without surgical treatment after day 14 after birth	114/1186 (10)	1.24 (0.98–1.55)	461/4685 (10)	1.11 (0.95–1.30)	239/3128 (8)	1.05 (0.90–1.23)	567/6743 (8)	Referent

Denominators vary to reflect missing values. I−E− is the baseline referent group for all comparisons and for calculation of adjusted RR, adjusted for all covariates including gestational age, birth weight, male gender, race, antenatal corticosteroid administration, surfactant administration, small for gestational age (birth weight <10th percentile for gender and gestational age as determined from growth curves by Alexander et al²⁶), 5-minute Apgar score and center. **P* < .05; ***P* < .001; ****P* < .01; *****P* ≤ .0001.

^a Concerning missing outcome data for infants, there were 13 infants (I+E+ = 1, I+E− = 4, I−E+ = 1, and I−E− = 7) with SIP in whom the specific date of documentation of SIP was missing. In addition, there were 61 infants (I+E+ = 3, I+E− = 11, I−E+ = 10, and I−E− = 37) for whom the cause of death between 12 h and 14 d after birth was missing.

^b Concerning the outcomes of NEC with intestinal perforation during first 14 d after birth and SIP after day 14, the adjusted analysis does not converge if center is included because the prevalence rates are low for these outcomes. Therefore, for these 2 outcomes, RR is adjusted for all other covariates except center.

TABLE 3 Nutritional Clinical Outcomes

Outcome	I+E+ <i>n</i> = 1186	I+E− <i>n</i> = 4688	I−E+ <i>n</i> = 3128	I−E− <i>n</i> = 6749
Days to reach full enteral feeds (p25, p75), median	19 (14, 29)*	27 (19, 39)	16 (11, 25)*	26 (18, 38)
Days of parenteral nutrition (p25, p75), median	19 (13, 33)*	28.5 (18, 44)**	17 (10, 29)*	29 (18, 44)
Days to regain birth wt (p25, p75), median	11 (7, 15)*	11 (7, 16)*	10 (7, 13)*	11 (8, 16)

I−E− is the baseline referent group for all comparisons and for significance of *P* values; p25, 25th percentile; p75, 75th percentile. **P* < .001; ***P* < .01.

that infants with intrauterine growth restriction have increased risk of SIP.²⁷

Several studies have examined the association of indomethacin treatment in infants and either SIP^{1,2,4–7,11,12} or NEC with intestinal perforation^{1,2,7,10–12} with inconsistent results. The Trial of Indomethacin Prophylaxis in Preterms² and a randomized trial by Ment et al⁴ reported no significant difference between the treatment and control groups for the outcomes of NEC or SIP. Prophylactic indomethacin was the intervention in both trials. A meta-analysis that included both of these trials showed no difference for the outcomes of NEC or SIP concerning treatment with prophylactic indomethacin compared with control groups.¹ A trial of dexamethasone and/or hypercapnia within the first 12 hours after birth reported that indomethacin treatment in ELBW infants during the first 14 days after birth was associated with increased risk of SIP.²⁹ Indomethacin use alone^{6,7} or in combination with postnatal hydrocortisone^{4,28} or dexamethasone^{13,29} may be associated with SIP. Some studies have shown that early indomethacin administration within the first 12,⁶ 24 hours,²⁹ or 3 days⁴ after birth was associated with SIP. However, a retrospective of 11 960 ELBW infants in the NRN showed that indomethacin administration for PDA treatment after 24 hours after birth, but not prophylactic indomethacin, was associated with higher risk of SIP (adjusted OR 1.61, 95% CI 1.25–2.08, *P* < .05).⁷ The association of postnatal corticosteroid use as a risk factor for increased rate of SIP in ELBW infants treated with prophylactic indomethacin has been

examined in 2 randomized controlled trials.^{28,29} ELBW infants who received concurrently prophylactic indomethacin and either hydrocortisone²⁸ or dexamethasone²⁹ had an increase in SIP in these trials.

A randomized controlled trial¹¹ and a case–control study⁸ have examined the safety and efficacy of indomethacin and concurrent enteral feeding. A study by Clyman et al in 177 premature infants comparing trophic feeds at 15 mL/kg/day versus no feeds during indomethacin or ibuprofen PDA treatment reported that infants fed during treatment required 3 to 4 fewer days to reach 120 mL/kg/day of enteral feeds without evidence of increased feeding intolerance or increased SIP or necrotizing enterocolitis.¹¹ Our study in contrast to that of Clyman et al examined prophylactic rather than therapeutic indomethacin in relation to early enteral nutrition. We did not examine the interaction of ibuprofen and early enteral feeding concerning SIP. An additional strength of our observational study is the large multicenter population with prospectively collected data concerning SIP. A limitation of this study, common to all nonrandomized clinical studies, is that although statistical models can adjust for known confounders (birth weight, gestational age, etc), they do not adjust for variables not included in the model but evident to the clinician. These variables may have influenced the decision to initiate or withhold feeds. The finding that any enteral feeding during the first 3 days after birth in the absence of prophylactic in-

domethacin was associated with a lower risk of SIP as compared with infants who did not receive prophylactic indomethacin and early feeding may reflect a selection bias. This finding of less SIP and improved chance of survival without severe neurodevelopmental impairment in those ELBW infants who received early feeds may represent a bias. Infants who were not fed early were of lower birth weight and gestational age, more likely to be male, less likely to have had antenatal corticosteroids, more likely to have received surfactant, and more likely to have a PDA ligation. Early feeding among ELBW infants may be a marker for infants who are less ill during the first 3 days of life.³⁰

Published studies reported that administration of prophylactic indomethacin to ELBW infants during the first 24 hours after birth reduced severe IVH and PDA^{1–3} and that early feedings were associated with decreased duration of parenteral nutrition and fewer days to achieve full enteral feeds and may have a protective effect regarding reduction of illness severity in ELBW infants.³⁰ This study shows that concurrent administration of prophylactic indomethacin and early enteral feeding is associated with a lower risk of SIP in ELBW infants. This provides supporting observational data to refute the practice of withholding feeds while infants receive prophylactic indomethacin.

ACKNOWLEDGMENTS

The National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) provided grant support for the NRN's GDB and Follow-up Studies.

Data collected at participating sites of the NICHD NRN were transmitted to RTI International, the data-coordinating center (DCC) for the network, which stored, managed, and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator) and Dr. Shampa Saha (DCC Statistician) had full access to all the data in the study and take

responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study: NRN Steering Committee Chair Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine; Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904): William Oh, MD, Betty R. Vohr, MD, Barbara Alksnis, PNP, Bonnie E. Stephens, MD, Yvette Yatchmink, MD, Robert Burke, MD, Angelita M. Hensman, RN, BSN, Teresa M. Leach, MEd CAES, Martha R. Leonard, BA BS, Lucy Noel, Rachel A. Vogt, MD, Victoria E. Watson, MS, CAS, Suzy Ventura; Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80): Avroy A. Fanaroff, MD, Deanne E. Wilson-Costello, MD, Bonnie S. Siner, RN, Harriet G. Friedman, MA; Cincinnati Children's Hospital Medical Center, University Hospital, and Good Samaritan Hospital (U10 HD27853, M01 RR8084): Kurt Schibler, MD, Edward F. Donovan, MD, Jean J. Steichen, MD, Kimberly Yoltan, PhD, Barbara Alexander, RN, Kate Bridges, MD, Cathy Grisby, BSN, CCRC, Marcia Worley Mersmann, RN, Holly L. Mincey, RN, BSN, Jody Hessling, RN, Teresa L. Gratton, PA; Duke University School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30): Ronald N. Goldberg, MD, C. Michael Cotten, MD, MHS, Kathy J. Auten, MSHS, Kimberley A. Fisher, PhD, FNP-BC, IBCLC, Katherine A. Foy, RN, Kathryn E. Gustafson, PhD, Melody B. Lohmeyer, RN, MSN; Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory University Hospital Midtown (U10 HD27851, M01 RR39): David P. Carlton, MD, Ira Adams-Chapman, MD, Ellen Hale, RN, Sheena Carter, PhD, Maureen Mulligan LaRossa, RN; NICHD: Linda L. Wright, MD, Elizabeth M. McClure,

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ABBREVIATIONS

CI—confidence interval

ELBW—extremely low birth weight

GDB—Generic Database

I+E+—infants who received prophylactic indomethacin during the first 24 hours and any enteral feeding during the first 3 days after birth

I+E—infants who received prophylactic indomethacin during the first 24 hours and did not receive enteral feeding during the first 3 days after birth

I-E+—infants who did not receive prophylactic indomethacin during the first 24 hours but did receive enteral feeding during the first 3 days after birth

I-E—infants who did not receive prophylactic indomethacin during the first 24 hours and did not receive enteral feeding during the first 3 days after birth

NDI—neurodevelopmental impairment

NEC—necrotizing enterocolitis

NRN—Neonatal Research Network

OR—odds ratio

PDA—patent ductus arteriosus

RR—relative risk

SIP—spontaneous intestinal perforation

Drs Kelleher, Salas, and Carlo conceptualized and designed the study, oversaw data analyses, and drafted and revised the manuscript; Drs Bhat, Ambalavanan, Stoll, Bell, Walsh, Laptook, Sanchez, Shankaran, Van Meurs, Ms Hale, Ms Newman, Ms Ball, and Drs Higgins and Carcelen assisted in study design and reviewed and revised the manuscript; Drs Saha and Das assisted in study design, performed the statistical analyses, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2014-0183

doi:10.1542/peds.2014-0183

Accepted for publication Aug 14, 2014

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: The National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development provided grant support for the Neonatal Research Network's Generic Database and Follow-up Studies.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.