Association between Use of Prophylactic Indomethacin and the Risk for Bronchopulmonary Dysplasia in Extremely Preterm Infants

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Objective To assess the association between prophylactic indomethacin and bronchopulmonary dysplasia (BPD) in a recent, large cohort of extremely preterm infants.

Study design Retrospective cohort study using prospectively collected data for infants with gestational ages < 29 weeks or birth weights of 401-1000 g born between 2008 and 2012 at participating hospitals of the National Institute of Child Health and Human Development Neonatal Research Network. Infants treated with indomethacin in the first 24 hours of life were compared with those who were not. Study outcomes were BPD, defined as use of supplemental oxygen at 36 weeks postmenstrual age among survivors to that time point, death, and the composite of death or BPD. Prespecified subgroup analyses were performed.

Results Prophylactic indomethacin use varied by hospital. Treatment of a patent ductus arteriosus after the first day of life was less common among 2587 infants who received prophylactic indomethacin compared with 5244 who did not (21.0% vs 36.1%, $P < .001$). After adjustment for potential confounders, use of prophylactic indomethacin was not associated with higher or lower odds of BPD (OR 0.89, 95% CI 0.72-1.10), death (OR 0.80, 95% CI 0.64-1.01), or death or BPD (OR 0.87, 95% CI 0.71-1.05). The only evidence of subgroup effects associated with prophylactic indomethacin were lower odds of death among infants with birth weights above the 10th percentile and those who were not treated for a patent ductus arteriosus after the first day of life.

Conclusions Prophylactic indomethacin was not associated with either reduced or increased risk for BPD or death. *(J Pediatr 2017;186:34-40).*

Trial registration ClinicalTrials.gov: NCT00063063

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The use of prophylactic indomethacin in preterm infants remains controversial.[1] Prophylactic indomethacin reduces the incidence of severe intraventricular hemorrhage and subsequent symptomatic patent ductus arteriosus (PDA).[2] However, prophylactic indomethacin has not been shown to prevent bronchopulmonary dysplasia (BPD), despite a strong association between PDA and the development of BPD.[2-7] The available data from randomized trials are consistent with the hypothesis that prophylactic indomethacin may adversely affect respiratory outcomes. The most recent Cochrane Review on prophylactic indomethacin included 9 RCTs that assessed supplemental oxygen use at 28 days of life and only 1 trial, the Trial of Indomethacin Prophylaxis in Preterms (TIPP) that assessed supplemental oxygen use at 36 weeks postmenstrual age (PMA).[2,8] Treatment with prophylactic indomethacin did not significantly reduce the rates of either BPD outcome, but the point estimates of the relative risks favored the control therapy for both definitions of BPD.[8]

BPD	Bronchopulmonary dysplasia
GDB	Generic Database
NRN	Neonatal Research Network
PDA	Patent ductus arteriosus
PMA	Postmenstrual age
RCTs	Randomized controlled trials
TIPP	Trial of Indomethacin Prophylaxis in Preterms

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A secondary analysis of TIPP data found that infants randomized to prophylactic indomethacin compared with placebo received a higher fraction of inspired oxygen (FiO_2) during the first week of life.[9] Van Overmeire et al[10] demonstrated a similar phenomenon in a randomized trial of early (day 3) vs late (day 7) treatment of echocardiography confirmed PDA. These studies suggest that early treatment with indomethacin may adversely affect early respiratory function and could lead to a small but important increase in the risk for BPD.

It is unlikely that further large placebo-controlled trials of prophylactic indomethacin will be conducted. Therefore, analyses of multicenter observational data may provide the only findings that can help resolve the remaining uncertainty about the risks and benefits of prophylactic indomethacin. To evaluate the potential association between prophylactic indomethacin and the risk for BPD at a PMA of 36 weeks, we conducted an analysis of data collected prospectively for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN) Generic Database (GDB).

Methods

The NRN GDB registry (ClinicalTrials.gov: NCT00063063) uses a predefined protocol to prospectively collect maternal and infant demographic and clinical data from birth through hospital discharge, death, or 120 days for all infants with gestational ages between 22 and $28^{6/7}$ weeks or birth weights from 401 to 1000 g born at participating NRN centers. Live born infants who survived the first 12 hours of life and were delivered at the 35 hospitals included in the NRN were evaluated in this analysis. The institutional review board at each study center approved the collection of GDB data. Written or oral parental consent was obtained at 3 centers and a waiver of consent was granted at the remaining centers.

Outcome and Exposure Definitions

The primary study outcome was BPD, defined as the use of supplemental oxygen at 36 weeks PMA among infants who survived to this time point. The secondary outcomes were death before 36 weeks PMA and the composite of death before 36 weeks PMA or BPD. We compared the risks for these outcomes between infants who received prophylactic indomethacin, defined as initiation of indomethacin within the first 24 hours of life, and infants who did not receive prophylactic indomethacin.

Statistical Analyses

Maternal complications of pregnancy and infant characteristics were compared between the infants who were treated with prophylactic indomethacin and those who were not using standard descriptive statistics. Rates of prophylactic indomethacin use at individual hospitals were calculated and reported graphically. The odds of the study outcomes were evaluated using logistic regression. The regression models were adjusted for several prespecified potential confounding variables and those that differed between infants who were and were not treated with prophylactic indomethacin with a *P* value of <.05 in the bivariate testing. These variables were included as fixed effects and fell into 1 of 3 groups: (1) maternal characteristics (gestational hypertension, multiple gestation pregnancy, rupture of maternal amniotic membranes for longer than 18 hours, treatment with antenatal antibiotics, treatment with antenatal corticosteroids, and cesarean delivery); (2) baseline neonatal characteristics (birth weight and gestational age (as continuous variables), sex, and birth weight <10th percentile determined using the Alexander fetal growth curves)[11]; and (3) neonatal morbidities occurring in the first 24 hours of life (intubation, receipt of chest compressions, or epinephrine in the delivery room, and mechanical ventilation at 24 hours of life). Hospital was included in all models as a random effect. Data from small hospitals that participated in the NRN as part of a single center and had similar prophylactic indomethacin treatment rates were combined.

We evaluated 5 infant subgroups for potential differences in the association between the use of prophylactic indomethacin and the study outcomes: gestational age (<26 weeks vs ≥26 weeks), birth weight percentile (<10th percentile vs ≥10th percentile), sex, exposure to antenatal corticosteroids (any treatment vs none), and medical or surgical treatment of a PDA after the first 24 hours of life (any treatment vs none). The same logistic regression models described above with the addition of a treatment by subgroup interaction term were used in these analyses. An interaction *P* value of <.05 was considered to indicate a statistically important subgroup effect. No adjustments for multiple comparisons were made in this exploratory observational study.

Lastly, we performed a post-hoc analysis to assess the risk for the study outcomes associated with the rate of prophylactic indomethacin use at the birth hospital. A 3-level categorical variable with approximately equal numbers of patients per group was added to the multivariable regression models: no use (no infants treated with prophylactic indomethacin during the study period); moderate use (greater than 0% but less than 60% of infants treated with prophylactic indomethacin); and high use (greater than or equal to 60% of infants treated with prophylactic indomethacin). All statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

Of the 7831 infants included in this analysis recruited between January 1, 2008 and December 31, 2012, 6749 (86.2%) were alive at 36 weeks PMA and were assessed for the primary outcome (**Figure 1**; available at www.jpeds.com). The characteristics of the study population are shown in **Table I**. Infants who received prophylactic indomethacin compared with those who did not were less mature at birth and were more likely to have a birth weight less than the 10th percentile, to be intubated or have received cardiopulmonary resuscitation in the delivery room, and to be intubated at 24 hours of life (**Table I**). Treatment with prophylactic indomethacin was associated with