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Comparative effectiveness and safety of indomethacin versus ibuprofen for the treatment of patent ductus arteriosus

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ABSTRACT

Background: Patent ductus arteriosus (PDA) is common in extremely premature infants and associated with increased morbidity and mortality. Medical management of PDA uses either indomethacin or ibuprofen. Despite numerous studies, uncertainty exists as to which drug is safer or more effective; we sought to fill this knowledge gap.

Methods: We identified infants <28 weeks gestational age discharged from neonatal intensive care units included in the Pediatrix Medical Group Clinical Data Warehouse between 2006 and 2012 who were treated with indomethacin or ibuprofen between postnatal days 2 and 14. Infants treated with both drugs or infants with a congenital malformation were excluded. We used multivariable logistic regression to determine the association of indomethacin versus ibuprofen on clinical outcomes.

Results: Of 6349 patients who met study criteria, 1177 (19%) received ibuprofen and 5172 (81%) received indomethacin. The median gestational age was 25 weeks (interquartile range 24–26), and 2894 (46%) infants were <750 g at birth. On unadjusted analysis, infants who received ibuprofen had significantly higher incidences of death prior to discharge, surgical ligation of the PDA prior to discharge, death or spontaneous intestinal perforation within 7 days of therapy, death or surgical ligation of the PDA prior to discharge, and an elevated creatinine within 7 days of treatment. However, on multivariable analysis, no significant differences in outcomes were observed (odds ratio for death/PDA ligation for ibuprofen vs. indomethacin = 1.12 [95% CI 0.91–1.39]).

Conclusions: We observed similar effectiveness and safety profiles for indomethacin and ibuprofen in the medical management of PDA in premature infants.

1. Introduction

The ductus arteriosus (DA) is a normal anatomic conduit in the fetus, allowing blood to bypass the pulmonary circuit [1]. The DA is kept open while in utero through a combination of prostaglandins, nitric oxide, and pressure differentials [2]. After birth, via contracture of the smooth muscle within its walls likely secondary to an increase in oxygen tension and a decrease in prostaglandins, the DA closes and becomes the ligamentum arteriosum [2]. Functional closure of the DA usually occurs within hours of birth in term infants; however, in premature infants, the DA frequently fails to close after birth or experiences substantial delay in closure [3]. This condition, known as patent ductus arteriosus (PDA) [4], has been associated with bronchopulmonary dysplasia (BPD), increased ventilation requirements, poor feeding tolerance, and increased mortality in premature infants [5,6].

Since the 1970s, indomethacin, an inhibitor of prostaglandin synthesis, has been used in the treatment of PDA [7–8]. However, indomethacin has been associated with adverse events, including increased risk of necrotizing enterocolitis and renal insufficiency [9–14]. To find a safer alternative to indomethacin, ibuprofen was approved for the treatment of PDA in 2006 [15]. However, ibuprofen has also recently been linked to adverse events including spontaneous intestinal perforation (SIP), leading to uncertainty over which drug has the better safety profile [16–18]. Further intensifying this debate, a voluntary recall by the supplier of ibuprofen in 2010 forced many clinicians to return to using indomethacin [19].

Abbreviations: BPD, bronchopulmonary dysplasia; FiO_2, fraction of inspired oxygen; GA, gestational age; PDA, patent ductus arteriosus; SGA, small for gestational age; SIP, spontaneous intestinal perforation.

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A number of studies have compared the safety and efficacy of ibuprofen and indomethacin [8,20–22]. These studies have consistently demonstrated similar effectiveness between the 2 drugs, but indomethacin tended to demonstrate a worse side effect profile [20]. Despite the available evidence, neonatologists continue to use both drugs for the treatment of PDA [23–25]. To better assess the risks and benefits of each drug, we performed a retrospective review to determine the safety and effectiveness of ibuprofen and indomethacin. We hypothesized that there would be no significant differences in effectiveness or safety between the 2 drugs.

2. Methods

2.1. Data source and study population

We obtained data for our study from the Pediatrix Medical Group Clinical Data Warehouse, a prospective clinical database that captures information from daily progress notes generated by clinicians on all infants discharged from 165 neonatal intensive care units managed by the Pediatrix Medical Group in the United States. We collected information on prenatal characteristics, demographics, timing and duration of exposure to ibuprofen or indomethacin, and clinical and laboratory diagnoses of interest, as well as clinical outcomes.

We included all inborn infants <28 weeks gestational age (GA) discharged between 2006 and 2012 who received either indomethacin or ibuprofen and were first exposed to either drug from postnatal day 2 to postnatal day 14. We excluded infants exposed to both drugs and infants diagnosed with a major congenital anomaly. We excluded infants treated on the first 2 days of life to eliminate infants receiving prophylaxis for intraventricular hemorrhage.

2.2. Definitions

We identified infants as exposed to indomethacin or ibuprofen and analyzed the first course of therapy for each infant. We defined small for gestational age (SGA) as <10th percentile for age [26]. As surrogates for severity of illness, we identified exposure to any inotropic medication (dopamine, dobutamine, epinephrine, milrinone, and phenylephrine) or systemic hydrocortisone, as well as any mechanical ventilator support or need for supplemental oxygen (FiO_2) on the first day of therapy. We defined renal insufficiency at the onset of therapy as any serum creatinine >1 mg/dL on the first day of therapy or up to 2 days prior. We identified several outcomes of interest: death prior to discharge, death or PDA requiring surgical ligation prior to discharge, SIP within 7 days of start of therapy, death or SIP within 7 days of start of therapy, death or BPD prior to discharge, serum creatinine >1 mg/dL within 7 days of the start of therapy, and the combined outcome of any one of these events. BPD was defined as patients who received continuous supplemental oxygen or respiratory support from a corrected GA of 36 0/7–36 6/7 weeks.

2.3. Statistical analysis

The unit of observation for this study was the infant. We used standard summary statistics, including medians (interquartile ranges) and counts (percentages), to describe continuous and categorical study variables. We described the use of indomethacin and ibuprofen by year over the course of the study, as well as variation in the use of the 2 drugs by site. We compared the distribution of predictor variables and the outcomes of interest between infants exposed to indomethacin versus ibuprofen using Wilcoxon rank sum and chi-square tests of association. We used multivariable mixed logistic regression with fixed effects for site to evaluate the association between indomethacin and ibuprofen exposure and each outcome of interest. We conducted standard model assumptions diagnostics and evaluation for collinearity [27]. We first evaluated a model including all plausible predictor variables available, including their interactions as covariates. Initial predictors included GA, SGA, inotrope use, hydrocortisone use on first day of therapy, creatinine > 1 mg/dL, mechanical ventilation, supplemental oxygen on first day of therapy, prenatal steroid exposure, discharge year, and postnatal age on first day of therapy. We then performed likelihood ratio tests to compare the full model to a priori determined reduced models and reported the most parsimonious model that fit the data well. A priori reduced models were produced by systematically dropping variables that were less likely to be related to the outcome. The final multivariable logistic regression model used site as a fixed effect and included the following covariates: GA, SGA status, prenatal steroid exposure, discharge year, postnatal age on the first day of therapy and the need for inotropic support, hydrocortisone use, mechanical ventilation, supplemental oxygen on the first day of therapy, and baseline creatinine > 1 mg/dL.

We further analyzed trends in the use of indomethacin and ibuprofen over the study period, as well as variation by center in the use of each drug following the removal of any site with <10 patients during the study period. All statistical analyses were conducted using Stata12 (College Station, TX). A $p < 0.05$ was defined as statistically significant. This study was approved by the institutional review board at the corresponding author's university.

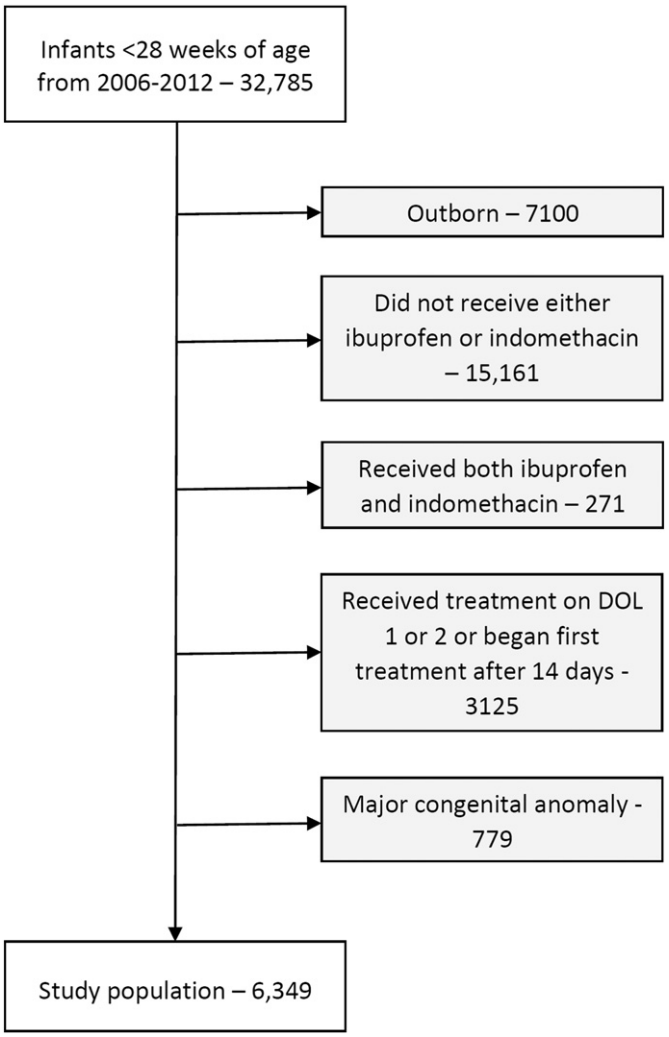

Fig. 1. Study cohort. DOL, day of life.