JAMA Pediatrics | Original Investigation

Comparative Effectiveness of Nonsteroidal Anti-inflammatory Drug Treatment vs No Treatment for Patent Ductus Arteriosus in Preterm Infants

Jonathan L. Slaughter, MD, MPH; Patricia B. Reagan, PhD; Thomas B. Newman, MD, MPH; Mark A. Klebanoff, MD, MPH

IMPORTANCE Patent ductus arteriosus (PDA) is associated with increased mortality and worsened respiratory outcomes, including bronchopulmonary dysplasia (BPD), in preterm infants. Nonsteroidal anti-inflammatory drugs (NSAIDs) are efficacious in closing PDA, but the effectiveness of NSAID-mediated PDA closure in improving mortality and preventing BPD is unclear.

OBJECTIVE To determine the effectiveness of NSAID treatment for PDA in reducing mortality and moderate/severe BPD at 36 weeks postmenstrual age.

DESIGN, SETTING, AND PARTICIPANTS This cohort study included 12 018 infants born at 28 gestational weeks or younger discharged between January 2006 and December 2013 from neonatal intensive care units in 25 US children's hospitals included in the Pediatric Health Information System. We performed an instrumental variable analysis that incorporated clinician preference–based, institutional variation in NSAID treatment frequency to determine the effect of NSAID treatment for PDA on mortality and BPD.

EXPOSURES Proportion of NSAID-treated infants born at each infant's institution within ±6 months of that infant's birth.

MAIN OUTCOMES AND MEASURES The primary composite outcome was death, moderate, or severe BPD at 36 weeks postmenstrual age.

RESULTS Of the 6370 male and 5648 female infants in this study, 4995 (42%) were white, 3176 (26%) were African American, 1823 (15%) were Hispanic, and 1555 (13%) were other races/ethnicities. The proportion of NSAID-treated infants at each infant's hospital within ±6 months of that infant's birth was associated with NSAID treatment and not associated with gestation, race/ethnicity, or sex. An infant's chances of receiving NSAID treatment increased by 0.84% (95% CI, 0.8-0.9; $P < .001$) for every 1% increase in the annual NSAID treatment percentage at a given hospital. An instrumental variable analysis demonstrated no association between NSAID treatment and the odds of mortality or BPD (odds ratio, 0.94; 95% CI, 0.70-1.25; $P = .69$), mortality (odds ratio, 0.73; 95% CI, 0.43-1.13; $P = .18$), or BPD (odds ratio, 1.01; 95% CI, 0.73-1.45; $P = .94$) in survivors.

CONCLUSIONS AND RELEVANCE When we incorporated clinician preference–based practice variation as an instrument to minimize the effect of unmeasured confounding, we detected no changes in the odds of mortality or moderate/severe BPD among similar preterm infants born at 28 weeks or younger following NSAID treatment for PDA initiated 2 to 28 days postnatally. Our findings agree with available randomized clinical trial evidence and support a conservative approach to PDA management.

JAMA Pediatr. 2017;171(3):e164354. doi:10.1001/jamapediatrics.2016.4354
Published online January 3, 2017.

Supplemental content

Author Affiliations: Department of Pediatrics, The Ohio State University College of Medicine and Nationwide Children's Hospital, Columbus (Slaughter, Klebanoff); Center for Perinatal Research, The Research Institute at Nationwide Children's Hospital, Columbus, Ohio (Slaughter, Klebanoff); Department of Economics, The Ohio State University, Columbus (Reagan); Center for Human Resource Research, The Ohio State University, Columbus (Reagan); Department of Epidemiology and Biostatistics, University of California–San Francisco (Newman); Department of Pediatrics, University of California–San Francisco (Newman).

Corresponding Author: Jonathan L. Slaughter, MD, MPH, Center for Perinatal Research, The Research Institute at Nationwide Children's Hospital, 575 Children's Crossroads, Research 3 Bldg, Columbus, OH 43215 (slaughter.84@osu.edu).

Patent ductus arteriosus (PDA) is highly prevalent in extremely preterm infants[1] and associated with increased mortality and worsened respiratory outcomes, including bronchopulmonary dysplasia (BPD).[2] Nonsteroidal anti-inflammatory drugs (NSAIDs) are efficacious in closing PDA, but the effectiveness of NSAID-mediated PDA closure in improving mortality, long-term respiratory outcomes, or neurodevelopment has never, to our knowledge, been clearly demonstrated.[3-6] Treatment of PDA with NSAIDs remains controversial.[1,7]

Previous randomized clinical trials (RCTs) to examine NSAID treatment of PDA did not find that NSAID treatment benefitted mortality, respiratory, or neurodevelopmental outcomes, but were powered to evaluate efficacy of ductal closure rather than longer-term outcomes such as mortality and BPD.[8] Several well-designed observational studies that controlled for measured confounders also did not detect an improvement in long-term outcomes following NSAID treatment for PDA.[9,10]

Unlike RCTs, observational investigations are prone to confounding by indication because of the inability to adjust for important unmeasured variables. The incorporation of naturally occurring treatment variations between health care clinicians into observational data analyses has been proposed as an instrument to minimize the effect of unmeasured confounding.[11-13] This is based on the assumption that, for treatments with limited evidence, practice variation is often because of clinician and institutional preferences rather than differences in patient characteristics between clinicians and institutions. The instrumental variable (IV) analysis uses the premise that if a treatment is effective there should, on average, be improvement in outcomes for similar patients as their clinicians' tendency to treat increases. We previously evaluated our assumption that clinician preference drives practice variation in the specific setting of preterm PDA management by electronically surveying clinicians at institutions participating in the Pediatric Health Information System (PHIS) database of US children's hospitals. We documented profound differences in opinion regarding treating PDA with NSAIDs.[14]

The objective of this investigation was to determine the effectiveness of NSAID treatment for PDA in reducing mortality and moderate/severe BPD at 36 weeks postmenstrual age. Given limited RCT evidence, the clinical importance of understanding the effectiveness of NSAID treatment to close PDA, and the controversy surrounding the topic, we conducted an IV analysis[11-13] in which we took advantage of practice variation because of physician preference as a means to control unmeasured confounding.

Key Points

Question Is nonsteroidal anti-inflammatory drug treatment of all preterm infants born at 28 weeks or younger with patent ductus arteriosus effective at reducing mortality and chronic lung disease?

Findings This cohort study that incorporated naturally occurring practice variation to reduce unmeasured confounding and included 12 018 preterm infants born at 28 weeks or younger found no significant association between nonsteroidal anti-inflammatory drug treatment and mortality or moderate to severe bronchopulmonary dysplasia.

Meaning For preterm infants born 28 weeks or younger with patent ductus arteriosus, our findings agree with the available randomized trial evidence and support a conservative approach to patent ductus arteriosus management.

Methods

Data Source

We derived the study cohort from neonates included in the PHIS database (Children's Hospital Association, Shawnee Mission, Kansas) with discharge dates between January 1, 2006, through December 31, 2013, from participating US children's hospitals. The Nationwide Children's Hospital institutional review board approved the study and waived consent because the research was deemed to involve no more than minimal risk, would not adversely affect the rights and welfare of the participants, and could not be carried out without a waiver.

Study Cohort

Our cohort was restricted to infants born at 28 weeks or younger. To prevent referral bias because of older infants referred from other hospitals for PDA management or management of complications associated with mortality or BPD, we only included infants who were admitted on their birth date. Postnatal day 2 was considered the first potential day of NSAID treatment for PDA, because prophylactic indomethacin treatment is normally initiated on days 0 to 1. Thus, we excluded those infants hospitalized for less than 3 days to ensure that all infants survived to be eligible for treatment on day 2 (eFigure 1 in the Supplement). We excluded those without a recorded discharge status (home, transfer, death), which was needed to calculate mortality and BPD outcomes. Because our IV analysis was dependent on determining the annual proportion of NSAID administration within a given hospital, we only included neonatal intensive care units with an average of at least 21 infants meeting inclusion criteria (150 or more infants over the 7-year study) in our primary analysis.

Because physicians' diagnoses of PDA are highly variable,[14,15] we did not require infants in our primary analysis to have an *International Classification of Diseases, Ninth Revision (ICD-9)* PDA diagnosis. Physicians who, based on personal preference, are less likely to treat PDA with NSAIDs may also be less likely to evaluate for and diagnose PDAs. A physician's degree of early surveillance affects PDA diagnosis, which is time-dependent because all infants have a patent ductus at birth, but at 25 to 28 weeks gestation, 35% close within 1 week.[1] Most physicians at the neonatal intensive care units included within PHIS use echocardiograms to inform their PDA treatment decisions, but some base treatment on the presence of a murmur, a less sensitive method.[14] Regardless of actual PDA presence, we assume that treated infants were more likely to receive a PDA diagnosis. Therefore, restricting our analysis

solely to infants formally diagnosed as having PDA may introduce bias. Because our IV analysis is based on physician preference-based variation in the annual proportion of NSAID administration per hospital, including infants without a PDA diagnosis should not bias our IV-based results. We evaluated this assumption in a sensitivity analysis.

Variables

In addition to demographic data, PHIS contains a record of medication administration, procedures, and respiratory treatments for each day of an infant's hospitalization, as determined from billing records. Thompson-Reuters Healthcare, the PHIS data processing partner, maps each hospital's daily charge codes to Clinical Transaction Classification codes to ensure comparability of charge-level data between institutions. The Clinical Transaction Classification codes we evaluated are shown in eTable 1 in the Supplement.

Gestational Age

Gestational age (GA) at delivery was defined using a multistep process. Gestational age was classified into groups—24 weeks or younger, 25 to 26 weeks, and 27 to 28 weeks—based on the *ICD-9* codes (eTable 1 in the Supplement). If the *ICD-9* code for GA was missing, we relied on the GA recorded in the patient's demographic file. Since GA determination (28 weeks or younger) was necessary for inclusion, we excluded infants when both forms of GA records were missing or when there was any discordance between the *International Classification of Diseases, Ninth Revision (ICD-9)* code and their demographic information (n = 6).

Definition of NSAID Treatment for PDA

An infant was considered to have been treated with NSAIDs for PDA when the first indomethacin or ibuprofen dose was given between 2 to 28 calendar days inclusive postnatally (birth date = day 0) or if the infant received NSAID (indomethacin and/or ibuprofen) on 4 or more days within the first 28 postnatal days. This allowed us to separate PDA treatment doses from prophylactic indomethacin dosing to prevent intraventricular hemorrhage, which typically starts on the birth date(day 0 or day 1 if it is a late-night admission) and is given daily for 3 consecutive days. Treatment for PDA with NSAIDs for infants who did not receive indomethacin prophylaxis would begin on or after postnatal day 2. Any infant who received indomethacin prophylaxis would receive more than 3 total NSAID doses if subsequently treated for PDA. Therefore, infants who received prophylactic indomethacin were still eligible for this study. We did not consider NSAID doses beyond 28 postnatal days because older infants might be treated with ibuprofen for pain control, and most RCTs investigating NSAID treatment of PDA have focused on treatment within the first postnatal month.[1,3,4,16] We evaluated treatment with either indomethacin or ibuprofen because both have similar efficacy in closing PDA.[4,17]

Definition of BPD Outcome

We used each infant's daily respiratory support modality record to determine BPD outcomes at 36 weeks postmenstrual age according to the National Institutes of Health consensus definition,[18] as recently clarified by Poindexter and Jobe.[19] We merged high-frequency and conventional ventilation codes to create a binary composite code designating daily administration of any invasive mechanical ventilation. We likewise created a composite code to designate daily administration of any noninvasive positive pressure ventilation modality inclusive of continuous positive airway pressure, bilevel positive airway pressure, intermittent positive pressure breathing, or noninvasive positive pressure ventilatory support.

To be diagnosed as having moderate/severe BPD, an infant had to receive respiratory support via invasive mechanical ventilation, noninvasive ventilation, or supplemental oxygen for 28 total (but not necessarily consecutive) days[19] and remain on invasive or noninvasive ventilation (severe BPD) or supplemental oxygen (moderate BPD) at 36 weeks postmenstrual age. For those infants transferred before 36 weeks postmenstrual age, we adapted a method of imputing BPD at the time of transfer from the method the National Institute of Child Health and Human Development Neonatal Research Network used to create its validated BPD prediction tool.[20] We imputed a diagnosis of severe BPD if the infant was receiving mechanical or positive pressure ventilation at the time of transfer (n = 129) and a diagnosis of moderate BPD (n = 316) if the infant was receiving oxygen.

Statistical Analysis

Our primary composite outcome was death or moderate/severe BPD at 36 weeks postmenstrual age. First, we estimated the effect of NSAID treatment on mortality/BPD using a generalized estimating equation (GEE) to adjust for gestational age, using heteroskedasticity-robust standard errors to account for clustering by institution.

Then, we incorporated periods of hospital-specific NSAID treatment for PDA surrounding each infant's birth as an IV to obtain an unbiased (exogenous) treatment effect[11-13] under the assumption that each preterm infant born in a period of higher preference-based NSAID treatment for PDA has a higher likelihood of treatment than infants born during periods of lower treatment. The IV estimates apply to infants who would be treated with NSAIDs based on their institution's inclination to treat PDA with NSAIDs.

For each infant in the cohort, we created an IV between 0 to 1 by incorporating the proportion of infants who were born at that infant's institution within ±6 months of their birth (excluding that infant) and treated for PDA with an NSAID per our definition. We used a 2-stage least squares regression model in which the first stage predicted treatment based on the value of the IV and the second stage incorporated the probability of treatment determined in the first stage. These models included heteroskedasticity-robust standard errors and adjusted for birth gestation. Because the standard output of 2-stage least squares models are risk differences, we calculated marginal odds ratios for comparison with the noninstrumented GEE output and 95% CIs via bias-corrected bootstrapping.[21]

A valid instrument should strongly affect or be associated with treatment by sharing a common cause and should have no direct or indirect effect on the outcome except through its association with the treatment.[13] If an instrument does not

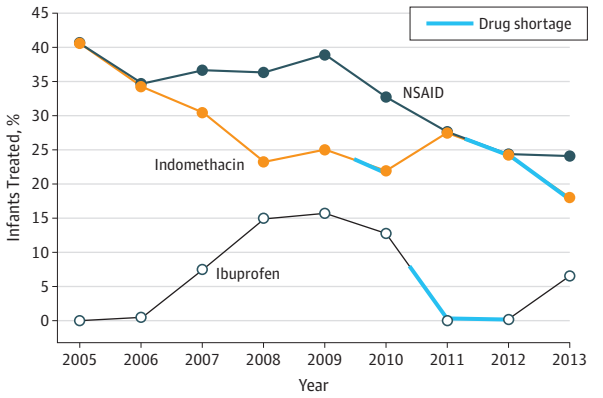
Table 1. Balance of Covariates Across Treatment Groups

Cohort (N = 12 018)	Total No. (%)	Treatment Frequency, No. (%)	
		Treated With NSAIDs (n = 3888 [32%])	Untreated (n = 8130 [68%])
Gestational age, wk			
27-28	5405 (45)	1325 (34)	4080 (50)
25-26	4217 (35)	1548 (40)	2669 (33)
24	1607 (13)	698 (18)	909 (11)
<24	789 (7)	317 (8)	472 (6)
Sex			
Male	6370 (53)	2068 (53)	4302 (53)
Female	5648 (47)	1820 (47)	3828 (47)
Race/ethnicity			
White	4995 (42)	1572 (40)	3423 (42)
African American	3176 (26)	947 (24)	2229 (27)
Hispanic	1823 (15)	671 (17)	1152 (14)
Other[a]	1555 (13)	558 (14)	997 (12)
Missing	469 (4)	140 (4)	329 (4)

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

[a] Other represents those infants with a reported race/ethnicity other than white, African American, or Hispanic.

Figure. Variation in Nonsteroidal Anti-inflammatory Drug (NSAID) Use Over Time



Annual percentage of infants treated with NSAIDs for patent ductus arteriosus. Blue lines indicate periods of reported drug shortages. Ibuprofen use first increases in 2006 following the US Food and Drug Administration's approval for patent ductus arteriosus treatment.

strongly predict receipt of treatment, it is considered weak and can increase bias.[13] We tested our instrument's strength by evaluating its effect on measured covariate balance, assessing its association with actual NSAID treatment, and conducting an *F* test to test whether its inclusion significantly contributed to the first stage of the IV model.[13]

To evaluate the sensitivity of our results, we ran additional IV models including sex, race/ethnicity, and a binary variable indicating prophylactic indomethacin treatment on the birth date. We also reran all analyses after restricting the cohort only to infants with an *ICD-9* PDA diagnosis. We conducted a time-varying Cox regression analysis[22-24] to evaluate the effect of immortal time bias on our noninstrumented GEE analysis and tested the effects of varying hospital sample size cutoffs on our instrumented estimates. Finally, we reran our analysis with an instrument that incorporated hospital-level NSAID treatment frequency in the 12 months before each infant's birth rather than a ±6-month interval. All analyses were conducted using Stata 14.1 (StataCorp).

Results

The cohort included 12 018 infants within 25 hospitals (eFigure 1 in the Supplement). **Table 1** shows the covariate balance among treated and untreated infants. Overall, 32% of infants were treated with NSAIDs for PDA, with 27% receiving indomethacin and 7% ibuprofen.

Variation in NSAID Treatment for PDA

Treatment with NSAIDs varied by both hospital (median use: 34.0%; 25th%-75th%: 21.5%-40.5%; range: 16.1%-54.7%) and year (**Figure**). The overall annual percentage of infants treated with NSAIDs dropped from 2005 (40.6%) to 2013 (24.1%). Temporary reductions in indomethacin and ibuprofen use corresponded to reported indomethacin shortages in late 2009[25] and 2011 to 2013[25,26] and an ibuprofen recall from July 2010 to November 2012[27] (Figure).[28]

Multivariable Regression Estimates

Unadjusted bivariate analyses are shown in eTable 2 in the Supplement. eTable 3 in the Supplement shows the unadjusted relationship between GA, sex, and race/ethnicity and NSAID treatment status. We excluded race/ethnicity and sex from our final models because they were not confounders as they were not associated with receipt of NSAID treatment. However, these variables were included in sensitivity analyses (below).

The noninstrumented GEE models, controlling only for gestation and hospital effect, showed a significant association between NSAID treatment and increased mortality/BPD (composite outcome) and NSAID treatment and increased moderate/severe BPD among survivors. Treatment with NSAIDs was associated with decreased mortality (**Table 2**) (eTable 4 in the Supplement).

Strength of the Instrument

Testing demonstrated that our instrument was strongly related to receipt of NSAID treatment. The first stage of our IV model showed that for every 1% increase in our instrument—the percentage of infants treated with NSAIDs at a given hospital within ±6 months of each infant's birth—an infant's chances of receiving NSAID treatment increased by 0.84% (95% CI, 0.8-0.9; $P < .001$). The F test$_{1,12\,013}$[13] (= 932) indicated our instrument contributed significantly to the IV model (F test >10 desirable). There were no significant associations between the instrument and gestation, sex, or race/ethnicity (eTable 5 in the Supplement), suggesting that neonatal intensive care units administering NSAIDs more frequently did not see sicker patients. **Table 3** shows the relationship between the percentile of infants within given GA categories and outcome measures

Table 2. Mortality and Bronchopulmonary Dysplasia According to NSAID Treatment of PDA[a,b]

Variable	GEE Odds Ratio (95% CI)[c]	*P* Value	Instrumental Variable[d]		
			Odds Ratio (95% CI)[e]	Risk Difference (95% CI)	*P* Value
Mortality or moderate/severe BPD[f]	1.31 (1.15-1.49)	<.001	0.94 (0.70-1.25)	−0.01 (−0.09 to 0.06)	.69
Mortality	0.57 (0.49-0.67)	<.001	0.73 (0.43-1.13)	−0.03 (−0.08 to 0.01)	.18
Moderate/severe BPD among survivors[f,g]	1.52 (1.35-1.72)	<.001	1.01 (0.73-1.45)	0.003 (−0.07 to 0.08)	.94

Abbreviations: BPD, bronchopulmonary dysplasia; GEE, generalized estimating equation; NSAID, nonsteroidal anti-inflammatory drug; PDA, patent ductus arteriosus.

[a] Models included gestational age adjustment.

[b] Odds ratios were marginal (population averaged).

[c] Models used included GEE models incorporating gaussian family, Logit link, and Exchangeable correlation structures with heteroskedasticity-robust standard errors (Huber-White sandwich estimator).

[d] Two-stage least squares instrumental variable models with heteroskedasticity-robust standard errors (Huber-White sandwich estimator).

[e] Bias-corrected bootstrap 95% CIs were constructed using 2000 replications with replacement.

[f] Denominator for BPD among survivors (n = 10 065).

[g] BPD imputed among transfers. BPD was imputed for 945 infants (8.3%).

Table 3. Balance of Gestational Age and Outcomes Across Treatment Groups and Levels of the Instrument

Covariates	Instrument Quartiles: % NSAID Treatment for PDA at Each Infant's Hospital Within ±6 mo of Birth[a,b]				Standardized Difference (Between 2 Lowest and 2 Highest Quartiles)
	0%-22.6% (n = 2996)	>22.6%-33.3% (n = 2943)	>33.3%-41.3% (n = 3072)	>41.3%-92.3% (n = 3007)	
Received NSAID treatment, No. (%)	518 (17.3)	821 (27.9)	1147 (37.3)	1402 (46.6)	0.42
Gestational age, No. (%), wk					
27-28	1307 (43.6)	1331 (45.2)	1392 (45.3)	1375 (45.7)	0.02
25-26	1061 (35.4)	1058 (36.0)	1070 (34.8)	1028 (34.2)	−0.02
24	421 (14.1)	379 (12.9)	390 (12.7)	417 (13.9)	−0.01
<24	207 (6.9)	175 (6.0)	220 (7.2)	187 (6.2)	0.01
Outcomes, No. (%)					
Mortality or moderate/severe BPD	1471 (49.1)	1265 (43.0)	1367 (44.5)	1408 (46.8)	−0.01
Mortality	374 (12.5)	351 (11.9)	388 (12.6)	355 (11.8)	0.00
Moderate/severe BPD[c]	1097 (41.8)	914 (35.3)	979 (36.5)	1053 (39.7)	−0.01

Abbreviations: BPD, bronchopulmonary dysplasia; NSAID, nonsteroidal anti-inflammatory drug; PDA, patent ductus arteriosus.

[a] Percentiles were derived using column *n* as the denominator.

[b] Median: 33.3%; 25th-75th: 22.6%-41.3%; range: 0%-92.3%.

[c] The denominator for percentage with moderate/severe BPD is based on the quartile number of survivors until discharge. Quartile 1 (0%-22.6%); n = 2622; quartile 2: (>22.6%-33.3%) n = 2592; quartile 3: (>33.3%-41.3%) n = 2684; quartile 4: (>41.3%-92.3%) n = 2652.

and increasing quartiles of the instrument. A standardized difference of greater than ±0.1 indicates significant correlation.[29] The percentile of infants receiving NSAIDs is directly correlated with increasing instrument values. However, GA distribution and outcomes are uncorrelated.

Instrumental Variable Results

Two-stage least squares IV models incorporating the annual proportion of NSAID treatment for PDA at each infant's hospital demonstrated no significant difference in odds between NSAID treatment and mortality or BPD, NSAID treatment and mortality, or NSAID treatment and BPD in survivors (Table 2) (eTable 4 in the Supplement).

Sensitivity Analyses

Outcome estimates remained similar, detecting no effect of NSAID treatment on mortality/BPD outcomes when we adjusted for race/ethnicity, sex, and prophylactic indomethacin treatment, and also when we restricted the cohort to only those infants with an *ICD-9* PDA diagnosis. An instrument that incorporated hospital-level NSAID treatment frequency in the 12 months preceding an infant's birth provided similar results as an instrument based on a ±6-month interval from birth (eTable 6 in the Supplement). Our IV results remained similar when we relaxed the hospital sample size restriction and included more hospitals than in our primary analysis (eTable 7 in the Supplement). Alternate IV modeling specifications (bivariate probit IV and generalized structural equation models)[13,30,31] produced results similar to the 2-stage least squares models (eTable 8 in the Supplement). Time-varying Cox regression models demonstrated that a high early mortality rate (immortal time bias) strongly influenced our non-instrumented GEE estimates (eTable 9 in the Supplement).

Discussion

We found no significant effect on mortality or BPD at 36 weeks after controlling for unmeasured confounders using IV analysis. This result aligns with meta-analyses constructed from the secondary outcomes of RCTs and well-designed observational investigations.[3-5,9,10,32,33]

Our instrument was a strong predictor of NSAID treatment and was not associated with our measured risk factors (gestation, sex, and race/ethnicity) for mortality and BPD. To our knowledge, no statistical test can completely verify the assumption that an instrument has no effect on the outcome apart from its association with the treatment.[11-13] Therefore, we conducted an investigation before this study to evaluate our assumption that caregiver preferences are the main contributors

to variation in NSAID treatment for PDA. We surveyed neonatal intensive care unit leaders at all hospitals included within our analysis and found wide variation in hospital-specific reasons for closing or not closing PDA with NSAIDs. In addition to wide between-hospital variation, respondents noted variation between physicians in preferences for NSAID treatment of PDA among 70% (n = 32) of hospitals.[14]

Immortal Time Bias and Confounding by Indication Because of Illness Severity

Our noninstrumented and biased GEE estimates differ considerably from our IV results. Although seemingly implausible based on existing literature, our GEE estimates (40% mortality odds reduction and 50% BPD odds increase) are similar to multivariable estimates from another large database cohort with limited markers for early illness severity.[34] We attribute the discrepancy between IV and noninstrumented analyses to confounding by indication because of illness severity[35] and immortal time bias, a period of follow-up when mortality cannot occur in treated participants who must by default survive until treatment.[23] The PHIS lacks acuity indexes, such as neonatal acute physiology scores, which might enable statistical adjustment for early illness severity. Severely ill infants are less likely to be treated with NSAIDs because of renal and hematological concerns.[36] Immortal time bias, present in our cohort (eTable 9 and eFigure 2 in the Supplement) and common in pharmacoepidemiological investigations,[23] leads to an erroneous, implausibly high reduction in mortality following treatment.[24] Instrumental variable analysis is robust to confounding by indication and immortal time bias.

Strengths and Limitations

Our investigation benefits from a large representative data set and sample size (n = 12 018) and the use of advanced methods to minimize unmeasured confounding. One limitation is that we assume our clinician preference–based instrument is unrelated to mortality/BPD risk except through its effect on whether an infant receives NSAID treatment. We also assume that institutions with increased NSAID treatment of PDA are not also increased or decreased users of another treatment that independently influences mortality and/or BPD risk.[21] Instrumental variables should produce unbiased estimates, but that validity comes with reduced precision and larger confidence intervals relative to noninstrumented regression analyses. However, our IV point estimates and 95% CI widths are similar in magnitude to RCT meta-analyses and other large observational studies that showed no effect of NSAID treatment for PDA on mortality or moderate/severe BPD.[3,4,9]

Instead of focusing on NSAID treatment for PDA at a single time point, our observational design allowed us to assess real-world treatment patterns between 2 to 28 days postnatal age. As in an RCT, our estimates apply to the population-average of all infants studied. Although NSAID treatment of all infants with PDA does not appear beneficial, our findings do not imply that some infants with certain risk factors may not benefit from PDA closure. Likewise, subgroups may exist for whom avoiding NSAIDs is beneficial.

Conclusions

When we incorporated clinician preference–based practice variation as an instrument to minimize the effect of unmeasured confounding, we detected no changes in the odds of mortality or moderate/severe BPD among infants born at 28 weeks' gestation or younger following NSAID treatment for PDA initiated between 2 to 28 days postnatal age. Our result agrees with available RCT evidence and previous well-designed observational investigations that similarly detected no effect.

ARTICLE INFORMATION

Accepted for Publication: October 4, 2016.

Published Online: January 3, 2017. doi:10.1001/jamapediatrics.2016.4354.

Author Contributions: Dr Slaughter had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: Slaughter, Reagan, Klebanoff.
Drafting of the manuscript: Slaughter, Reagan.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: All authors.
Obtained funding: Slaughter.
Administrative, technical, or material support: Slaughter.
Study supervision: Klebanoff.

Conflict of Interest Disclosures: None reported.

Funding/Support: This investigation was supported by grant 5K08HL121182 from the National Heart, Lung, and Blood Institute at the National Institutes of Health.

Role of the Funder/Sponsor: The National Heart, Lung, and Blood Institute had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

1. Clyman RI, Couto J, Murphy GM. Patent ductus arteriosus: are current neonatal treatment options better or worse than no treatment at all? *Semin Perinatol*. 2012;36(2):123-129.

2. Noori S, McCoy M, Friedlich P, et al. Failure of ductus arteriosus closure is associated with increased mortality in preterm infants. *Pediatrics*. 2009;123(1):e138-e144.

3. Cooke L, Steer P, Woodgate P. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. *Cochrane Database Syst Rev*. 2003;(2):CD003745.

4. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. *Cochrane Database Syst Rev*. 2015;(2):CD003481.

5. Benitz WE; Committee on Fetus and Newborn, American Academy of Pediatrics. Patent ductus arteriosus in preterm infants. *Pediatrics*. 2016;137(1):e20153730.

6. Bose CL, Laughon MM. Patent ductus arteriosus: lack of evidence for common treatments. *Arch Dis Child Fetal Neonatal Ed*. 2007;92(6):F498-F502.

7. Benitz WE. Patent ductus arteriosus: to treat or not to treat? *Arch Dis Child Fetal Neonatal Ed*. 2012;97(2):F80-F82.

8. Clyman RI, Chorne N. Patent ductus arteriosus: evidence for and against treatment. *J Pediatr*. 2007;150(3):216-219.

9. Madan JC, Kendrick D, Hagadorn JI, Frantz ID III; National Institute of Child Health and Human Development Neonatal Research Network. Patent ductus arteriosus therapy: impact on neonatal and 18-month outcome. *Pediatrics*. 2009;123(2):674-681.

10. Mirea L, Sankaran K, Seshia M, et al; Canadian Neonatal Network. Treatment of patent ductus arteriosus and neonatal mortality/morbidities:

adjustment for treatment selection bias. *J Pediatr*. 2012;161(4):689-694.e1.

11. Rassen JA, Brookhart MA, Glynn RJ, Mittleman MA, Schneeweiss S. Instrumental variables II: instrumental variable application—in 25 variations, the physician prescribing preference generally was strong and reduced covariate imbalance. *J Clin Epidemiol*. 2009;62(12):1233-1241.

12. Rassen JA, Brookhart MA, Glynn RJ, Mittleman MA, Schneeweiss S. Instrumental variables I: instrumental variables exploit natural variation in nonexperimental data to estimate causal relationships. *J Clin Epidemiol*. 2009;62(12):1226-1232.

13. Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. *Pharmacoepidemiol Drug Saf*. 2010;19(6):537-554.

14. Slaughter JL, Reagan PB, Bapat RV, Newman TB, Klebanoff MA. Nonsteroidal anti-inflammatory administration and patent ductus arteriosus ligation, a survey of practice preferences at US children's hospitals. *Eur J Pediatr*. 2016;175(6):775-783.

15. Evans N. Diagnosis of the preterm patent ductus arteriosus: clinical signs, biomarkers, or ultrasound? *Semin Perinatol*. 2012;36(2):114-122.

16. Lainwala S, Hussain N. Treatment of patent ductus arteriosus with cyclo-oxygenase inhibitors beyond 2 weeks of age in very low birth weight infants. *Am J Perinatol*. 2016;33(6):584-589.

17. Gulack BC, Laughon MM, Clark RH, Sankar MN, Hornik CP, Smith PB. Comparative effectiveness and safety of indomethacin versus ibuprofen for the treatment of patent ductus arteriosus. *Early Hum Dev*. 2015;91(12):725-729.

18. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2001;163(7):1723-1729.

19. Poindexter BB, Jobe AH. The diagnostic conundrum of bronchopulmonary dysplasia. *J Pediatr*. 2015;167(3):517-518.

20. Laughon MM, Langer JC, Bose CL, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Prediction of bronchopulmonary dysplasia by postnatal age in extremely premature infants. *Am J Respir Crit Care Med*. 2011;183(12):1715-1722.

21. Newman TB, Vittinghoff E, McCulloch CE. Efficacy of phototherapy for newborns with hyperbilirubinemia: a cautionary example of an instrumental variable analysis. *Med Decis Making*. 2012;32(1):83-92.

22. Hosmer DW Jr, Lemeshow S, May S. *Applied Survival Analysis: Regression Modeling of Time to Event Data*. 2nd ed. Hoboken, NJ: John Wiley and Sons, Inc; 2008.

23. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol*. 2008;167(4):492-499.

24. Suissa S. Immortal time bias in observational studies of drug effects. *Pharmacoepidemiol Drug Saf*. 2007;16(3):241-249.

25. Thompson CA. Pharmacy news: Bedford recalls indomethacin injection lot 1948138. American Society of Health System Pharmacists website. http://www.ashp.org/menu/News/PharmacyNews/NewsArticle.aspx?id=3560. Accessed August 21, 2016.

26. Chandramouli J. Indomethacin injection. American Society of Health System Pharmacists website. http://www.ashp.org/menu/DrugShortages/CurrentShortages/Bulletin.aspx?id=596. Published October 22, 2014. Accessed August 21, 2016.

27. Chandramouli J. Ibuprofen lysine injection. American Society of Health System Pharmacists website. http://www.ashp.org/menu/DrugShortages/ResolvedShortages/Bulletin.aspx?Source=Resolved&Type=Rss&Id=669. Published November 20, 2010. Accessed August 21, 2016.

28. Drug approval package: NeoProfen (ibuprofen lysine) injection. US Food & Drug Administration website. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/21-903s000TOC.cfm. Published April 22, 2008. Accessed August 21, 2016.

29. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput*. 2009;38(6):1228-1234. dx.doi.org/10.1080/03610910902859574

30. Hernán MA, Robins JM. Instruments for causal inference: an epidemiologist's dream? *Epidemiology*. 2006;17(4):360-372.

31. Greenland S, Brumback B. An overview of relations among causal modelling methods. *Int J Epidemiol*. 2002;31(5):1030-1037.

32. Jones LJ, Craven PD, Attia J, Thakkinstian A, Wright I. Network meta-analysis of indomethacin versus ibuprofen versus placebo for PDA in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2011;96(1):F45-F52.

33. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? *J Perinatol*. 2010;30(4):241-252.

34. Laughon M, Bose C, Clark R. Treatment strategies to prevent or close a patent ductus arteriosus in preterm infants and outcomes. *J Perinatol*. 2007;27(3):164-170.

35. Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. *Designing Clinical Research*. Philadelphia, PA: Lippincott Williams & Wilkins; 2013.

36. Hermes-DeSantis ER, Clyman RI. Patent ductus arteriosus: pathophysiology and management. *J Perinatol*. 2006;26(suppl 1):S14-S18.