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Effects of Indomethacin Prophylaxis Timing on IVH and PDA in Extremely Low Birth Weight (ELBW) Infants

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Abstract

Objective—Indomethacin prophylaxis (IP) reduces the risk of intraventricular hemorrhage (IVH) and patent ductus arteriosus (PDA) in preterm infants. However, the optimal time to administer IP has not been determined. We hypothesized that IP at 6 h is associated with a lower incidence of IVH or death than if administered at >6–24 h of age.

Methods—We performed a retrospective cohort study of ELBW infants (<1,000g birth weight) treated in the Neonatal ICUs in the Neonatal Research Network from 2003 to 2010 and who received IP in the first 24 hours of age. Infants were dichotomized based upon receipt of IP at 6 or >6–24h of age. The primary outcomes were IVH alone and IVH or death. Secondary outcomes

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Hussnain Mirza, Abbot R. Laptook, William Oh, Betty R. Vohr, Barbara J. Stoll, Sarah Kandefer, Barbara S. Stonestreet, and the members of Generic Database Subcommittee of the NICHD Neonatal Research Network fulfill the contribution criteria to the paper according to the ICMJE guidelines. Each one of the above mentioned authors had a

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- Drafting the work or revising it critically for important intellectual content.
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were PDA alone and PDA or death. We used multivariable analyses to determine associations between the age of IP and the study outcomes expressed as an odds ratio (OR) and 95% confidence interval (CI).

Results—IP was given at 6 h to 2340 infants and at >6–24h to 1915 infants. Infants given IP at 6 h had more antenatal steroid exposure, more in-born and less cardiopulmonary resuscitation ($p<0.01$). After multivariable analyses, age of IP receipt was not associated with IVH, and IVH or death but PDA receiving treatment/ligation or death was lower among IP at 6 h compared to IP at >6–24h (OR:0.83,95% CI:0.71–0.98).

Conclusion—IP at 6 h of age is not associated with less IVH or death, but is associated with less PDA receiving treatment/ligation or death.

Keywords

Indomethacin Prophylaxis; Time of Indomethacin Prophylaxis; IVH; PDA; Preterm Infants

INTRODUCTION

Intraventricular hemorrhage (IVH) is a major cause of poor neurodevelopmental outcome among extremely premature infants.(1, 2) More than 50% of all IVH in Very Low Birth Weight (VLBW) infants occurs in the first 6 to 8 hours of age.(3) Indomethacin prophylaxis reduces the risk of IVH and patent ductus arteriosus (PDA) in preterm infants.(4–6) Two time points have been used for indomethacin prophylaxis in different randomized controlled trials i.e. between 6 and 12 h of age in the trial by Ment, *et. al* (5) and less than 6 h of age in the trial by Schmidt *et.al*. (6) However, the initial dose of indomethacin may be administered over a wide time interval in clinical practice. To the best of our knowledge, the optimal time for indomethacin prophylaxis has not been established.

In the Neonatal Research Network database, a large proportion (46%) of VLBW infants (2003–07) developed a PDA; 71% of these infants received medical treatment and 27% of them received surgical ligation.(7) The effect of indomethacin prophylaxis timing upon the incidence of symptomatic PDA receiving medical or surgical treatment has not been examined.

Since the risk for IVH is reported to be highest in the initial hours following the birth, we hypothesized that administering indomethacin prophylaxis within 6 hours of age is associated with a lower incidence of IVH or death among extremely low birth weight (ELBW) infants compared with administration after 6 hours of age. We also evaluated the effects of indomethacin prophylaxis administered at 6 hours compared to after 6 hours of age on the incidence of PDA receiving treatment (medical or surgical) or death in ELBW infants.

PATIENTS AND METHODS

This retrospective cohort study included infants with birth weights 1000 grams who received indomethacin prophylaxis up to 24 h of age and were admitted to the 18 participating neonatal intensive care units (NICUs) in the Eunice Kennedy Shriver National

Institute of Child Health and Human Development Neonatal Research Network (NRN). The NRN is a consortium of academic tertiary care NICUs in the United States with a research focus on neonatal care, particularly extremely low birth weight (ELBW) infants. Each participating NRN site had Institutional Review Board approval for data collection for the NRN Generic Data Base (GDB). Exclusion criteria included death within 12 h after birth, unknown time of indomethacin administration, genetic syndromes, congenital anomalies, or an unavailable head ultrasound report. We dichotomized the study cohort into groups based upon the timing of the first dose of prophylactic indomethacin *i.e.* indomethacin administration ≤ 6 hours of age or > 6 to 24 h of age.

Data items collected were part of the GDB, which is an ongoing survey of neonatal morbidity and mortality. Trained research nurses abstracted data from medical records guided by the predefined criteria in a manual of operation and electronically transmitted the data to the NRN data center (RTI International, North Carolina). Data from each center were reviewed monthly with a series of edits by the data center to insure reliability. Data were retrieved from the GDB for calendar years 2003–10 from all participating centers in the NRN that included maternal characteristics and problems of pregnancy, neonatal demographics, delivery room events and morbidities during the course of hospitalization.

The primary outcomes were IVH (all grades), IVH or death, severe IVH (grade 3 and 4) and severe IVH or death. Secondary outcomes were PDA, PDA or death, PDA receiving medical or surgical treatment, and PDA receiving medical or surgical treatment or death. The diagnosis of IVH was based upon head ultrasound results. Ultrasound findings were used to establish the severity of IVH as described by Papile *et al.*(8) The Neonatal Research Network database contains the results of the worst head ultrasound within the first 28 days of age. The diagnosis of PDA was based upon the echocardiography requested for clinical indications: universal echocardiographic screening for PDA was not performed. A decision for treatment of a PDA (medical or ligation) was also based upon the clinical assessment of the providers in each center.

Maternal and neonatal variables were compared between groups using Student's t-tests for continuous variables and chi-square comparisons for categorical variables. Unadjusted odds ratios were calculated for IVH, IVH or death, severe IVH and severe IVH or death. Unadjusted risk for the primary outcome by indomethacin timing was also assessed by gender and gestation. Multivariable analyses were performed to adjust for the following covariates: network center, gestational age, maternal hypertension, maternal antibiotics, any antenatal steroids (either one or two doses), cesarean section, race, male sex, SGA, chest compressions in delivery room, outborn, PDA, and admission temperature. Results of multivariable analyses are reported as odds ratio and 95% confidence intervals (9, 10). Adjusted odds ratios were assessed for interactions by sex or gestation for IVH, IVH or death, severe IVH and severe IVH or death.

The incidence of PDA and PDA receiving medical treatment or ligation were determined in both groups (indomethacin at ≤ 6 h and > 6 –24 h). Multivariable analyses were performed using the same covariates as the analyses for IVH.

The analyses listed above for IVH and PDA indicated a higher proportion of outborn infants in the group receiving IP >6–24 hours compared to those in the ≤6 h group (15% vs 3%). Due to the unmeasured variables that may be associated with outborn status, a second set of multivariable analyses were performed for the outcomes of IVH, IVH or death, PDA and PDA or death among inborn infants only.

RESULTS

During the study period (2003–10), 13,754 infants with a birth weight ≥1000 g were admitted to the participating centers in the NRN. Indomethacin prophylaxis (IP) was not given to 9,172 infants. The latter included infants who died prior to 12 h of age or had missing information regarding indomethacin prophylaxis. Of 4,582 infants who received indomethacin prophylaxis, 327 infants were excluded due to congenital syndromes or anomalies (n=100), missing head ultrasound reports (n=6), unknown time of IP (n=187) or the administration of indomethacin after 24 h of age (n=34). This left 4,255 infants available for analysis. The first prophylactic dose of indomethacin was given at ≤6 h of age in 2,340 infants and at >6 to 24 h of age in 1,915 infants. The median time for the administration of the first prophylactic dose of indomethacin was 3.9 h (IQR range 2.8–4.8 h) for infants treated at ≤6 h, and 8.7 h (IQR range 7–12 h) for those treated between >6 and 24 h of age (Figure 2).

Maternal characteristics and delivery room events are summarized in Table 1. Mothers of infants given IP at ≤6 h of age had more hypertension, receipt of antibiotics, and antenatal steroids ($P<0.001$). The incidence of chorioamnionitis was higher in the group receiving indomethacin >6–24 h of age. Neonatal characteristics of the cohort are described in the Table 2. Infants receiving IP at ≤6 h of age had, less chest compressions in the delivery room ($p<0.001$). Upon admission to the NICU infants receiving IP at ≤6 h of age had higher admission temperatures and a lower percentage of out-borns ($p<0.0001$).

Bivariate analyses indicated lower incidences of IVH or death and severe IVH or death in the group receiving IP at ≤6 h of age compared to IP at >6 to 24 h of age. The incidence of PDA or death, PDA receiving medical or surgical treatment or death was also lower when indomethacin was administered at ≤6 h of age (Table 3).

However, there was no significant difference in the incidence of any IVH related outcomes after adjustment using multivariable analyses (Table 4).

After adjusting for covariates, the odds of infants with a PDA receiving medical or surgical treatment were lower among infants receiving IP at ≤6 h compared to later administration (OR 0.81, 95% CI 0.67–0.98). Similar odds ratios were found when PDA outcomes were combined with death (Table 5).

When analyses were limited to in-born infants, there was a total of 3,904 infants; 2,267 received IP at ≤6 hours and 1,637 infants received IP at >6–24 hours. Bivariate comparisons between these two groups showed differences in the same variables as the combined in-born and out-born cohort in Table 1 and 2, except that there were no differences in any or complete antenatal steroids. Multivariable analyses indicated that there

were no associations between the time of IP and any of the IVH related outcomes. Similar to the combined in-born and out-born cohort, IP at 6 hours among only in-born infants was associated with a lower incidence of PDA receiving medical treatment or ligation (OR 0.79, 95% CI; 0.65–0.96) and PDA receiving medical treatment/ligation and or death (OR 0.81, 95% CI; 0.69–0.97).

A secondary analysis was performed to examine potential interactions between time of IP and sex or gestation for outcomes involving IVH. Results of bivariate analysis by sex and gestation are summarized in the online appendix. No interactions were identified between gestation or sex and the time of IP administration for any outcome involving IVH after adjustment for covariates on multivariable analyses.

There were no differences in the incidences of necrotizing enterocolitis (12% vs. 13%, $p=0.29$), spontaneous intestinal perforation (6% vs. 5%, $p=0.25$), retinopathy of prematurity receiving treatment (11% vs. 12%, $p=0.2$) and BPD (38% vs. 36%, $p=0.58$) between the two groups.

DISCUSSION

We previously reported no effect of early indomethacin prophylaxis on the incidence of IVH among premature infants with a birth weight ≥ 1250 grams; however, severe IVH among extremely premature (< 27 weeks) female infants was lower when IP was administered at 6 h. This was an important but unexpected finding and we questioned whether the finding reflected chance due to the small sample size.⁽¹¹⁾ Data available from the NICHD Neonatal Research Network Generic Database provided the opportunity to examine the time of administration of indomethacin in a larger cohort derived from multiple centers. We confirmed that indomethacin prophylaxis before 6 hours of age does not decrease the incidence of IVH or death compared to later administration up to 24 h of age. Similar findings were reported by Yanowitz et al.⁽¹²⁾ In this larger cohort, we did not find an interaction by sex or gestation and the incidences of any IVH related outcomes in association with the timing of indomethacin prophylaxis.

The increased risks of IVH are associated with hemodynamic instability and changes in cerebral blood flow.^(13, 14) These hemodynamic changes are more likely to occur with increased frequency during the early hours after delivery. Since indomethacin could attenuate the development of fluctuations in cerebral blood flow in the early hours after birth,^(15–17) we hypothesized that IP at 6 h would decrease the incidence of IVH. The results of the current study did not support our hypothesis.

We acknowledge that the gap in the median time of drug administration (3.9 vs. 8.7 h) between the two groups was not large. However, it is unlikely that a wider gap exists with regard to IP timing as the practice is largely based upon two RCTs, in which indomethacin was administered either ≤ 6 hours⁽⁶⁾ or between 6 to 12 hours of age.⁽⁵⁾ Alternatively, advances in both obstetrical and neonatal practices may have changed the timing of highest risk for IVH. Thus, the benefit of indomethacin prophylaxis in reducing IVH may extend to the time intervals beyond the initial few hours after the delivery.

We considered analyzing the time of indomethacin administration as a continuous variable for the entire cohort. However, indomethacin prophylaxis timing data was not normally distributed. Over the 24 hours study period there were multiple time points at which very few infants (< 2% of the cohort) received indomethacin prophylaxis. Due to the uneven distribution of data along the 24 hours timeline, treating the time of indomethacin administration as a continuous variable was not felt to be more informative.

Indomethacin treatment within the first 48 hours is associated with higher rates of PDA closure compared to indomethacin treatment after 48 hours.(18) However, differences in the rate of PDA closure have not been previously examined with reference to the timing of indomethacin prophylaxis. Our adjusted results indicate a significant association between early indomethacin prophylaxis (≤ 6 h of age) and a lower incidence of PDA receiving medical treatment or surgical ligation or death as compared with administration at > 6 to 24 h of age. These observations may reflect the decreased response of the ductus arteriosus to indomethacin with increasing postnatal age. (19) This phenomenon has been attributed to increased endogenous production of nitric oxide in the ductal endothelium after the first 24 hours of age (19) and to the production of inflammatory cytokines, which can contribute to ductal vasodilatation.(20)

Since indomethacin can affect other organ systems,(21, 22) we compared the incidences of potential untoward effects of indomethacin prophylaxis ≤ 6 h compared to > 6 h-24 h of age. There was no difference between the two groups in the incidences of necrotizing enterocolitis, spontaneous intestinal perforation (SIP), retinopathy of prematurity requiring intervention and bronchopulmonary dysplasia.

The strengths of this study include a large patient cohort from multiple centers. We have used data from NICHD Neonatal Research Network, which has pre-defined morbidities and have been abstracted by trained research personnel. There are several limitations of our study. This was a retrospective study of a non-randomized cohort and is subject to bias by unmeasured confounders. The infants in the early prophylaxis group appeared less sick compared with the infants in the group that was treated later, i.e. less chest compressions and less exposure to antenatal steroids etc. Nonetheless, we have adjusted the results for differences in confounding variables. Although adjustment for illness scores would have been of interest to separate critically sick infants, the Generic database does not capture an illness severity score.

CONCLUSION

We conclude that administration of prophylactic indomethacin at ≤ 6 hours of age was not associated with a lower incidence of IVH or death in ELBW infants. However, medical treatment or surgical ligation of PDA or death was significantly less frequent among the infants who received indomethacin prophylaxis ≤ 6 h of age compared to later administration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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WHAT IS ALREADY KNOWN ON THIS TOPIC

- Prophylactic indomethacin reduces the incidence of IVH in preterm infants
- Indomethacin prophylaxis for IVH also reduces the risk for PDA
- In clinical practice, prophylactic indomethacin timing can be variable

WHAT THIS STUDY ADDS

- Timing of indomethacin prophylaxis does not decrease the incidence of IVH or death
- Indomethacin prophylaxis at 6h of age is associated with lower incidence of PDA requiring medical or surgical treatment or death

Figure 1.
Median time for actual administration of indomethacin prophylaxis in the two groups; at < 6 h or $> 6-24$ h.

Table 1**Maternal Characteristics and Delivery Room Events**

Features[‡]	Time of Indomethacin		p
	6 hours (n=2,340)	> 6–24 hours (n=1,915)	
Maternal Age	27 ± 6.3	27 ± 6.6	0.74
Singleton Pregnancy	1759 (75 %)	1404 (73 %)	0.17
Maternal Diabetes	104 (4 %)	79 (4 %)	0.70
Maternal Hypertension	685 (29 %)	500 (26 %)	0.03
Antepartum Hemorrhage	457 (20 %)	340 (18 %)	0.17
PROM	374 (16 %)	291 (15 %)	0.44
Chorioamnionitis ^{*‡}	173 (12 %)	160 (16 %)	0.01
Maternal Antibiotics	1576 (67 %)	1140 (60 %)	<0.0001
Any Antenatal Steroids	2063 (89 %)	1550 (80 %)	<0.0001
Complete Antenatal Steroids	1324 (56 %)	920 (48 %)	0.02
C-Section	1536 (65 %)	1272 (66 %)	0.12
Resuscitation in LDR			
Endotracheal Intubation	1780 (76 %)	1483 (77 %)	0.27
Chest Compressions	149 (6 %)	219 (11 %)	<0.0001
Epinephrine [*]	34 (< 2 %)	38 (2 %)	0.05
Low Apgar (<5 @ 5 minutes)	392(17 %)	360 (19 %)	0.07

[‡]Values represent either the mean ± standard deviation or proportions expressed as a percentage

^{*}When data are available.

[‡]Chorioamnionitis information available for only 1,384 infants in < 6 h group (n=2,340) and for only 981 infants in the > 6 – 24 h group (n=1,915)

Table 2

Neonatal Characteristics of Study Cohort

Features [‡]	Time of Indomethacin		P
	6 hours (n=2,340)	> 6–24 hours (n=1,915)	
Gestational Age (weeks)	25 ^{+5/7}	25 ^{+4/7}	0.19
Birth Weight (grams)	747 ± 148	741 ± 145	0.16
Male	1150 (49 %)	927 (48 %)	0.64
Admission Temperature	36.1 ± 1.1	35.8 ± 1.1	<0.0001
Race (Whites)	1303 (56 %)	995 (52 %)	0.05
Outborn	73 (3 %)	278 (15 %)	<0.0001
Respiratory Support (24 hours) [±]	2255 (97 %)	1875 (98 %)	<0.01
Use of Surfactant	2028 (86 %)	1701 (89 %)	0.04
Pneumothorax	161 (7 %)	132 (7 %)	1.00
Early Onset Sepsis	43 (2 %)	48 (< 3 %)	0.14

[‡]Values represent either the mean ± standard deviation or proportions expressed as a percentage

[±]Any invasive or noninvasive positive pressure ventilation

Table 3

Indomethacin Timing & Unadjusted Risk for IVH and PDA

Primary Outcome	Time of Indomethacin		P
	6 hours (n=2,340)	> 6–24 hours (n=1,915)	
Total IVH (any grade)	747 (32 %)	630 (33 %)	0.39
Total IVH or Death	976 (42 %)	871 (45 %)	0.01
Severe IVH (grade 3/4)	413 (17 %)	347 (18 %)	0.60
Severe IVH or Death	711 (30 %)	647 (34 %)	0.02
PDA	778 (33 %)	688 (36 %)	0.07
PDA or death	1088 (46.5%)	984 (51.5%)	<0.001
PDA receiving treatment	500 (22 %)	564 (30 %)	<0.001
PDA receiving treatment or death	858 (37.1%)	900 (47.2%)	<0.001

Table 4

Effect of Indomethacin Prophylaxis Timing (≤ 6 h of age) on IVH or Death

Clinical Outcomes	Adjusted Odd's Ratio (95% CI) ^a
Total IVH (Any Grade)	1.00 (0.84 – 1.19)
Total IVH or Death	0.95 (0.82 – 1.13)
Severe IVH (Grade 3/4)	1.03 (0.84 – 1.27)
Severe IVH or Death	1.01 (0.85 – 1.20)

^aMultivariable analyses adjusted for the following covariates: Network center, gestational age, maternal hypertension, maternal antibiotics, antenatal steroids, C-section, race, male sex, SGA, chest compressions in delivery room, outborn, PDA and admission temperature. Odds ratios < 1 in the multivariable logistic regression favored the ≤6hrs group, hence the reference was the >6–24 hours group

Table 5

Effect of Indomethacin Prophylaxis Timing (≤ 6 h of age) on PDA or Death

Clinical Outcomes	Adjusted Odd's Ratio (95% CI) ^a
PDA	0.88 (0.74 – 1.05)
PDA or Death	0.88 (0.75 – 1.04)
PDA receiving treatment/ligation	0.81 (0.67 – 0.98)
PDA receiving treatment/ligation or Death	0.83 (0.71 – 0.98)

^aMultivariable analysis to adjust for the following covariates: Network center, gestational age, maternal hypertension, maternal antibiotics, antenatal steroids, C-section, race, male gender, SGA, chest compressions in delivery room, outborn, and admission temperature. Odds ratios < 1 in the multivariable logistic regression favored the <6hrs group, hence the reference was the >6–24 hours group