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ARTICLE

Prevention and 18-Month Outcomes of Serious Pulmonary Hemorrhage in Extremely Low Birth Weight Infants: Results From the Trial of Indomethacin Prophylaxis in Preterms

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ABSTRACT

OBJECTIVES. A patent ductus arteriosus is a risk factor for pulmonary hemorrhage; however, despite halving the incidence of patent ductus arteriosus, indomethacin prophylaxis did not reduce the rate of pulmonary hemorrhage in the Trial of Indomethacin Prophylaxis in Preterms. Inclusion of mild bleeds after trauma to the upper airways may have masked a beneficial drug effect. Using the Trial of Indomethacin Prophylaxis in Preterms database, we studied the effect of prophylactic indomethacin on the prevention of serious hemorrhages in extremely low birth weight infants. We also compared the 18-month outcomes of infants with and without a serious pulmonary bleed.

METHODS. Pulmonary hemorrhage was classified as serious when it was treated with increased ventilator support, a higher concentration of oxygen, or transfusion of blood products. The cumulative risk for serious pulmonary hemorrhage was estimated for the first week of life and for the entire NICU stay. Poor outcome at a corrected age of 18 months was death or survival with cerebral palsy, cognitive delay, blindness, and/or deafness.

RESULTS. A total of 123 (10.2%) of 1202 infants developed a serious pulmonary hemorrhage. During week 1, prophylactic indomethacin reduced the risk for serious pulmonary hemorrhage by 35%; however, during the entire NICU stay, the risk for such hemorrhages was decreased by only 23%. A reduced risk for patent ductus arteriosus explained 80% of the beneficial effect of prophylactic indomethacin on serious pulmonary bleeds. The risks for death or for survival with neurosensory impairment were doubled after a serious pulmonary hemorrhage.

CONCLUSIONS. Extremely low birth weight infants with serious pulmonary hemorrhage have an increased risk for poor long-term outcome. Prophylactic indomethacin reduces the rate of early serious pulmonary hemorrhage, mainly through its action on patent ductus arteriosus. Prophylactic indomethacin is less effective in preventing serious pulmonary hemorrhages that occur after the first week of life.

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This trial has been registered at www.clinicaltrials.gov (identifier NCT00009646).

Key Words
extremely low birth weight, pulmonary hemorrhage, indomethacin prophylaxis

Abbreviations
PDA—patent ductus arteriosus
TIPP—Trial of Indomethacin Prophylaxis in Preterms
ELBW—extremely low birth weight

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PATENT DUCTUS ARTERIOSUS (PDA) is a risk factor for the development of pulmonary hemorrhage in preterm infants[1–3]; however, despite halving the incidence of PDA in the Trial of Indomethacin Prophylaxis in Preterms (TIPP), prophylactic indomethacin did not reduce the rate of pulmonary hemorrhage in this large sample of 1202 extremely low birth weight (ELBW) infants.[4] We hypothesized after the completion of the TIPP that the inclusion of mild cases of pulmonary hemorrhage may have masked a beneficial effect of prophylactic indomethacin. Mild hemorrhages were characterized prospectively as blood-tinged tracheal aspirates that did not require any change in therapy. Traumatic airway management[5] rather than high pulmonary blood flow as a result of a PDA[3] may

have been responsible for mild cases of pulmonary hemorrhage in the TIPP study population. In this exploratory and posthoc analysis, we excluded all mild cases to determine the effect of prophylactic indomethacin on the cumulative risk for serious pulmonary hemorrhage.

Infants with pulmonary hemorrhage are often very sick and may have worse short- and long-term outcomes than infants without pulmonary hemorrhage. Two retrospective, single-center studies previously reported higher mortality rates but no apparent increases in long-term morbidity after pulmonary hemorrhage in very low birth weight children.[6,7] Our second objective was to compare the outcomes at a corrected age of 18 months in infants with and without a serious pulmonary hemorrhage in this large and international data set.

METHODS

Study Population

Infants with birth weights of 500 to 999 g were enrolled in the TIPP between January 1996 and March 1998.[4] The research ethics boards of all 32 participating clinical centers (located in Canada, the United States, Australia, New Zealand, and Hong Kong) approved the trial protocol. Written informed consent was obtained from a parent or guardian of each infant. The primary goal of the TIPP was to determine whether prophylactic administration of indomethacin improves survival without neurosensory impairment in ELBW infants.[4] All 1202 TIPP participants were included in this study.

The details of the randomization and intervention have been reported.[4] Briefly, eligible infants were randomly assigned soon after birth to receive indomethacin, 0.1 mg/kg body weight (Indocid P.D.A.; Merck Frosst, Kirkland, Quebec, Canada, and Merck, West Point, PA), or an equivalent volume of normal saline. Three drug doses were given during a period of 48 hours. Each dose was infused intravenously during 20 minutes.

Pulmonary Hemorrhage

Pulmonary hemorrhage was a prespecified secondary outcome in the TIPP and diagnosed whenever a blood-tinged tracheal aspirate was obtained.[4] Information was also collected about the severity of the bleed. Mild hemorrhages required no changes in the treatment of the infants. Moderate hemorrhages were treated only with increased ventilator and/or oxygen support, whereas severe hemorrhages required the transfusion of blood products. Moderate and severe cases were analyzed together and described as serious pulmonary hemorrhages in this report. A total of 64 infants with mild pulmonary hemorrhage, 35 in the prophylactic indomethacin group and 29 in the placebo group, were classified as having no serious pulmonary hemorrhage in this study.

Patent Ductus Arteriosus

PDA was also a prespecified secondary outcome in the TIPP. PDA was diagnosed by echocardiography, which was requested only when there was a clinical suspicion of the condition. Because clinical signs are not sufficiently accurate, left-to-right shunting through the PDA had to be confirmed by echocardiography with Doppler flow studies before drug or surgical therapy to close the duct was undertaken.[8]

Outcomes at a Corrected Age of 18 Months

Death before a corrected age of 18 months or survival with neurosensory impairment was the primary outcome in the TIPP. Neurosensory impairment was the presence of $\geq$1 of the following: cerebral palsy, cognitive delay, hearing loss requiring amplification, and bilateral blindness.[4] All 18-month assessments were performed prospectively according to a standardized protocol. Cerebral palsy was diagnosed when the child had nonprogressive motor impairment characterized by abnormal muscle tone and decreased range or control of movements. Cognitive delay was defined as a mental development index score $<$70 on the Bayley Scales of Infant Development II.[9] The score was assumed to be $<$70 when the child could not be tested because of severe developmental delay. Audiometry was performed to determine the presence or absence of hearing loss. A central adjudication committee that was unaware of the group assignments reviewed the results of audiologic tests for all infants who had potential deafness and whose hearing had not been amplified. Blindness was defined as a corrected visual acuity of $<$20/200. Follow-up was targeted for a corrected age of 18 months, but the protocol allowed a window of 18 to 21 months (12–21 months for audiometry). Efforts to conduct assessments continued beyond a corrected age of 21 months to maximize ascertainment of the long-term outcome.

Statistical Analysis

Baseline differences between the subgroups of infants with and without a serious pulmonary hemorrhage were compared with a χ^2 test for categorical variables and a t test for quantitative data. The cumulative risk for serious pulmonary hemorrhage over time since randomization was estimated using the Kaplan-Meier procedure and compared between the prophylactic indomethacin and placebo groups with a Mantel-Haenszel log rank test.[10]

The effect of prophylactic indomethacin on the prevention of serious pulmonary hemorrhage was estimated from a Cox proportional hazard model.[10] Analyses were performed both unadjusted and with adjustment for the following important baseline factors: small for gestational age status,[11] gender, gestational age, and use of antenatal steroids. An additional analysis was conducted to determine to what extent this treatment effect could be explained via closure of the PDA. A time-dependent variable was created with an initial value of 0 that was switched to a value of 1 on and after the day of the first echocardiogram showing a left-to-right ductal shunt. The β coefficient associated with prophylactic indomethacin in a Cox model that contained both baseline factors and the time-dependent indicator variable

TABLE 1 **Baseline Characteristics**

Characteristic	With Pulmonary Hemorrhage ($n = 123$), *n* (%)	Without Pulmonary Hemorrhage ($n = 1079$), *n* (%)	*P*
Maternal education			
Junior only	38 (30.9)	312 (28.9)	<.0001
High school	26 (21.1)	312 (28.9)	
University	36 (29.3)	386 (35.8)	
Unknown[a]	23 (18.7)	69 (6.4)	
Antenatal steroids	91 (74.0)	873 (80.9)	.07
Gestational age, mean (SD), wk	25.2 (1.72)	26.0 (1.87)	<.0001
Males	74 (60.1)	541 (50.1)	.037
SGA[b]	20 (16.3)	226 (20.9)	.24
Multiple birth	43 (35.0)	276 (25.6)	.031
Surfactant use on day 1	105 (85.4)	730 (67.7)	<.0001

SGA indicates small for gestational age.

[a] Of the 23 infants with unknown maternal education in the group with pulmonary hemorrhage, 22 (96%) died before the first discharge home.

[b] SGA status was defined as birth weight <10th percentile for gestational age.[11]

for PDA represented that part of the indomethacin effect on serious pulmonary hemorrhage that could not be explained by an intermediary effect on PDA closure.

The composite outcome at a corrected age of 18 months and its components were dichotomous. The influence of serious pulmonary hemorrhage on 18-month outcomes was estimated using odds ratios and associated 95% confidence intervals. Logistic regression was used to adjust for the following prespecified baseline variables: level of maternal education, use of antenatal steroids, gestational age at birth, gender, and multiple births. All analyses were conducted with SAS software (SAS Institute, Cary NC).

RESULTS

Study Population

Of the 1202 infants who were enrolled in the TIPP, 123 (10.2%) developed a serious pulmonary hemorrhage. Infants with a pulmonary hemorrhage were less mature and more likely to be male, to be the product of a multiple birth, and to receive surfactant on day 1 than infants without pulmonary hemorrhage (Table 1).

Prophylactic Indomethacin and the Risk for Serious Pulmonary Hemorrhage

During the first week of life, prophylactic indomethacin significantly reduced the cumulative risk for serious pulmonary hemorrhage (Fig 1); however, the beneficial effect of prophylactic indomethacin weakened after the first few days of life. As a result, prophylactic indomethacin did not significantly reduce the cumulative risk for all serious pulmonary hemorrhages that occurred during the entire stay in the NICU (Fig 2).

PDA is an important risk factor for pulmonary hemorrhage. Prophylactic indomethacin halved the incidence of a symptomatic PDA in the TIPP study population (Fig 3); therefore, we examined whether a reduced risk for pulmonary hemorrhage after prophylactic indomethacin could be explained by its promotion of PDA closure. After adjustment for the use of antenatal steroids, gestational age, gender, and small for gestational age status, prophylactic indomethacin reduced the risk for all serious pulmonary hemorrhage by 26%. In con-

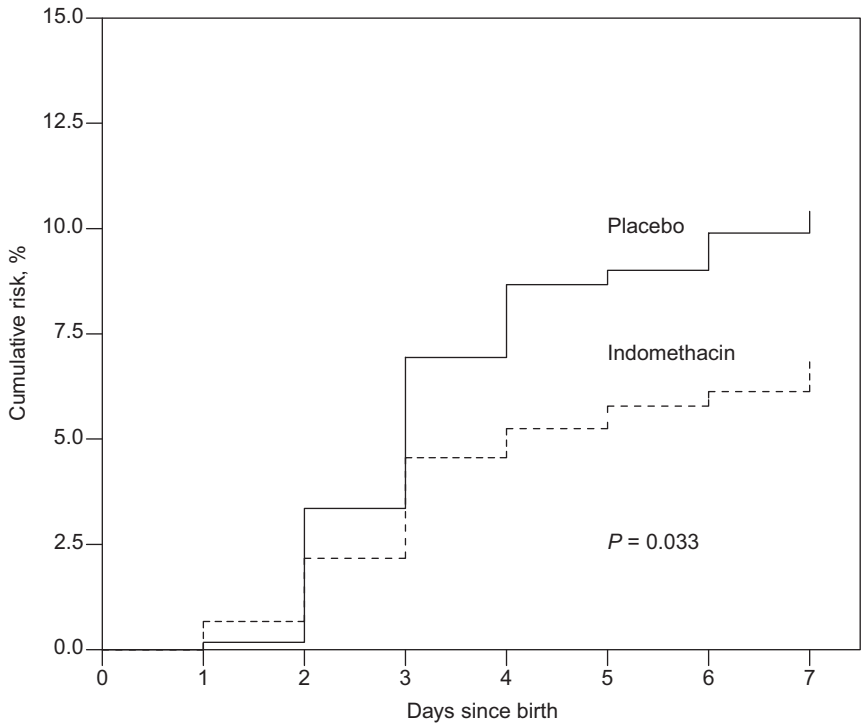

FIGURE 1
Kaplan-Meier estimates of the cumulative risk for serious pulmonary hemorrhage in prophylactic indomethacin and placebo groups during the first week of life.

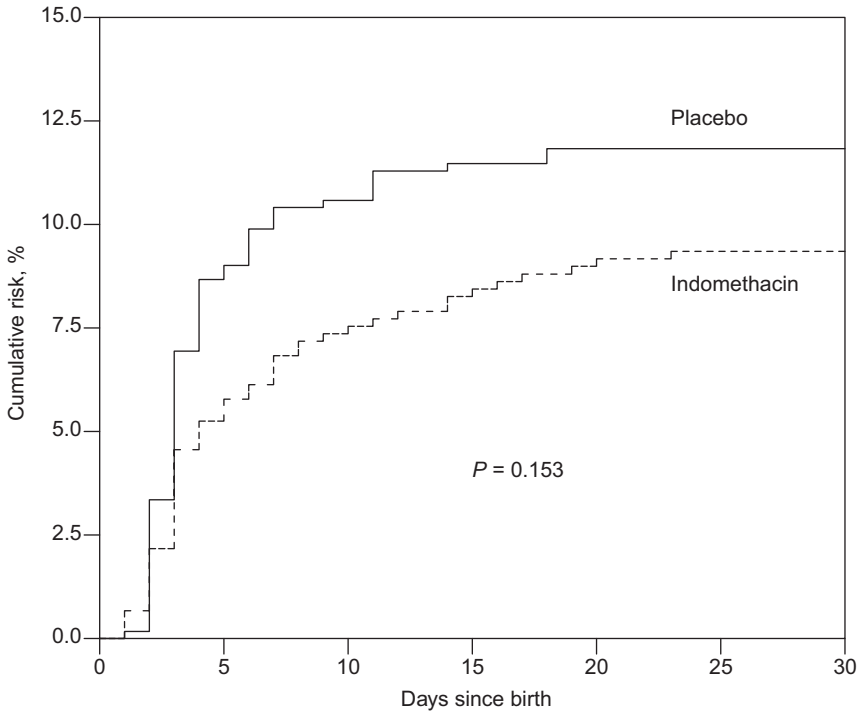

FIGURE 2
Kaplan-Meier estimates of the cumulative risk for serious pulmonary hemorrhage in prophylactic indomethacin and placebo groups during the entire NICU stay.

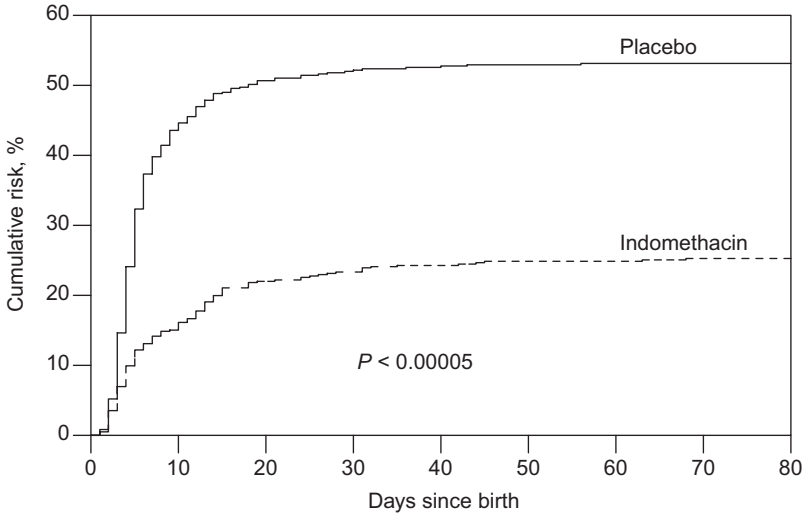

FIGURE 3
Kaplan-Meier estimates of the cumulative risk for PDA in the prophylactic indomethacin and placebo groups.

trast, after further addition of an indicator variable for the diagnosis of a PDA that preceded the pulmonary hemorrhage, the remaining risk reduction associated with prophylactic indomethacin was only 5.1% (Table 2). Prevention of PDA explained 80% of the observed risk reduction for pulmonary hemorrhage after prophylactic indomethacin.

TABLE 2 **Estimated Effect of Prophylactic Indomethacin on the Risk for Serious Pulmonary Hemorrhage**

Model	Risk Reduction, %	95% CI	*P*
Unadjusted	22.9	−10.1 to 46.0	.153
Adjusted model 1[a]	26.0	−5.8 to 48.2	.099
Adjusted model 2[b]	5.1	−37.2 to 34.4	.780

CI indicates confidence interval.
[a] Adjusted for antenatal steroids, gestational age, gender, and SGA.
[b] Adjusted for antenatal steroids, gestational age, gender, SGA, and previous PDA.

18-Month Outcomes After Serious Pulmonary Hemorrhage

Adequate data for the analysis of the 18-month composite outcome of death or neurosensory impairment were available for 122 (99%) of 123 infants with serious pulmonary hemorrhage and for 1021 (95%) of 1079 infants without hemorrhage. Table 3 shows that infants with serious pulmonary hemorrhage had a significantly increased risk for death or impairment in survivors. The risks for death, cerebral palsy, and cognitive delay all were increased after an episode of serious pulmonary hemorrhage (Table 3).

TABLE 3 **Outcomes at a Corrected Age of 18 Months in Infants With and Without Serious Neonatal Pulmonary Hemorrhage**

Outcome	Event Rate, *n/N* (%)		Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]	*P*[b]
	With Pulmonary Hemorrhage	Without Pulmonary Hemorrhage			
Composite: death or impairment(s)	92/122 (75.4)	440/1021 (43.1)	4.05 (2.6–6.22)	3.36 (2.15–5.24)	<.0001
Components					
Death before 18 mo	58/123 (47.2)	178/1066 (16.7)	4.45 (3.02–6.57)	3.62 (2.38–5.49)	<.0001
Cerebral palsy	17/64 (26.6)	96/880 (10.9)	2.95 (1.63–5.35)	2.86 (1.56–5.22)	.0006
Cognitive delay (MDI <70)	29/62 (46.7)	206/839 (24.6)	2.70 (1.60–4.56)	2.40 (1.46–4.13)	.0015
Blindness	3/64 (4.7)	13/873 (1.5)	3.25 (0.90–11.7)	2.92 (0.79–10.8)	.11
Deafness	2/63 (3.2)	18/859 (2.1)	1.53 (0.35–6.76)	1.56 (0.34–7.16)	.57

OR indicates odds ratio; MDI, mental development index.

[a] Adjusted for antenatal steroids, gestational age, gender, multiple birth, and mother's education.

[b] *P* values are for the adjusted ORs.

Outcomes at 18 months by randomized allocation of indomethacin prophylaxis or placebo were as follows: in the 2 subgroups of infants with serious pulmonary hemorrhage, the incidence of death or neurosensory impairment was 40 (76%) of 53 after prophylactic indomethacin and 52 (75%) of 69 after placebo. In the 2 subgroups of infants without serious pulmonary hemorrhage, the incidence of death or neurosensory impairment was 231 (44%) of 521 after prophylactic indomethacin and 209 (42%) of 500 after placebo.

DISCUSSION

This exploratory and posthoc analysis of the TIPP database showed that prophylactic indomethacin reduced the risk for serious pulmonary hemorrhage during the first week of life. Prophylactic indomethacin was less effective in preventing hemorrhages that occurred later during the NICU stay. A reduced risk for PDA explained 80% of the observed beneficial effect of prophylactic indomethacin on serious pulmonary bleeds. We also demonstrated, in this large international cohort of ELBW infants, that a serious pulmonary hemorrhage is associated with increased risks for both death and neurosensory impairments in survivors at a corrected age of 18 months.

It has been known for some time that a PDA is a risk factor for pulmonary hemorrhage in preterm infants.[1–3] Kluckow et al[3] performed a comprehensive and longitudinal echocardiographic study in very preterm infants and reported that pulmonary hemorrhage was associated with large ductal shunts and high estimates of pulmonary blood flow.

In this analysis, a reduced risk for PDA explained most of the favorable effect of prophylactic indomethacin on the prevention of serious pulmonary hemorrhage. This finding confirms the important role of PDA in the pathogenesis of pulmonary hemorrhage. Moreover, these data suggest that ductal closure is the most likely mechanism for the observed risk reduction of serious pulmonary bleeds after indomethacin prophylaxis; however, inability of indomethacin to cause tight constriction of the ductus in some extremely preterm infants may lead to later recurrence of PDA.[12] We speculate that such recurrence of large ductal shunts may explain why prophylactic indomethacin was less effective in preventing pulmonary hemorrhages that occurred after the first week of life.

Our data on mortality are consistent with the findings by 2 other groups of investigators who also reported an increased risk for death after a serious pulmonary hemorrhage in very low birth weight infants[6,7]; however, neither of the 2 previous single-center, retrospective studies reported an increased risk for neurosensory impairments among survivors.[6,7] In contrast, we have shown in this analysis that survivors of a serious pulmonary hemorrhage may face substantially increased risks for cerebral palsy and cognitive delay. This is not surprising because infants with serious pulmonary hemorrhage are more likely to acquire neonatal brain injury.[13] We suspect that lack of statistical power may account for the failure of previous studies to detect the increased long-term risks: in the TIPP, 64 survivors of a serious pulmonary hemorrhage were assessed at 18 months, compared with 24 survivors in the study by Tomaszewska et al[6] and 39 survivors in the report by Pandit et al.[7]

Although our data were collected prospectively, the limitations of this study include that all analyses were designed posthoc. Our results have generated new hypotheses, but they should not be accepted as conclusive evidence until they have been confirmed in future research studies. Importantly, the unadjusted reduction in the relative risk for serious pulmonary hemorrhage after prophylactic indomethacin was 23%, whereas our study had 80% power to detect a true relative risk reduction of only 40%.

Despite these caveats, we conclude that ELBW infants with serious pulmonary hemorrhage may have an increased risk for death or neurosensory impairment at a corrected age of 18 months. Indomethacin prophylaxis seems to reduce early serious hemorrhage, mainly through its action on PDA; however, indomethacin prophylaxis may be less effective in preventing serious pulmonary hemorrhages that occur after the first week of life.

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