Published in final edited form as:

Neonatology. 2018 ; 113(2): 183–186. doi:10.1159/000485172.

Effect of prophylactic indomethacin in extremely low birth weight infants based on predicted risk of severe intraventricular hemorrhage

Elizabeth E. Foglia, MD, MSCE¹, Robin S. Roberts, MSc², Jason Z. Stoller, MD¹, Peter G. Davis, MD³, Ross Haslam, AO, MBBS, FRACP⁴, Barbara Schmidt, MD, MSc^{1,2}, and Trial of Indomethacin Prophylaxis in Preterms Investigators

¹Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia PA

²Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada

³Department of Newborn Research, Royal Women's Hospital, Melbourne, Victoria, Australia

⁴Department of Newborn Medicine, Women's and Children's Hospital and University of Adelaide, Adelaide, SA, Australia

Abstract

Background: Prophylactic indomethacin reduces the risk of severe intraventricular hemorrhage (IVH) but does not reduce death or neurodevelopmental impairment (NDI) among extremely low birth weight (ELBW) infants. Some investigators have suggested that prophylactic indomethacin may have a greater treatment effect on severe IVH among infants at high risk for severe IVH.

Objective: To determine if the relative treatment effects of prophylactic indomethacin on severe IVH and the composite outcome of death or NDI vary based on risk of severe IVH.

Methods: Post-hoc analysis of the Trial of Indomethacin Prophylaxis in Preterms (TIPP). We generated a model to predict the risk for severe IVH based on gestational age, birth weight, antenatal steroids, delivery mode, outborn status, sex, and 5-minute Apgar score, and we divided TIPP participants into risk quartiles. We used logistic regression to determine the adjusted Odds Ratios (aOR) of severe IVH and death or NDI based on indomethacin treatment for each quartile.

Results: The relative treatment effects of prophylactic indomethacin on severe IVH did not vary based on predicted risk of severe IVH: Quartile 1: aOR 0.68 (95% Confidence Interval [CI] 0.19, 2.37); Quartile 2: aOR 0.61 (95% CI 0.27, 1.42); Quartile 3: aOR 0.63 (95% CI 0.31, 1.31); Quartile 4: aOR 0.58 (95% CI 0.32, 1.05). The relative treatment effect of prophylactic indomethacin on death or NDI did not vary significantly between quartiles.

Corresponding Author: Elizabeth E. Foglia, MD MSCE, Hospital of the University of Pennsylvania, 3400 Spruce Street, 8th Floor, Ravdin Building, Division of Neonatology, Philadelphia, PA 19104, USA, T (215) 662-3228, F (215) 349-8831, foglia@email.chop.edu.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Conclusions: These findings do not support selective prophylactic indomethacin treatment to improve long-term outcomes of ELBW infants at high risk for severe IVH.

Keywords

extremely low birth weight infant; brain injury; indomethacin; neurodevelopmental disability

Introduction

Severe brain injury is an important prognostic indicator of death or neurodevelopmental impairment (NDI) in extremely low birth weight (ELBW) infants. [1] In the Trial of Indomethacin Prophylaxis in Preterms (TIPP), prophylactic indomethacin reduced the risk of severe (grade III or IV) intraventricular hemorrhage (IVH) from 13% to 9% (adjusted Odds Ratio [aOR] 0.6, 95% Confidence Interval [CI] 0.4–0.9) but did not reduce the risk of the composite outcome death or NDI (aOR 1.1, 95% CI 0.8–1.4). [2]

Some investigators have suggested that prophylactic indomethacin may have a greater treatment effect on severe IVH among infants at high risk for severe IVH. [3–5] Using clinical characteristics that are available at or soon after birth, these authors developed predictive models for severe IVH that would allow for targeted prophylactic indomethacin therapy among high-risk infants. [3,4] We sought to determine if the relative treatment effects of prophylactic indomethacin on severe IVH or the composite outcome of death or NDI vary based on the baseline risk of severe IVH in ELBW infants.

Methods

This was a post-hoc analysis of the TIPP trial ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00009646) Identifier NCT00009646). [2] Briefly, in the TIPP study 1202 preterm infants with birth weight between 500 and 999 grams were randomly assigned to either prophylactic indomethacin or placebo treatment soon after birth, with a primary outcome of death or NDI at 18 months corrected age. We used Stata version 14.0 (Statacorp, College Station, TX) to develop a predictive model for severe IVH risk among control infants with IVH outcome ascertainment. The model included previously published covariates by Singh et al.: [3] gestational age, birth weight, antenatal steroids, delivery mode, outborn status, sex, and 5-minute Apgar score. These covariates were well balanced between the intervention and control arms of the parent TIPP trial. [2] We used the same covariates as Singh et al. but developed our own model for the present analysis because the model developed by Singh et al. included infants up to 34 weeks gestation, [3] who were more mature than the TIPP population. [2]

Using this model, we calculated the predicted risk of severe IVH for each TIPP participant, and we used these values to generate quartiles of predicted risk for severe IVH within the entire TIPP population. We sought to determine whether the treatment effect of prophylactic indomethacin on severe IVH varies based on baseline IVH risk using a logistic regression model with an interaction term (indomethacin treatment $\times$ predicted risk quartile), after adjustment for center and multiple gestation. A significant interaction term would indicate that the indomethacin treatment effect varies based on baseline risk of severe IVH. We used logistic regression to determine the aOR of severe IVH based on indomethacin treatment for

each predicted risk quartile, adjusting for center and multiple gestation. We repeated this analysis for the composite outcome of death or NDI, adjusting for center, multiple gestation, and maternal education.

We used the original TIPP definitions for all exposures and outcomes.[2] Results with $p < 0.05$ were considered statistically significant. TIPP was conducted with local Institutional Review Board approvals and parental informed consent for all enrolled infants.

Results

The predicted risk for severe IVH was calculated for 1196/1202 TIPP participants. The remaining six infants were excluded, due to missing 5-minute Apgar score. The numbers of infants in the Indomethacin and Placebo groups were similar across risk quartiles (Table 1).

In multivariable logistic regression, the adjusted interaction term for indomethacin and predicted IVH risk was not significant for the outcome of severe IVH ($p = 0.76$) or death or NDI ($p = 0.11$). The relative treatment effects of prophylactic indomethacin on the outcomes of severe IVH and death or NDI did not vary significantly based on baseline risk of severe IVH (Table 2, Figure).

Discussion

Although prophylactic indomethacin reduces the risk of severe IVH, it does not reduce the risk for death or NDI in extremely preterm infants.[6] Despite this, some investigators promote a targeted approach to indomethacin prophylaxis among infants at highest risk for severe IVH.[3–5] We undertook this analysis to determine if the relative treatment effects of prophylactic indomethacin vary based on the baseline risk of severe IVH for the following two outcomes: severe IVH and death or NDI. We found little evidence that the relative effects of prophylactic indomethacin therapy differ for either of these outcomes in ELBW infants based on predicted risk for severe IVH.

The adjusted odds ratios for severe IVH were similar for all four risk quartiles in this study. In addition, the adjusted interaction term was not statistically significant. These findings indicate that the relative treatment effect of prophylactic indomethacin on severe IVH does not vary based on the baseline risk of severe IVH.

However, the absolute treatment effects of prophylactic indomethacin on severe IVH are dependent on the baseline rate of severe IVH in a given population. Although no aOR for any quartile was statistically significant, our study results provide a useful illustration of this concept. As an example, the absolute risk reduction for severe IVH in the lowest risk quartile was 1.4%, which corresponds to a number needed to treat to prevent severe IVH of 71. In contrast, the baseline rate of severe IVH was much higher in the highest risk quartile. In this quartile, the absolute risk reduction was 8.9%, for a number needed to treat to prevent severe IVH of 11.

There were no significant differences in the rate of death or NDI between treatment groups for any risk quartile in our study. These results are consistent with previous findings that

prophylactic indomethacin does not improve neurodevelopmental outcomes for ELBW infants,[2,6] even among high-risk preterm infants.

We acknowledge that the TIPP trial was published in 2001, potentially limiting generalizability. In addition, we developed our predictive model for severe IVH using previously published covariates from a validated model, but our model was not validated in an external cohort. Last, the TIPP trial was not powered to detect a significant difference in NDI or death within quartiles of study participants.

Despite these limitations, the TIPP study population provides a unique opportunity to study the interaction between indomethacin treatment and predicted risk of severe IVH in ELBW infants. Because treatment with prophylactic indomethacin was randomly assigned and baseline characteristics were well balanced between treatment arms, our study avoids many biases inherent to observational studies investigating the impact of non-random indomethacin exposure in preterm infants.[3] In addition, the TIPP study assessed neurodevelopment at 18 months corrected age, providing the ability to investigate the impact of targeted indomethacin prophylaxis on important long-term outcomes in the highest risk infants.

In summary, the relative effects of prophylactic indomethacin on severe IVH or the composite outcome of death or NDI do not vary based on baseline predicted risk for severe IVH. These findings do not support selective prophylactic indomethacin treatment to improve long-term outcomes in ELBW infants at high risk for severe IVH.

Acknowledgments

Funding

This study was supported by a grant from the Medical Research Council of Canada (MT-13288) and a NICHD Career Development Award (K23HD084727 to EEF)

References

1. Schmidt B, Asztalos EV, Roberts RS, Robertson CMT, Suave RS, Whitfield MF; Trial of Indomethacin Prophylaxis in Preterms (TIPP) Investigators. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. *JAMA* 2003; 289:1124–9. [PubMed: 12622582]
2. Schmidt B, Davis P, Moddemann D Ohlsson A, Roberts RS, Saigal S, Solimano A, Vincer M, Wright LL; Trial of Indomethacin Prophylaxis in Preterms Investigators. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *N Engl J Med* 2001; 344:1966–72. [PubMed: 11430325]
3. Singh R, Gorstein SV, Bednarek F, Chou JH, McGowan EC, Visintainer PF. A predictive model for SIVH risk in preterm infants and targeted indomethacin therapy for prevention. *Sci Rep* 2013; 3:2539. [PubMed: 23995978]
4. Luque MJ, Tapia JL, Villarroel L, Marshall G, Musante G, Carlo W, Kattan J, Neocosur Neonatal Network. A risk prediction model for severe intraventricular hemorrhage in very low birth weight infants and the effect of prophylactic indomethacin. *J Perinatol* 2014; 34:43–8. [PubMed: 24113396]

5. Lea CL, Smith-Collins A, Luyt K. Protecting the premature brain: current evidence-based strategies for minimising perinatal brain injury in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2017; 102:F176–82. [PubMed: 28011793]
6. Fowle PW, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. *Cochrane Database Syst Rev* 2010; (7):CD000174.

Figure.

Panel A: Adjusted Odds Ratio and 95% Confidence Interval (CI) for indomethacin treatment on severe intraventricular hemorrhage (IVH), adjusted for center and multiple gestation.

Panel B: Adjusted Odds Ratio and 95% Confidence Interval (CI) for indomethacin treatment on death or neurodevelopmental impairment (NDI), adjusted for center, multiple gestation, and maternal education.

Table 1:

Quartiles of predicted risk for severe intraventricular hemorrhage, based on treatment allocation. Predicted risk of severe IVH was calculated according to the following covariates: gestational age, birth weight, antenatal steroids, delivery mode, outborn status, sex, and 5-minute Apgar score

Predicted risk quartile	Mean predicted risk	Indomethacin group (n=599)	Placebo group (n=597)
1	5.4%	138 (23%)	161 (27%)
2	8.5%	161 (27%)	138 (23%)
3	13.0%	150 (25%)	149 (25%)
4	29.1%	150 (25%)	149 (25%)

Table 2:

Incidence, adjusted odds ratios (aOR), and 95% confidence intervals (95% CI) for severe intraventricular hemorrhage and death or neurodevelopmental impairment based on treatment allocation for each risk quartile

Risk Quartile	Severe Intraventricular Hemorrhage			Death or Neurodevelopmental Impairment		
	Indomethacin	Placebo	aOR 95% CI	Indomethacin	Placebo	aOR 95% CI
1	4/132 (3.0%)	7/158 (4.4%)	0.68 (0.19, 2.37)	44/129 (34.1%)	41/150 (27.3%)	1.38 (0.81, 2.33)
2	11/157 (7.0%)	14/133 (10.5%)	0.61 (0.27, 1.42)	67/153 (43.8%)	44/130 (33.8%)	1.64 (0.98, 2.77)
3	14/143 (9.8%)	20/140 (14.3%)	0.63 (0.31, 1.31)	69/144 (47.9%)	81/141 (57.4%)	0.67 (0.41, 1.10)
4	23/136 (16.9%)	34/132 (25.8%)	0.58 (0.32, 1.05)	90/146 (61.6%)	93/144 (64.6%)	0.96 (0.58, 1.59)