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Effects of prophylactic indomethacin in extremely low birth weight infants with and without adequate exposure to antenatal steroids

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Abstract

Objective—To examine if antenatal steroids modify the immediate and long-term effects of prophylactic indomethacin in extremely low birth weight infants.

Design—Post-hoc subgroup analysis of data from the Trial of Indomethacin Prophylaxis in Preterms.

Setting—Thirty-two neonatal intensive care units in Canada, the United States, Australia, New Zealand, and Hong Kong.

Participants—A total of 1195 infants with birth weights of 500 to 999 g and known exposure to antenatal steroids. We defined as "adequate" any exposure to antenatal steroids that occurred at least 24 hours before delivery.

Intervention—Indomethacin or placebo intravenously once daily for the first three days.

Outcome Measures—Death or survival to 18 months with 1 or more of cerebral palsy, cognitive delay, severe hearing loss, and bilateral blindness; severe peri-and intraventricular hemorrhage; patent ductus arteriosus; and surgical closure of a patent ductus arteriosus.

Results—Of the 1195 infants in this analysis cohort, 670 had adequate and 525 had inadequate exposure to antenatal steroids. There was little statistical evidence of heterogeneity in the effects of prophylactic indomethacin between the subgroups for any of the outcomes. The adjusted p values for interaction were as low as 0.15 for the end point of death or impairment at 18 months, and as high as 0.80 for the outcome of surgical duct closure.

Conclusion—There was little evidence that the effects of prophylactic indomethacin vary in extremely low birth weight infants with and without adequate exposure to antenatal steroids.

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

Although indomethacin prophylaxis reduces the risks of severe periventricular and intraventricular hemorrhages (grades 3 and 4 PIVH), patent ductus arteriosus (PDA) and the use of surgery to close a PDA in extremely low birth weight (ELBW) infants, this therapy has not been shown to improve the longer-term outcome of death or disability at 18 months.[1,2] Antenatal corticosteroids given to women with threatened preterm birth also reduce the risk of PIVH.[3,4] We hypothesized that ELBW infants without adequate exposure to antenatal steroids benefit more from indomethacin prophylaxis than infants who had adequate exposure to antenatal steroids. We tested this hypothesis in a post-hoc subgroup analysis of the Trial of Indomethacin Prophylaxis in Preterms (TIPP) data set.

METHODS

STUDY PARTICIPANTS

Infants with birth weights of 500 to 999 g were enrolled in the TIPP between 1996 and 1998 and followed to a corrected age of 18 months.[1] The research ethics boards of all 32 participating clinical centers (located in Canada, the United States, Australia, New Zealand, and Honk Kong) approved the trial protocol, and written informed consent was obtained from a parent or guardian of each infant. The details of the randomization to indomethacin or placebo and the administration of the study drug doses have been previously reported.[1] The primary goal of the TIPP was to determine whether prophylactic indomethacin improves survival without neurodevelopmental impairment in ELBW infants.

ANTENATAL STEROID EXPOSURE

The TIPP Case Report Form recorded the use of antenatal steroids as one of the following 4 mutually exclusive regimens: 1) No antenatal steroids, 2) antenatal steroids < 24 hours before delivery, 3) antenatal steroids between 24 hours and 7 days before delivery, 4) antenatal steroids > 7 days before delivery. For the present analysis we compared subgroups of study subjects with and without adequate exposure to antenatal steroids where “adequate” was defined as any exposure to antenatal steroids that occurred at least 24 hours before delivery. In a secondary analysis, an additional comparison was performed after the cohort was divided further into subgroups of the 4 mutually exclusive regimens of antenatal steroid exposure.

OUTCOME MEASURES

To limit the possibility of type I errors only the following outcomes were examined for heterogeneity of the indomethacin prophylaxis effect: The primary composite TIPP outcome at 18 months of death or neurodevelopmental impairment; the 5 components of this composite outcome: death, cerebral palsy, cognitive delay, deafness, and blindness; and the secondary TIPP outcomes that showed significant treatment effects in the overall trial: PDA, surgical closure of a PDA and severe (grades 3 and 4) PIVH.[1]

Cerebral palsy was diagnosed if the child had non-progressive motor impairment characterized by abnormal muscle tone and decreased range or control of movements. Cognitive delay was defined as a Mental Development Index score below 70 on the Bayley Scales of Infant Development II. The score was assumed to be less than 70 if the child could not be tested due to 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 with potential deafness whose hearing had not been amplified. Blindness was defined as a corrected visual acuity of less than 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 to 21 months for audiometry).

PDA was a pre-specified secondary outcome in the TIPP. PDA was diagnosed by echocardiography, which was requested only when there was a clinical suspicion of the condition. 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.

Cranial ultrasonography was recommended between the 5th and 8th days of life, between the 21st and 28th days and between 34 and 36 weeks of postmenstrual age if the infant was still in the study center at that time. The scans were read locally, and copies of the written reports were sent to the coordinating center. Peri-and intraventricular hemorrhages of grade 3 and 4 were considered severe.

STATISTICAL ANALYSIS

The statistical significance of the observed difference in the size of the treatment effect (odds ratio) between subgroups was determined via a test of treatment by subgroup interaction in a logistic regression model. The models also included adjustment for center and birth weight stratum as for the original TIPP analyses. Additional adjusted analyses were performed with the following prognostically important baseline variables: Gestational age, sex, multiple births, and mother's education. A significant p-value for a test of treatment by subgroup interaction would indicate that the effect of prophylactic indomethacin is different for infants with and without adequate antenatal steroid exposure.

The present subgroup analysis is posthoc and was not considered when we performed our power calculations during the design phase of this trial. The sample size for the original TIPP had been preset at 600 patients per treatment group. This size of study would have yielded >80% power to detect a 25% proportional treatment effect (alpha=0.05, two-sided) for a control group event rate of at least 30%.

RESULTS

STUDY PARTICIPANTS

Of the 1202 TIPP participants, 525 had inadequate exposure to antenatal steroids: 231 infants had no antenatal steroid exposure and the mothers of 294 infants received steroids less than 24 hours before delivery. A total of 670 infants had adequate exposure to antenatal steroids: 500 infants were exposed between 24 hours and 7 days before delivery, and the mothers of 170 infants received steroids more than 7 days before delivery. Data concerning the use of antenatal steroids were missing for seven infants. A total of 1136 children in this analysis cohort had complete data for the composite outcome of death or neurodevelopmental impairment at a corrected age of 18 months. The baseline characteristics before enrollment in the TIPP of these 1136 infants and of their mothers in the two subgroups with and without adequate use of antenatal steroids are shown in table 1.

OUTCOME EVENT RATES IN THE 4 SUBGROUPS

Outcome event rates in the 4 subgroups are shown in table 2. There was little statistical evidence of heterogeneity in the effects of prophylactic indomethacin between subgroups for any of the outcomes assessed in either the unadjusted or adjusted analyses (table 2). Importantly, the observed risk of severe PIVH was twice as high in infants with inadequate antenatal steroid exposure compared with adequately exposed TIPP study participants (table 2). Similarly, there was little evidence of variable beneficial effects of prophylactic indomethacin on the outcomes of death or disability, death, severe IVH, PDA and PDA ligation after the study cohort was divided into further subgroups according to the presence or absence as well as the timing of antenatal steroid use. Both the unadjusted analyses and

all analyses that were adjusted for center and birth weight stratum yielded non-significant interaction p values (data not shown).

COMMENT

The international Trial of Indomethacin Prophylaxis in Preterms is the single-largest trial of this intervention in very preterm infants, and the only trial to date with a long-term primary outcome of death or neurodevelopmental impairment in survivors.[1,2] However, almost a decade after the publication of the main results of the TIPP, neonatal practitioners remain divided into proponents and opponents of indomethacin prophylaxis for extremely preterm infants.[5] Those who prescribe prophylactic indomethacin can claim to practice “evidence based neonatology” because this therapy has been shown to reduce the rates of severe PIVH, PDA and PDA ligation.[1,2] Those who do not prescribe prophylactic indomethacin can also claim that their practice is “evidence-based” because this therapy does not increase survival or reduce disability in the longer term[1,2] and it is not cost-effective.[6] In addition, the long-standing conviction that early pharmacologic closure of a PDA is a desirable outcome has recently been questioned.[7,8] Lastly, alternative strategies are available to reduce the incidence of PIVH. They include the routine use of antenatal steroids and better regionalization of neonatal intensive care.[3,4,9]

In the absence of adequate antenatal steroid treatment, and thus in a preterm baby at heightened risk of PIVH, one might expect an added benefit of prophylactic indomethacin. However, in the present analysis we found no statistically significant heterogeneity for either the neonatal outcomes or longer-term effects of prophylactic indomethacin by antenatal steroid exposure. This is in contrast to the previously documented weak differential effect of prophylactic indomethacin by sex.[10,11] When interpreting either of these posthoc subgroup analyses, readers should be mindful of the strengths but also of the pitfalls of subgroup analyses. [12]

The TIPP has been criticized for having had insufficient statistical power to detect a small but clinically important beneficial effect of indomethacin prophylaxis on outcomes at 18 months.[5] It is important to stress that the converse is equally true: The TIPP had insufficient statistical power to rule out a small but clinically important harmful effect of indomethacin prophylaxis on outcomes at 18 months, in the study overall, and in particular, in the present subgroup analysis by antenatal steroid exposure. Clinicians who care for ELBW infants with adequate exposure to antenatal steroids may find it unsettling that the primary outcome of death or disability appeared to occur more often after prophylactic indomethacin than after placebo in the present analysis.

With these caveats, we conclude that there is little evidence that the effects of prophylactic indomethacin vary in ELBW infants with and without adequate exposure to antenatal steroids.

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Barbara Schmidt and Robin Roberts have had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Abbreviations

ELBW	Extremely low birth weight
PIVH	Peri/intraventricular hemorrhage
PDA	Patent ductus arteriosus
TIPP	Trial of Indomethacin Prophylaxis in Preterms

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Appendix

The TIPP Investigators include the following individuals:

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Table 1

Baseline characteristics of the study population by subgroup

Baseline characteristics	Antenatal steroids†	
	Adequate (n=635)	Inadequate (n=501)
Mothers		
Age (years) – mean (SD) ‡	29.0 (6.8)	28.7 (7.1)
Ethnicity – no. (%)		
Caucasian	462 (73.0)	318 (64.6)
Black	73 (11.5)	80 (16.3)
Asian	35 (5.5)	32 (6.5)
Other	63 (10.0)	62 (12.6)
Education – no. (%)		
Junior high school only	183 (28.8)	149 (29.7)
Completed high school	175 (27.6)	141 (28.1)
Some college or university	245 (38.6)	157 (31.3)
Unknown	32 (5.0)	54 (10.8)
Single parent – no. (%)	158 (24.9)	139 (27.7)
Preeclampsia or eclampsia – no. (%)	112 (17.6)	64 (12.8)
Tocolysis – no. (%)	142 (22.4)	70 (14.0)
C-section – no. (%)	358 (56.4)	226 (45.1)
Infants		
Birth weight (g) – mean (SD) ‡	785 (131)	773 (130)
Gestational age (wks) – means (SD) ‡	26.1 (1.9)	25.7 (1.8)
Female – no. (%)	319 (50.2)	237 (47.3)
Birth weight <10th percentile – no. (%)	151 (23.8)	86 (17.2)
Inborn – no. (%)	632 (99.5)	464 (92.6)
Singleton – no. (%)	463 (72.9)	372 (74.3)
Apgar score at 5 min – median (IQR) §	8 (7–9)	7 (6–8)
Surfactant – no. (%)	446 (70.2)	419 (83.6)
Surfactant on day 1 – no. (%)	404 (63.6)	386 (77.0)

† Includes 1136 infants with known antenatal steroid use and known primary outcome at 18 months.

‡ SD, standard deviation.

§ IQR, interquartile range.

Table 2

Outcomes at 18 months, severe periventricular or intraventricular hemorrhage, PDA and surgical closure of PDA by exposure to antenatal steroids

Outcome	Antenatal steroids	Indomethacin n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)†	P value for interaction		
					Unadjusted	Adjusted for center/BW‡	Adjusted for other factors§
Death or impairment	Adequate	145/319 (45.5)	127/316 (40.2)	1.24 (0.90, 1.70)	0.13	0.10	0.15
	Inadequate	123/250 (49.2)	133/251 (53.0)	0.86 (0.61, 1.22)			
Death	Adequate	60/332 (18.1)	45/331 (13.6)	1.40 (0.92, 2.14)	0.22	0.28	0.16
	Inadequate	64/258 (24.8)	66/261 (25.3)	0.97 (0.66, 1.45)			
Cerebral palsy	Adequate	37/270 (13.7)	31/281 (11.0)	1.28 (0.77, 2.13)	0.23	0.23¶	0.27
	Inadequate	19/193 (9.8)	24/194 (12.4)	0.77 (0.41, 1.46)			
Cognitive delay	Adequate	68/257 (26.5)	62/269 (23.0)	1.20 (0.81, 1.78)	0.34	0.25	0.26
	Inadequate	49/183 (26.8)	54/186 (29.0)	0.89 (0.57, 1.41)			
Deafness	Adequate	7/264 (2.7)	5/276 (1.8)	1.48 (0.46, 4.72)	0.34	0.34¶	0.72
	Inadequate	3/188 (1.6)	5/188 (2.7)	0.59 (0.14, 2.52)			
Blindness	Adequate	4/268 (1.5)	5/277 (1.8)	0.82 (0.22, 3.11)	0.30	0.29¶	0.53
	Inadequate	5/193 (2.6)	2/193 (1.0)	2.54 (0.49, 13.3)			
Severe P/IVH	Adequate	21/321 (6.5)	28/322 (8.7)	0.73 (0.41, 1.32)	0.62	0.63	0.53
	Inadequate	31/245 (12.7)	47/243 (19.3)	0.60 (0.37, 0.99)			
Patent ductus arteriosus (PDA)	Adequate	72/335 (21.5)	157/335 (46.9)	0.31 (0.22, 0.43)	0.89	0.99	0.78
	Inadequate	69/261 (26.4)	144/264 (54.5)	0.30 (0.21, 0.43)			
Surgical closure of PDA	Adequate	21/335 (6.3)	40/335 (11.9)	0.49 (0.28, 0.86)	0.97	0.94¶	0.80
	Inadequate	18/261 (6.9)	34/264 (12.9)	0.50 (0.28, 0.91)			

†CI, Confidence interval.

‡BW, Birth weight stratum.

§In addition, adjusted for gestational age, gender, multiple births and mother's education.

¶Adjusted for birth weight stratum only.