LONG-TERM EFFECTS OF INDOMETHACIN PROPHYLAXIS IN EXTREMELY-LOW-BIRTH-WEIGHT INFANTS

Barbara Schmidt, M.D., Peter Davis, M.D., Diane Moddemann, M.D., Arne Ohlsson, M.D., Robin S. Roberts, M.Sc., Saroj Saigal, M.D., Alfonso Solimano, M.D., Michael Vincer, M.D., and Linda L. Wright, M.D., for the Trial of Indomethacin Prophylaxis in Preterms Investigators*

ABSTRACT

Background   The prophylactic administration of indomethacin reduces the frequency of patent ductus arteriosus and severe intraventricular hemorrhage in very-low-birth-weight infants (those with birth weights below 1500 g). Whether prophylaxis with indomethacin confers any long-term benefits that outweigh the risks of drug-induced reductions in renal, intestinal, and cerebral blood flow is not known.

Methods   Soon after they were born, we randomly assigned 1202 infants with birth weights of 500 to 999 g (extremely low birth weight) to receive either indomethacin (0.1 mg per kilogram of body weight) or placebo intravenously once daily for three days. The primary outcome was a composite of death, cerebral palsy, cognitive delay, deafness, and blindness at a corrected age of 18 months. Secondary long-term outcomes were hydrocephalus necessitating the placement of a shunt, seizure disorder, and microcephaly within the same time frame. Secondary short-term outcomes were patent ductus arteriosus, pulmonary hemorrhage, chronic lung disease, ultrasonographic evidence of intracranial abnormalities, necrotizing enterocolitis, and retinopathy.

Results   Of the 574 infants with data on the primary outcome who were assigned to prophylaxis with indomethacin, 271 (47 percent) died or survived with impairments, as compared with 261 of the 569 infants (46 percent) assigned to placebo (odds ratio, 1.1; 95 percent confidence interval, 0.8 to 1.4; P=0.61). Indomethacin reduced the incidence of patent ductus arteriosus (24 percent, vs. 50 percent in the placebo group; odds ratio, 0.3; P<0.001) and of severe periventricular and intraventricular hemorrhage (9 percent, vs. 13 percent in the placebo group; odds ratio, 0.6; P=0.02). No other outcomes were altered by the prophylactic administration of indomethacin.

Conclusions   In extremely-low-birth-weight infants, prophylaxis with indomethacin does not improve the rate of survival without neurosensory impairment at 18 months, despite the fact that it reduces the frequency of patent ductus arteriosus and severe periventricular and intraventricular hemorrhage. (N Engl J Med 2001;344:1966-72.)

THE prophylactic administration of indomethacin reduces the incidence of patent ductus arteriosus and severe intraventricular hemorrhage in very-low-birth-weight infants (those with birth weights below 1500 g).[1] Our current understanding of the mechanisms by which indomethacin prevents intraventricular hemorrhage is speculative[2] and indicates that a decrease in cerebral perfusion may be involved.[3,4] Although such a decrease may provide protection against intraventricular hemorrhage,[4] it may also increase the risk of brain ischemia.[3] Knowledge about the effects of indomethacin prophylaxis on neurologic development is therefore crucial, but few data are available on its longer-term motor, sensory, and cognitive effects.[1]

We undertook this study to determine whether the prophylactic administration of indomethacin improves survival without neurosensory impairment in extremely-low-birth-weight infants (those with birth weights below 1000 g). A secondary goal was to obtain additional information about the effects of indomethacin on the incidence of patent ductus arteriosus, pulmonary hemorrhage, chronic lung disease, necrotizing enterocolitis, intracranial abnormalities, and retinopathy.

METHODS

Study Infants

Infants with birth weights ranging from 500 to 999 g were considered for enrollment when they were two hours old. The criteria for exclusion are listed in Figure 1. A history, a physical examination, and a platelet count were the only screening tests prescribed by the protocol. The research-ethics boards of all 32 participating clinical centers approved the protocol, and written informed consent was obtained from a parent or guardian of each infant. Investigational-new-drug applications were filed with Health Canada and the U.S. Food and Drug Administration because indomethacin is not approved for prophylactic administration in preterm infants in either country. Clinical-trial-notification applications were filed in Australia. The recruitment of infants began at different
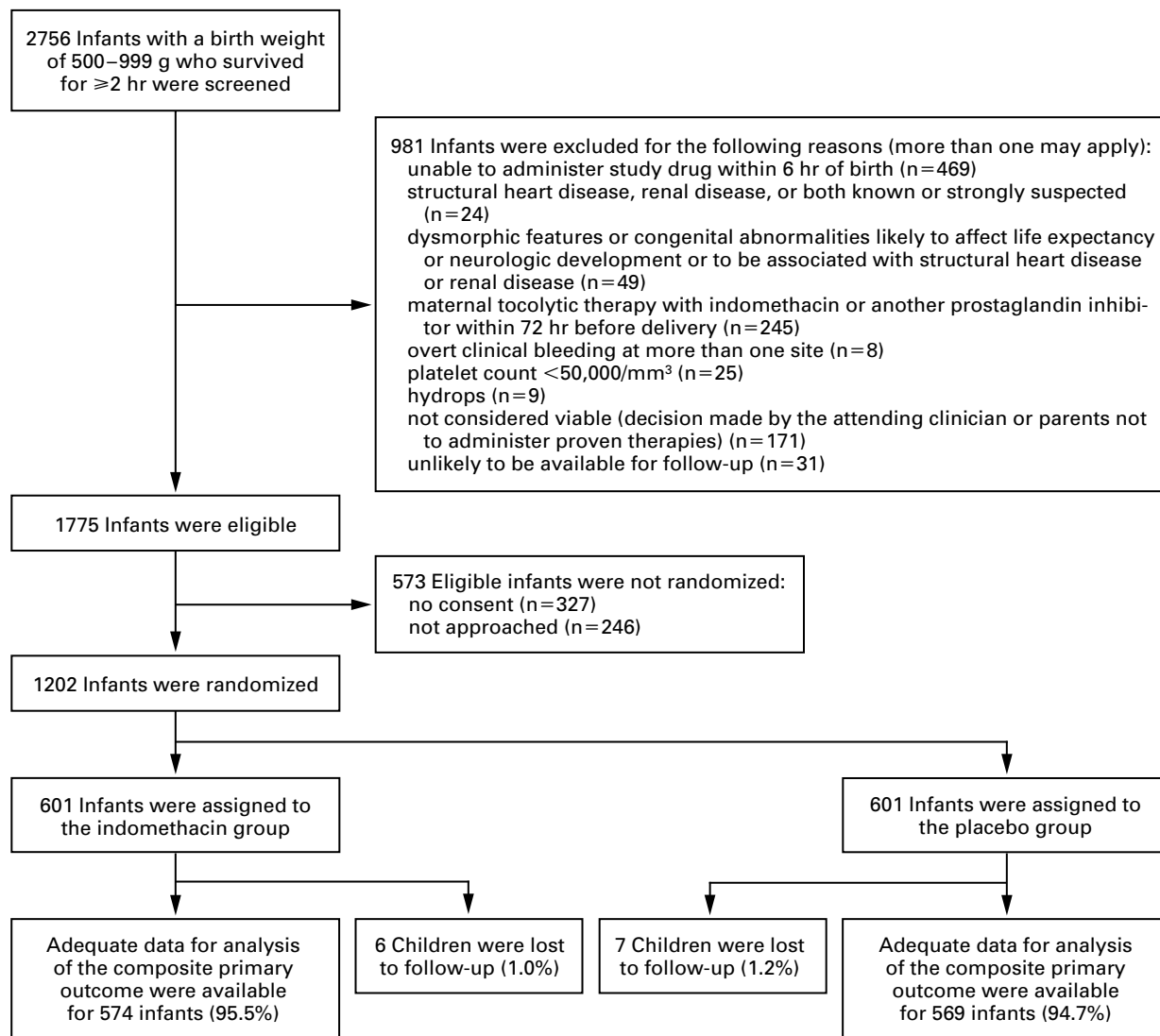
Figure 1. Numbers of Infants Who Were Screened and Randomly Assigned to the Indomethacin and Placebo Groups, and Numbers for Whom Follow-up Data Were Available.

times in different centers, between January 1996 and October 1997. Enrollment was completed in March 1998.

Randomization

A computer-generated randomization scheme was used to assign the infants (in random blocks of two or four) to treatment groups in a 1:1 ratio. Randomization was stratified according to birth weight (500 to 749 g vs. 750 to 999 g) and according to study center. Each study pharmacist received a binder containing the sequence of treatment-group assignments for each birth-weight stratum from a statistician at the coordinating center who was not otherwise involved in the trial. At each study center, access to the binder was restricted to selected pharmacy personnel.

Intervention

The infants received either indomethacin, 0.1 mg per kilogram of body weight (Indocid P.D.A., Merck Frosst, Kirkland, Que.,

Canada, and Merck, West Point, Pa.), or an equivalent volume of normal saline. Three doses were given at 24-hour intervals. Each dose was infused intravenously over a period of 20 minutes. Since even a small volume of reconstituted indomethacin has a slightly yellow tinge, all syringes were partially masked with yellow tape.

Primary Outcome

The primary outcome was death before a corrected age of 18 months or documentation in survivors of one or more of the following: cerebral palsy, cognitive delay, hearing loss requiring amplification, and bilateral blindness. Cerebral palsy was diagnosed if the child had nonprogressive motor impairment characterized by abnormal muscle tone and a decreased range or control of movements. Cognitive delay was defined as a Mental Development Index score of less than 70 (2 SD below the mean of 100) on the Bayley Scales of Infant Development II.[5] A score between 85 and 114 is classified as normal, and scores lower than 70 suggest that cog-

nitive development is markedly delayed.[5] The score was assumed to be less than 70 if 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 with potential deafness whose hearing had not been amplified. Blindness was defined as a corrected visual acuity of less than 20/200. A follow-up evaluation 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 audiologic testing). Efforts to conduct assessments continued beyond a corrected age of 21 months in an attempt to ensure the completeness of the results. Home visits or assessments in facilities not participating in the study were permitted when necessary.

Documentation of the composite primary outcome required confirmation that the infant had died or had survived with any one of the four types of impairment, and documentation of the absence of the primary outcome required confirmation that the infant had survived without any impairment. Since a single missing component of the follow-up assessment would result in a designation of "missing" for the primary outcome, the steering committee developed detailed a priori criteria to determine what constituted adequate evidence of the presence or absence of each component of the primary outcome. These criteria required an in-person assessment by an appropriate health professional and the completion of the psychometric assessment during or after the permissible time window. In cases in which it was difficult to obtain audiometric test results, deafness requiring amplification of hearing was assumed to be absent if there was no indication of hearing loss during the clinical examination and the Bayley test. This assumption was made in the cases of 27 children.

Secondary Outcomes

Hydrocephalus necessitating the placement of a shunt, seizure disorder, and microcephaly (a head circumference below the 3rd percentile for a reference population of normal children[6]) were secondary long-term outcomes. While the infants were hospitalized in the neonatal intensive care unit, various short-term outcomes were assessed. Patent ductus arteriosus was diagnosed by echocardiography and Doppler flow studies, which were requested only when there was a clinical suspicion of the condition. Left-to-right ductal shunting had to be confirmed by echocardiography with Doppler flow before drug or surgical therapy to close the duct was undertaken.[7] Pulmonary hemorrhage was diagnosed if a blood-tinged tracheal aspirate was obtained. Chronic lung disease was defined by the need for supplemental oxygen at 36 weeks of postmenstrual age.[8]

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 hospitalized in the study center at that time. The scans were read locally, and copies of the written reports were sent to the coordinating center. Hemorrhages were analyzed separately so that we could compare our results with those of previous investigators. Hemorrhages of grade 3 or 4 were considered severe.[9] Several types of lesions were considered as a group because they all indicate probable damage to the cerebral white matter[10]; these included echodense intraparenchymal lesions, periventricular leukomalacia, porencephalic cysts, and ventriculomegaly with or without intraventricular hemorrhage. Necrotizing enterocolitis was diagnosed during surgery, at autopsy, or by a finding of pneumatosis intestinalis, hepatobiliary gas, or free intraperitoneal air on radiography. Retinopathy was diagnosed according to the international classification.[11,12]

Statistical Analysis

All primary and secondary outcomes were dichotomous. Since randomization was stratified according to birth weight and study center, the analyses of outcomes were adjusted for these two factors with the use of a logistic-regression model[13] that included terms for treatment, birth-weight stratum, center (smaller centers were combined), and interactions between birth weight and center when appropriate. The regression coefficient associated with treatment in the fitted model yielded a point estimate and confidence interval for the treatment effect expressed as an odds ratio. The quotient of the estimated coefficient and its standard error was used as a z-test statistic for the null hypothesis of no treatment effect. Cumulative mortality was estimated with the Kaplan–Meier[13] method. All P values are two-sided and have not been adjusted for multiple testing.

An external safety monitoring committee reviewed the study data every four to six months during the enrollment phase. With the exception of this monitoring committee and the local study pharmacists, no one involved in the study or in the care and follow-up of the infants was aware of the treatment-group assignments.

RESULTS

Study Infants and Intervention

The numbers of infants who were eligible for the study, the numbers assigned to receive indomethacin or placebo, and the numbers for whom follow-up data were available are shown in Figure 1. A total of 1202 infants were enrolled — 505 in Canada; 384 in Australia, New Zealand, and Hong Kong; and 313 in the United States. The base-line characteristics of the infants in the two groups and of their mothers were similar (Table 1). A total of 92 percent of the infants were given at least two doses of either indomethacin or placebo, and the infants in each group received an identical mean (±SD) total dose of study drug that was equivalent to 0.27 ± 0.07 mg of indomethacin per kilogram. The number of doses received, the reasons for withholding one or more doses, and the age of the infants at the time the first dose was administered are shown in Table 2.

Primary Outcome at a Corrected Age of 18 Months

Adequate data for an analysis of the composite primary outcome were available for 1143 of the infants who were enrolled in the study (95 percent). Indomethacin prophylaxis did not improve the rate of survival without neurosensory impairment (Table 3). Adjustments for prespecified and prognostically important base-line characteristics (presence or absence of antenatal administration of glucocorticoids, mother's educational level, infant's gestational age, and presence or absence of a multiple birth) yielded the same odds ratio. There was also little evidence that indomethacin prophylaxis altered the rates of any of the individual components of the primary outcome (Fig. 2 and Table 3). The mean (±SD) Mental Development Index score was 83 ± 18 in the indomethacin group and 84 ± 18 in the placebo group. The median age at follow-up was 18.5 months (interquartile range, 18.1 to 19.5) in the indomethacin group and 18.4 months (18.1 to 19.3) in the placebo group.

A single predefined subgroup analysis showed a consistent lack of an effect of indomethacin treatment in each birth-weight stratum. A total of 152 of the 240 infants in the indomethacin group with birth weights between 500 and 749 g (63 percent) died

TABLE 1. BASE-LINE CHARACTERISTICS OF THE INFANTS AND THEIR MOTHERS.*

CHARACTERISTIC	INDOMETHACIN GROUP (N=601)	PLACEBO GROUP (N=601)
Mothers		
Age — yr	29±7	29±7
Racial or ethnic background — no. (%)		
White	414 (69)	404 (67)
Black	81 (13)	85 (14)
Asian	31 (5)	42 (7)
Other or unknown	75 (12)	70 (12)
Level of education — no. (%)		
Junior high school only	175 (29)	175 (29)
Completed high school	163 (27)	175 (29)
Some college or university	220 (37)	202 (34)
Unknown	43 (7)	49 (8)
Single parent — no. (%)	155 (26)	167 (28)
Preeclampsia or eclampsia — no. (%)	91 (15)	97 (16)
Tocolysis <7 days before delivery — no. (%)	109 (18)	117 (19)
Antenatal glucocorticoid administration — no. (%)	481 (80)	483 (80)
<24 hr before delivery	146 (24)	148 (25)
24 hr to 7 days before delivery	242 (40)	258 (43)
>7 days before delivery	93 (15)	77 (13)
Cesarean section	309 (51)	315 (52)
Infants		
Birth weight — g	782±131	783±130
Gestational age — wk	25.9±1.8	26.0±1.9
Female sex — no. (%)	292 (49)	295 (49)
Birth weight <10th percentile for gestational age — no. (%)†	113 (19)	133 (22)
Born in study center — no. (%)	579 (96)	581 (97)
Singleton birth — no. (%)	447 (74)	436 (73)
Apgar score at 5 min		
Median	8	8
Interquartile range	6–8	6–8
Received surfactant on day 1 — no. (%)	426 (71)	409 (68)

*Plus−minus values are means ±SD.

†The 10th percentile for gestational age in a normal population was as reported by Arbuckle and Sherman.[14]

TABLE 2. NUMBER OF DOSES OF STUDY DRUG ADMINISTERED, REASONS FOR WITHHOLDING DOSES, AND AGE AT FIRST DOSE.

VARIABLE	INDOMETHACIN GROUP (N=601)	PLACEBO GROUP (N=601)
Doses received — no. of infants (%)		
3	485 (81)	483 (80)
2	64 (11)	70 (12)
1	49 (8)	38 (6)
0	3 (<1)	10 (2)
Reasons for withholding doses — no. of infants (%)*		
Overt bleeding	4 (1)	9 (1)
Oliguria	44 (7)	22 (4)
Confirmed or suspected necrotizing enterocolitis	1 (<1)	4 (1)
Consent withdrawn	0	0
Infant died	27 (4)	27 (4)
Age at first dose — no. of infants (%)		
≤6 hr	517 (86)	522 (87)
>6 to 12 hr	78 (13)	65 (11)
>12 to 18 hr	1 (<1)	1 (<1)
>18 hr	1 (<1)	0
Unknown or no doses given	4 (1)	13 (2)

*Values are the numbers and percentages of infants missing at least one dose for the specified reason. Not all reasons for withholding doses are listed. Oliguria was defined as urine output of less than 0.5 ml per kilogram of body weight per hour during the 24 hours preceding either the second or the third dose.

tricular hemorrhage were identical in the two treatment groups, the risk of grade 3 or grade 4 hemorrhages was lower in the indomethacin group (Table 4). However, the incidence of any type of lesion indicative of injury to the cerebral white matter was similar in the two groups, as was the incidence of all other secondary short-term outcomes (Table 4).

DISCUSSION

We found that the use of indomethacin prophylaxis to reduce the incidence of patent ductus arteriosus and of severe periventricular and intraventricular hemorrhage in extremely-low-birth-weight infants did not improve the rate of survival without neurosensory impairment at a corrected age of 18 months. Also, indomethacin prophylaxis did not reduce the incidence of any of the individual events included in the composite primary outcome in this trial. Moreover, it is unlikely that indomethacin prophylaxis will be beneficial in the smallest infants, since we found no differential treatment effect in an analysis stratified according to birth weight.

It is unlikely that we missed a clinically important long-term effect of indomethacin. A post hoc calculation confirmed that we would have been able to detect a 20 percent reduction in risk, had it existed, with a power of 90 percent, and we think that our estimate of the long-term effects of indomethacin prophylaxis is unbiased. The investigators and anyone

or survived with one or more impairments, as compared with 146 of the 241 infants in the placebo group in that birth-weight stratum (61 percent). The corresponding rates for infants with birth weights between 750 and 999 g were 119 of the 334 infants in the indomethacin group (36 percent), and 115 of the 328 infants in the placebo group (35 percent).

Secondary Outcomes

Among the survivors, the incidence rates of hydrocephalus requiring the placement of a shunt, seizure disorder, and microcephaly were not affected by the administration of indomethacin (Table 4). Indomethacin prophylaxis reduced the incidence of patent ductus arteriosus. Consistent with this reduction, the need for drug or surgical therapy to close the duct was also reduced in the infants in the indomethacin group (Table 4).

Although the rates of periventricular and intraven-

TABLE 3. PRIMARY OUTCOME OF DEATH OR NEUROSENSORY IMPAIRMENT.*

OUTCOME	EVENT RATE		ODDS RATIO		
	INDOMETHACIN GROUP	PLACEBO GROUP	UNADJUSTED	ADJUSTED (95% CI)	P VALUE
	no./total no. (%)				
Composite					
Death or impairment	271/574 (47)	261/569 (46)	1.1	1.1 (0.8–1.4)	0.61
Components					
Death before 18 mo of corrected age†	125/595 (21)	111/594 (19)	1.2	1.2 (0.9–1.6)	0.27
Cerebral palsy‡	58/467 (12)	55/477 (12)	1.1	1.1 (0.7–1.6)	0.64
Cognitive delay (MDI <70)‡	118/444 (27)	117/457 (26)	1.1	1.0 (0.8–1.4)	0.86
Hearing loss requiring amplification‡	10/456 (2)	10/466 (2)	1.0	1.0 (0.4–2.5)	0.93
Bilateral blindness‡	9/465 (2)	7/472 (1)	1.3	1.3 (0.5–3.6)	0.58

*Odds ratios have been adjusted for the birth-weight stratum and center, except for the odds ratios for hearing loss and bilateral blindness, which were adjusted only for the birth-weight stratum. P values are for the adjusted odds ratios. CI denotes confidence interval, and MDI Mental Development Index.

†These data do not include the 13 infants who were lost to follow-up at 18 months.

‡Data for this outcome exclude infants who died before scheduled tests and those who were alive but were not tested or were lost to follow-up.
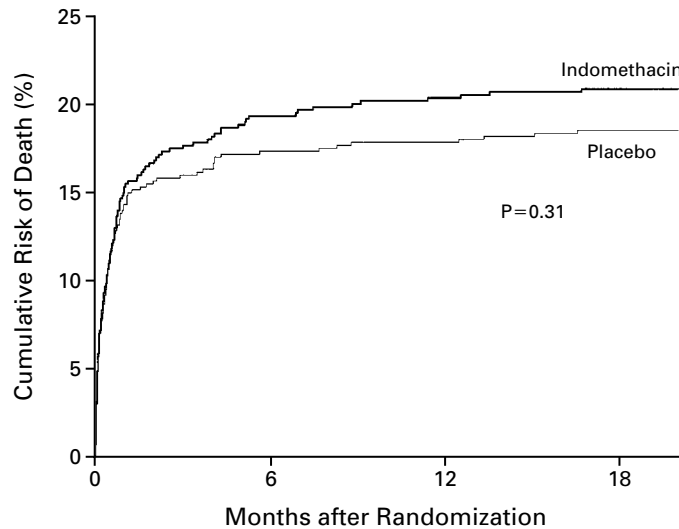
Figure 2. Kaplan–Meier Estimates of the Cumulative Risk of Death in the Indomethacin and Placebo Groups.

For infants with unknown status at 18 months, these estimates include information on the last dates on which the infants were known to be alive.

involved in the care or follow-up of the infants in the study remained unaware of the treatment-group assignments throughout the trial, and ascertainment of the primary outcome toward the end of the second year of life was nearly complete. This is important because preterm infants who are followed up with ease may not have the same outcomes as those who are followed up with difficulty.[15] In this trial, only 13 children were entirely lost to follow-up, and the analysis of the primary outcome was based on results from 95 percent of all the infants who had been assigned to a treatment group.

TABLE 4. LONG-TERM AND SHORT-TERM SECONDARY OUTCOMES IN THE INFANTS IN THE INDOMETHACIN AND PLACEBO GROUPS.

OUTCOME	EVENT RATE		ODDS RATIO*		
	INDOMETHACIN GROUP	PLACEBO GROUP	UN-ADJUSTED	ADJUSTED (95% CI)	P VALUE
	no./total no. (%)				
Long-term					
Hydrocephalus with shunt†	15/470 (3)	9/480 (2)	1.7	1.7 (0.7–3.9)	0.21
Seizure disorder†	8/470 (2)	7/483 (1)	1.2	1.2 (0.4–3.3)	0.76
Microcephaly†	49/461 (11)	54/475 (11)	0.9	0.9 (0.6–1.4)	0.77
Short-term					
Patent ductus arteriosus	142/601 (24)	301/601 (50)	0.3	0.3 (0.2–0.4)	<0.001
Indomethacin for closure of patent ductus arteriosus	100/601 (17)	276/601 (46)	0.2	0.2 (0.2–0.3)	<0.001
Surgical closure of patent ductus arteriosus	40/601 (7)	74/601 (12)	0.5	0.5 (0.3–0.8)	0.001
Pulmonary hemorrhage	89/601 (15)	98/601 (16)	0.9	0.9 (0.6–1.2)	0.45
Need for supplemental oxygen at postmenstrual age of 36 wk‡	225/496 (45)	215/503 (43)	1.1	1.2 (0.9–1.5)	0.26
Need for supplemental oxygen at discharge to home§	97/487 (20)	88/496 (18)	1.2	1.2 (0.9–1.6)	0.32
Necrotizing enterocolitis	64/601 (11)	58/601 (10)	1.1	1.1 (0.8–1.7)	0.53
Gastrointestinal perforation	36/601 (6)	32/601 (5)	1.1	1.2 (0.7–1.9)	0.56
Periventricular or intraventricular hemorrhage†	236/569 (41)	234/567 (41)	1.0	1.0 (0.8–1.3)	0.86
Severe (grade 3 or 4) periventricular or intraventricular hemorrhage†	52/569 (9)	75/567 (13)	0.7	0.6 (0.4–0.9)	0.02
Intraparenchymal echodensities, periventricular leukomalacia, porencephalic cysts, or ventriculomegaly†	125/563 (22)	142/562 (25)	0.8	0.8 (0.6–1.1)	0.23
Bilateral retinopathy†	315/507 (62)	301/521 (58)	1.2	1.2 (0.9–1.6)	0.16

*Odds ratios have been adjusted for the birth-weight stratum and center, except for the odds ratios for hydrocephalus, seizure disorder, microcephaly, and need for oxygen at discharge to home, which have been adjusted only for the birth-weight stratum. P values are for the adjusted odds ratios. CI denotes confidence interval.

†Data for this outcome exclude infants who died before scheduled tests and those who were alive but were not tested or were lost to follow-up.

‡A total of 103 infants in the indomethacin group and 96 in the placebo group died before a postmenstrual age of 36 weeks. In two infants in each group the need for supplemental oxygen at this age was unknown.

§A total of 110 infants in the indomethacin group and 100 in the placebo group died before discharge to home. In four infants in the indomethacin group and five in the placebo group the need for supplemental oxygen at discharge to home was unknown.

Information about the long-term effects of indomethacin prophylaxis has been derived primarily from a trial by Ment et al.[16] In that study, indomethacin prophylaxis also failed to reduce the rates of cerebral palsy, deafness, and blindness.[17,18] However, Ment et al. reported a favorable effect of indomethacin prophylaxis on cognitive function in a subgroup of children who spoke English as their only language at 4.5 years of age.[18] Our trial, however, was designed to test different hypotheses from those of the trial by Ment et al., and we had different criteria for enrollment, different primary end points, and different rates of follow-up. For example, we did not exclude infants with preexisting periventricular or intraventricular hemorrhage. Our relatively unrestrictive criteria for eligibility should increase the generalizability of our results.[19]

We administered the Bayley Scales of Infant Development II at a corrected age of 18 months and found that more than one quarter of all the surviving infants had moderate-to-severe cognitive delays, defined as a Mental Development Index score of less than 70. Although this finding is alarming, it is consistent with those of two recent studies that used the same scales to measure the cognitive function of extremely-low-birth-weight infants at a corrected age of 18 months and of 30 months, respectively.[20,21] The validity of the Mental Development Index score at this age as a predictor of later intellectual functioning remains to be determined. However, we doubt that extended follow-up will uncover substantial benefits of prophylaxis with indomethacin.

In our trial, indomethacin did not reduce the incidence of lesions that may signify white-matter injury, although it did reduce the incidence of severe periventricular and intraventricular hemorrhage. Why, then, did this reduction not translate into a better long-term outcome? Severe hemorrhage was associ-

ated with a poor outcome, but the incidence of severe hemorrhage was quite low, and the absolute reduction in incidence associated with indomethacin prophylaxis was small (4 percentage points). This reduction in the incidence of severe hemorrhage would account for an absolute reduction of only 1.6 percent in the primary outcome.

On the basis of the previously documented short-term benefits, many clinicians have adopted a policy of administering indomethacin prophylaxis in very-low-birth-weight infants, although others have remained skeptical of this approach.[2] What are the implications of our findings for the care of very preterm infants? Indomethacin prophylaxis reduces the need for medical and surgical closure of the ductus arteriosus. Approximately 20 infants must receive indomethacin prophylaxis to avert one operation.[22] Our results suggest that closure of the ductus with the prophylactic administration of indomethacin can be achieved without serious adverse effects on outcomes such as necrotizing enterocolitis or retinopathy. However, indomethacin prophylaxis should not be prescribed with the expectation that the chances of survival without neurosensory impairment will be improved. We must look elsewhere in our quest to reduce the high rates of adverse outcomes in extremely-low-birth-weight infants.

APPENDIX

In addition to the authors, who formed the Steering Committee, the following institutions and persons participated in the trial: **Canada:** *British Columbia Children's Hospital, Vancouver* — M. Whitfield, F. Germain, J. Tomlinson; *Royal Alexandra Hospital, Edmonton, Alta.* — A. Peliowski, P. Etches, B. Young; *Glenrose Rehabilitation Hospital, Edmonton, Alta.* — C. Robertson; *Foothills Hospital and Alberta Children's Hospital, Calgary* — D. McMillan, R. Sauve, L. Bourcier, H. Christianson; *Royal University Hospital, Saskatoon, Sask.* — K. Sankaran, B. Andreychuk; *Health Sciences Centre, Winnipeg, Man.* — M. Seshia, O. Casiro, V. Debooy, V. Cook; *St. Boniface Hospital, Winnipeg, Man.* — C. Cronin, N. Granke; *The Salvation Army Grace Hospital, Windsor, Ont.* — C. Nwaesei, L. St. Aubin; *St. Joseph's Health Centre, London, Ont.* — D. Reid, D. Lee, C. Kenyon, L. Whitty, J. Farrell; *Hamilton Health Sciences, Hamilton, Ont.* — P. Gillie, J. Dix, B. Zhang; *Women's College Hospital, Toronto* — E. Asztalos, L. Wiley; *Hospital for Sick Children, Toronto* — A. James; *Kingston General Hospital, Kingston, Ont.* — K. Young Tai, M. Clarke; *IWK Grace Health Centre, Halifax, N.S.* — S. Stone. **Australia:** *King Edward Memorial Hospital for Women, Perth* — R. Kohan, N. French, H. Benninger; *Women's and Children's Hospital, Adelaide* — C. Barnett, R. Haslam, J. Ramsay; *Royal Women's Hospital, Melbourne* — L. Doyle, B. Faber, K. Callanan; *Mercy Hospital for Women, Melbourne* — S. Fraser; *Westmead Hospital, Westmead* — K. Lui, M. Rochefort, E. McAvoy; *Royal Women's Hospital, Brisbane* — P. Colditz, M. Pritchard; *Mater Mothers' Hospital, Brisbane* — P. Steer, D. Tudehope, V. Flenady, J. Hegarty. **New Zealand:** *National Women's Hospital and Middlemore Hospital, Auckland* — L. Mildenhall, W. Smith, L. McCarthy. **Hong Kong:** *Prince of Wales Hospital, Shatin* — T. Fok. **United States:** *Stanford University Medical Center, Palo Alto, Calif.* — D. Stevenson, B. Fleisher, B. Ball; *University of New Mexico School of Medicine, Albuquerque* — L. Papile, G. Laadt, C. Backstrom; *University of Texas Southwestern Medical Center at Dallas* — J. Tyson, S. Broyles, S. Madison; *University of Alabama, Birmingham* — W. Carlo, K. Nelson, M. Collins, S. Johnson; *Children's Hospital of Michigan, Detroit* — S. Shankaran, V. Delaney-Black, G. Muran, D. Driscoll; *Emory University, Atlanta* — B. Stoll, N. Simon, E. Hale; *Case Western Reserve University, Cleveland* — A. Fanaroff, D. Wilson, M. Hack, N. Newman; *University of Miami, Miami* — C. Bauer, A. Worth, W. Griffin; *Brown University, Providence, R.I.* — W. Oh, B. Vohr, A. Hensman. *External Safety Monitoring Committee:* M. Gent, W. Fraser, M. Perlman. *Bayley Scales of Infant Development II Certification:* R. Adkins. *Audiology Central Adjudication Committee:* L. Elden, C. Robertson, B. Vohr. *Consultant Pharmacist:* S. Gray. *Coordinating and Methods Center:* K. Thorpe (junior biostatistician); N. LaPierre (trial coordinator).

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