Factors Associated With Permanent Closure of the Ductus Arteriosus: A Role for Prolonged Indomethacin Therapy

Dolores Quinn, RN; Bruce Cooper, PhD; and Ronald I. Clyman, MD

ABSTRACT. Background. The most important factor determining anatomic remodeling and permanent closure of the ductus arteriosus is the degree of ductus constriction after indomethacin treatment. Muscular constriction produces a region of ischemic hypoxia in the middle of the ductus muscle media that initiates the process of permanent closure. Previous studies have shown that infants delivered before 28 weeks’ gestation, who still have evidence of ductus flow on Doppler examination (performed after the standard 3-dose course of indomethacin), have a high likelihood (>85%) chance of reopening their ductus in the future. In contrast, if there is no evidence of luminal patency on the posttreatment Doppler examination, the incidence of ductus reopening is <20%.

In the following study, we examined infants who still had a patent ductus on Doppler examination after a 3-dose course of indomethacin, to identify which factors might be associated with permanent ductus closure. We hypothesized that infants who received additional doses of indomethacin after the standard 3-dose course might develop an even tighter degree of ductus constriction and increase their chance of developing permanent closure.

Methods. We performed a retrospective cohort study of preterm infants (<26% weeks’ gestation) who were treated with indomethacin. Between 12 and 24 hours after the third dose of indomethacin, infants were examined for the presence or absence of ductus-related signs, and an echocardiogram was performed. Infants responded to the initial 3 doses of indomethacin in 1 of 3 ways: 1) the ductus was closed clinically (absent clinical signs) with no evidence of luminal flow on Doppler examination (“clinically closed”; n = 214); 2) the ductus was closed clinically, but a small amount of left-to-right luminal flow was evident on Doppler examination (“partially closed”; n = 69); or 3) the ductus was open clinically and echocardiographically (“nonresponder”; n = 30). Nonresponders underwent surgical ligation (n = 30). Infants with a partially closed ductus formed our study population.

We used a hierarchical regression model to identify which, if any, of the following factors might be associated with permanent anatomic closure in the 69 infants with a partially closed ductus: 1) gestational age, 2) exposure to antenatal steroids, 3) birth weight, 4) sex, 5) presence and severity of respiratory distress, 6) fluid administration during the first 96 hours after birth, 7) indomethacin treatment approach (prophylactic vs symptomatic), 8) year of birth, 9) use of surfactant, 10) preeclampsia, 11) chorioamnionitis, 12) bacterial sepsis, 13) necrotizing enterocolitis, or 14) duration of indomethacin treatment (standard 3-dose course vs prolonged 6-dose course). Infants who received the standard 3-dose course of indomethacin treatment were given 0.2, 0.1, and 0.1 mg/kg indomethacin during a 48-hour period. Infants who received the prolonged 6-dose course of indomethacin treatment were given a fourth, fifth, and sixth dose of 0.1 mg/kg at 24 hour-intervals, starting 24 hours after the third dose.

Results. Sixty-eight of the 69 infants survived long enough to complete all of the study evaluations. Seventy-five percent (51/68) reopened their ductus and became symptomatic; 71% (48/68) were eventually ligated. Only gestational age and duration of indomethacin treatment were significantly and independently associated with permanent closure. A prolonged 6-dose course of indomethacin was more likely than the standard 3-dose course to be associated with an increased incidence of echocardiographic closure, a decreased incidence of symptomatic reopening (odds ratio: 0.19; 95% confidence interval: 0.04–0.96), and a decreased incidence of ductus ligation (odds ratio: 0.14; 95% confidence interval: 0.03–0.68).

Discussion. Several older studies have suggested that a longer initial course of indomethacin therapy may be more effective in producing permanent ductus closure than the standard 3-dose course. In contrast, more recent studies have found that a longer course of indomethacin is no more effective than the standard 3-dose course in producing permanent closure. We hypothesize that the different outcomes among these studies may be attributable to differences in the degree of ductus constriction during the standard 3-dose course of indomethacin. Both the increased use of antenatal steroids and the earlier use of indomethacin has increased the effectiveness of the standard 3-dose course of indomethacin in recent years. We hypothesize that, in contrast with earlier studies, a significant proportion of the infants in the recent studies may have developed complete Doppler closure with just 3 doses of indomethacin (as occurred in 214 of the 313 infants treated with the standard 3-dose course in our study). Because the degree of ductus constriction seems to determine the rate of anatomic remodeling and permanent closure, daily echocardiographic evaluations of ductal patency may be the best way to decide when indomethacin therapy is no longer needed. Our study suggests that infants who still have evidence of luminal patency, after a standard 3-dose course of indomethacin, may be likely to benefit from a longer course of indomethacin. Future randomized trials that examine the benefits of different lengths of indomethacin treatment may wish to take this into consideration.

Conclusions. Despite the increased effectiveness of a prolonged course of indomethacin, the rates of ductus...
The most important determinant of permanent ductus closure after a standard 3-dose course of indomethacin treatment is the initial degree of ductus constriction.\textsuperscript{1–4} Muscular constriction produces a region of ischemic hypoxia in the middle of the ductus muscle media. The hypoxic signal initiates the process of anatomic remodeling and permanent closure.\textsuperscript{3,5,6} Infants born at <28 weeks’ gestation, who have no evidence of luminal flow on a Doppler examination, performed 12 to 24 hours after the third dose of indomethacin, have an 80% to 90% chance of staying closed permanently.\textsuperscript{4}

Previously, we observed that even when the ductus is clinically closed, if any luminal flow is detected on the posttreatment Doppler examination, the chances are <15% that it will remain closed; 85% of these infants will develop symptoms of clinical reopening at some time in the future.\textsuperscript{1} Numerous factors have been shown to play a role in both spontaneous and indomethacin-induced ductus closure: gestational age, exposure to antenatal steroids, presence of respiratory distress, fluid intake, postnatal age at the time of treatment, and duration of indomethacin treatment.\textsuperscript{1,2,7–14} However, at this point in time, no studies have determined which factors predict permanent ductus closure when Doppler-detectable luminal flow is still present after the standard 3-dose course of indomethacin.

Therefore, we performed a retrospective study of infants who still had a patent ductus on Doppler examination after a 3-dose course of indomethacin, to identify which factors might be associated with permanent ductus closure. We hypothesized that infants who received additional doses of indomethacin after the standard 3-dose course might develop an even tighter degree of ductus constriction and increase their chance of developing permanent closure.

METHODS

We performed a retrospective cohort study of preterm infants using a prospectively maintained neonatal database. This study was reviewed and approved by the Committee on Human Research at the University of California San Francisco. Between January 1992 and June 2000, 417 preterm infants (delivered between 24 and 28 weeks’ gestation) were admitted to the William H. Tooley Intensive Care Nursery within the first 15 hours after birth before ductus-related signs (a murmur, with or without either increased precordial activity or bounding pulses) became apparent (n = 191); and 2) symptomatic treatment: infants were treated only after ductus-related signs appeared (mean age = 3 days; n = 150). The prophylactic treatment approach was introduced after December 31, 1994, as a change in nursery protocol. Both prophylactically and symptomatically treated infants were initially given 3 doses of indomethacin (0.2, 0.1, and 0.1 mg/kg during a 48-hour period).

Evaluation of Initial Treatment Responses

Between 12 and 24 hours after the third dose of indomethacin, infants were examined for the presence or absence of ductus-related signs (see above), and an echocardiogram was performed with a 5- or 7-MHz transducer interfaced with a model 128 XP echocardiographic system (Acuson, Inc, Mountain View, CA). Color Doppler measurements of flow within the ductus arteriosus and 2-dimensional measurements of ductal size were made, the left atrial/aortic ratio was calculated, and retrograde flow within the descending aorta was evaluated. Both continuous-wave and pulsed-wave Doppler probes were used to confirm the presence, direction, and timing of ductus flow. Luminal blood flow was considered to be absent if no retrograde color Doppler flow was present either in the region of the ductus or in the pulmonary artery and normal anterograde diastolic flow was present in the descending aorta in the region of the ductus. In no instance was luminal blood flow detected by pulsed Doppler if color Doppler failed to detect its presence. If any color Doppler flow was seen in the region of the ductus, no matter how small, the ductus was considered to have persistent flow through its lumen.

Classification of Initial Treatment Responses

Twenty-eight of the 341 indomethacin-treated infants died before completing the initial 3 doses. The remaining 313 infants responded to the initial 3 doses of indomethacin in 1 of 3 ways: 1) the ductus was closed clinically (absent clinical signs) with no evidence of luminal flow on Doppler examination (“completely closed”; n = 214); the ductus was closed clinically, but a small amount of left-to-right luminal flow was evident on Doppler examination (“partially closed”; n = 69); or 3) the ductus was open clinically and echocardiographically (“nonresponder”; n = 30).

Infants with a partially closed ductus formed our study population. Nonresponders underwent surgical ligation (n = 30). Infants with a completely closed ductus were monitored for clinical findings suggestive of ductus reopening. If any recurred, another echocardiogram was performed. If this documented the presence of luminal blood flow, the ductus was considered to have reopened (n = 25/214; 12%). The infant was treated with a second 3-dose course of indomethacin or underwent surgical ligation (n = 25/214; 12%).

Study Population: Partially Closed Ductus

During the time interval of our study (1992–2000), 2 separate approaches were used to treat infants with a partially closed ductus:

1) Standard 3-Dose Course of Indomethacin (n = 22)

After the initial 3 doses of indomethacin, infants with a partially closed ductus were monitored for clinical signs suggestive of ductus reopening. A second echocardiogram was performed between 4 and 6 days after the third dose of indomethacin to see whether the ductus had undergone any additional constriction. If any clinical findings recurred, another echocardiogram was performed. If this documented the presence of both increased ductus diameter and increased luminal blood flow, the ductus was considered to have reopened, and the infant was treated with a second course of indomethacin or surgically ligated. The decision to treat the second course of indomethacin or surgical ligation was made by the attending neonatologist and was based on the severity of the clinical symptoms and whether there were any contraindications to the use of indomethacin.

2) Prolonged Course of Indomethacin (n = 47)

After the initial 3 indomethacin doses, infants with a partially closed ductus were given an additional fourth, fifth, and sixth
dose of 0.1 mg/kg indomethacin every 24 hours, starting 24 hours after the third dose. A second echocardiogram was performed within 36 hours of the sixth dose of indomethacin. Infants were monitored and treated for ductus reopenings as described above (see “Standard 3-Dose Course of Indomethacin”). This indomethacin treatment approach was introduced after December 31, 1995, as a change in nursery protocol. The change in nursery protocol only applied to infants delivered at ≥26% weeks’ gestation who had a partially closed ductus after 3 doses of indomethacin.

The effectiveness of each treatment approach was evaluated in infants who survived for >21 days; this enabled us to complete the necessary clinical and echocardiographic follow-up examinations. Twenty-two (100%) of the infants who received the standard 3-dose course of indomethacin and 46 (98%) of the infants who received the prolonged course of indomethacin survived long enough to complete all of the study evaluations.

Statistical Analysis

We were particularly interested in determining which predictive factors were associated with the following outcomes: 1) ductus closure on the second Doppler examination (performed 4–6 days after the third dose of indomethacin), 2) incidence of symptomatic ductus reopening, and 3) need for surgical ligation. We used a hierarchical regression model to examine the independent effects of the following predictive factors on each of the outcome measures: 1) gestational age (24 and 28 weeks vs 26 and 27 weeks), 2) exposure to antenatal betamethasone, 3) birth weight, 4) sex, 5) presence of respiratory distress syndrome, 6) fluid administration during the first 96 hours after birth, 7) indomethacin treatment approach (prophylactic vs symptomatic), 8) year of birth (1992–1997 vs 1998–2000), 9) mean airway pressure (Paw) at 24 hours after delivery, 10) fraction of inspired oxygen (FiO₂) requirement at 24 hours after delivery, 11) use of surfactant, 12) preeclampsia, 13) chorioamnionitis, 14) bacterial sepsisemia, 15) necrotizing enterocolitis (NEC), or 16) length of indomethacin treatment (standard 3-dose course vs prolonged 6-dose course).

Although we examined the independent effects of each of these factors, we paid particular attention to the effects that a prolonged treatment course had on the incidence of permanent ductus closure. Therefore, each predictive factor was entered into the hierarchical regression model in the following order: first, either: 1) gestational age, 2) antenatal betamethasone, 3) birth weight, 4) sex, 5) respiratory distress syndrome, 6) fluid administration, 7) indomethacin treatment approach, 8) year of birth, 9) Paw, 10) FiO₂ requirement, 11) use of surfactant, 12) presence of preeclampsia, 13) chorioamnionitis, 14) bacterial sepsisemia, 15) necrotizing enterocolitis (NEC), or 16) length of indomethacin treatment (standard 3-dose course vs prolonged 6-dose course). Each independent predictor was examined for its predictive utility at the step of entry. We examined the predictive contribution of “length of indomethacin treatment” after the contributions of each of the other predictors were accounted for. In addition, interactions among the predictors were tested at a third step.

This analytic strategy was conducted through the use of binary logistic regression when the outcome criterion was binary (eg, ductus ligated vs ductus not ligated). This method is justified in the case of all categorical variables when one is designated as a response variable and the others are predictors, as in the present study. When one of the predictors was ordinal (eg, birth weight, fluid administration, etc) a logistic regression with hierarchical entry was used. The predictive significance of each predictor was determined through the change in the likelihood-ratio χ² statistic at the step of entry, and the associated odds ratio was reported as the effect size.

Least-squares regression was used for the analysis of quantitative outcome criteria (eg, peak creatinine concentration after indomethacin). The significance of each predictor was tested through the F test for the change in R² at the step of entry (using the error term at the final step).

The significance level for hypothesis tests was P < .05. Results are presented as means ± standard deviations, percentages, and correlation coefficients, depending on the levels of measurement.

RESULTS

During the period of our study, 69 infants (Table 1) still had evidence of ductus luminal flow on Doppler examination 12 to 24 hours after the third dose of indomethacin and were considered to have a partially closed ductus. By 4 to 6 days after the third dose of indomethacin, 47/69 (68%) still had persistent Doppler detectable luminal flow (Table 1). Fifty-one (75%) of 68 ultimately developed new clinical symptoms that required additional therapy and were considered to have reopened their ductus; 48/68 (71%) of the group were surgically ligated. We used a hierarchical regression model to examine the factors that were associated with delayed ductus closure (on echocardiogram), symptomatic ductus reopening, and ductus ligation. The initial univariate analysis found that 3 variables (length of indomethacin treatment, gestational age, and year of birth) correlated with any of these outcomes. However, the hierarchical regression models showed that only 2 factors (length of indomethacin treatment and gestational age) were significantly and independently associated with permanent ductus closure.

Infants with a partially closed ductus that were treated with additional doses of indomethacin (prolonged course), had a greater degree of delayed ductus closure on Doppler examination (22/47; 47%) than those treated with the standard 3-dose course (0/22; P < .0005; Fig 1). There were no differences between the infants treated with the prolonged course of indomethacin and those treated with the standard 3-dose course in any of the neonatal or perinatal risk factors (Table 2) except for the year of delivery.
birth and the use of prophylactic indomethacin. The improved effectiveness of the prolonged course of indomethacin on delayed Doppler closure was independent of both the year of birth and the use of prophylactic treatment, as well as the infants' gestation, exposure to antenatal betamethasone, birth weight, sex, presence or absence of respiratory distress, septicemia or NEC, fluid administration during the first 96 hours after birth, use of surfactant, Paw, and FiO₂ requirements.

The prolonged course of indomethacin treatment also led to a lower rate of symptomatic ductus reopening and surgical ligation (Fig 1). Both the lower rates of symptomatic reopening (odds ratio: 0.19, 95% confidence interval: 0.04–0.96; P < .025) and surgical ligation (odds ratio: 0.14, 95% confidence interval: 0.03–0.68; P < .005) were independent of the infants' gestation, exposure to antenatal betamethasone, birth weight, sex, presence or absence of respiratory distress, septicemia or NEC, fluid administration during the first 96 hours after birth, year of birth, use of surfactant, Paw, and FiO₂ requirements, or use of prophylactic or symptomatic treatment approach.

The other factor that was independently related to the incidence of symptomatic ductus reopening and ductus ligation was the infant's gestational age. The more immature the infant was, the more likely the ductus was to be ligated (odds ratio: 4.6, 95% confidence interval: 1.3–16.8; P < .025). None of the other independent predictors had any significant effect on the rate of echocardiographic closure, the incidence of symptomatic reopening, or the need for surgical ligation (data not shown).

Other Neonatal Morbidities

We examined whether the prolonged course of indomethacin was associated with any neonatal morbidities: intracranial hemorrhage (grades III/IV¹⁷), NEC, (associated with either bowel perforation or

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Fig 1. A prolonged course of indomethacin decreases the incidence of ductus patency, reopening and the need for surgical ligation in infants with a partially closed ductus. Infants were treated with either a standard 3-dose course (no additional doses, open columns) or a prolonged course (6 doses) (additional doses, closed columns) of indomethacin. Numbers in parentheses indicate the number of infants in each gestational age group. A, Delayed ductus response on the second Doppler examination. Examination was performed 4 to 6 days after the third dose of indomethacin. Columns represent the percentage of infants with an open ductus. B, Ductus reopening. Columns represent the percentage of infants who develop a symptomatic patent ductus arteriosus after indomethacin treatment. C, Ductus ligation. Columns represent the percentage of infants who were ligated.
factors no longer play a significant role in determin-
completely by the third dose of indomethacin, these
findings suggest that if the ductus has not closed
ous and indomethacin-induced closure.1,2,10
degree of ductus constriction during both spontane-
prophylactic use of indomethacin affect the rate and
intake, exposure to antenatal betamethasone, and
a decreased incidence of ductus ligation.

Similarly, although “year of birth” was initially
found to be a significant predictor of ductus out-
comes, this was no longer the case once “length of
indomethacin treatment” was included in the statis-
tical model. We also examined the outcomes of in-
fants who were delivered at 28 and 29 weeks’ gesta-
tion. We chose to examine this group, because there
was no change in ductus treatment approach during
the prolonged course of indomethacin did not alter any
of these outcomes.

### DISCUSSION

We found that infants who had no clinical evi-
dence of a patent ductus, but who still had Doppler
evidence of ductus luminal flow (after the third dose
of indomethacin), were likely (75%) to develop
symptomatic ductus reopening in the future. We
found that a prolonged course of indomethacin (6
doses) was more likely to produce permanent ductus
closure than the standard 3-dose course. The pro-
longed course of indomethacin was associated with
an increased incidence of echocardiographic closure,
a decreased incidence of symptomatic reopening,
and a decreased incidence of ductus ligation.

Previous studies have shown that factors like fluid
intake, exposure to antenatal betamethasone, and
prophylactic use of indomethacin affect the rate and
degree of ductus constriction during both spontane-
ous and indomethacin-induced closure.1,2,10–14 Our
findings suggest that if the ductus has not closed
completely by the third dose of indomethacin, these
factors no longer play a significant role in determin-
ing which infants will ultimately close their ductus
and which will need additional therapies.

During the 8½-year period of this study, there was
an increase both in the use of prophylactic indometh-
acin and in the use of a prolonged course of indo-
methacin to treat a patent ductus arteriosus. We used
a hierarchical regression model and found that the
response of the partially closed ductus to a pro-
longed course of indomethacin was not affected by
the mode of indomethacin therapy (prophylactic or
symptomatic) or the infant’s year of birth or by any
of the other perinatal variables. Although subtle
changes in nursery management may have affected
the outcomes of this study, we think that it is un-
likely that the increased rate of ductus closure and
the decreased incidence of ductus reopening and
surgical ligation were attributable to some unrecog-
nized change in nursery practice. In our nursery, the
use of postnatal dexamethasone was reserved for
infants older than 21 days and, therefore, should not
have affected the outcomes of the current study.

All infants were exposed to tocolytic medications; no difference was seen in the incidence of exposure
to magnesium sulfate or β-adrenergic agents (data not shown).

### TABLE 2. Comparison of Antenatal and Postnatal Variables Among Infants <27 Weeks’ Gestation Who Received Either a Standard (3-Dose) Course or a Prolonged (6-Dose) Course of Indomethacin to Treat Their Partially Closed Ductus

<table>
<thead>
<tr>
<th>Standard (3-Dose) Course</th>
<th>Prolonged Course</th>
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<tbody>
<tr>
<td><em>n</em> = 22</td>
<td><em>n</em> = 47</td>
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<tr>
<td>Gender (% male)</td>
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<tr>
<td>46</td>
<td>51</td>
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<tr>
<td>RDS (%)</td>
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<td>86</td>
<td>94</td>
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<tr>
<td>Surfactant treatment (%)</td>
<td></td>
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<tr>
<td>95</td>
<td>98</td>
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<tr>
<td>Paw at 24 h after birth (cm H2O)</td>
<td>8.1 ± 1.6</td>
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<td>Fio2 at 24 h after birth</td>
<td>0.37 ± 0.18</td>
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<tr>
<td>CLD (%)</td>
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<td>24</td>
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<td>NEC (%)</td>
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<td>10</td>
<td>11</td>
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<td>ICH [grade III/IV] (%)</td>
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<td>9</td>
<td>9</td>
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<td>PVL (%)</td>
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<td>10</td>
<td>4</td>
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<td>Death (%)</td>
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<td>Prophylactic indomethacin (%)</td>
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<tr>
<td>Year of birth (&lt;1998) (%)</td>
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<tr>
<td>77</td>
<td>30†</td>
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<td>Fluid intake (mL/kg/d)</td>
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<tr>
<td>24 h</td>
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<td>48 h</td>
<td>104 ± 21</td>
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<td>72 h</td>
<td>126 ± 28</td>
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<td>96 h</td>
<td>141 ± 28</td>
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<tr>
<td>Maternal factors</td>
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<td>Betamethasone (%)</td>
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<td>64</td>
<td>74</td>
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<td>Preeclampsia (%)</td>
<td></td>
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<td>0</td>
<td>11</td>
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<td>Chorioamnionitis (%)</td>
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<td>23</td>
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<tr>
<td>Indomethacin (%)</td>
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RDS indicates respiratory distress syndrome; CLD, chronic lung disease (requirement for supplemental oxygen at 36 weeks after conception); ICH [grade III/IV], grade 3 or 4 intracranial hemorrhage; PVL, periventricular leukomalacia; fluid intake, total fluids administered during previous 24-hour period.

* Values with ± are expressed as mean ± SD.
† Statistically significant (*P* < .05).
indomethacin therapy is no longer needed.22,23 Our
recent studies have found that a longer course of
indomethacin is no more effective than the standard
3-dose course in producing permanent closure.18–23
We hypothesize that the different outcomes among
these studies may be attributable to differences in the
degree of ductus constriction during the standard
3-dose course of indomethacin. Both the increased
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Despite the increased effectiveness of a prolonged
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and surgical ligation were still very high in in-

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