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Neurodevelopmental Outcomes Following Two Different Treatment Approaches (Early Ligation versus Selective Ligation) for Patent Ductus Arteriosus

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Abstract

Objective—To examine whether a change in the approach to management of persistent patent ductus arteriosus (PDA), from “early ligation” to “selective ligation,” is associated with an increased risk of abnormal neurodevelopmental outcome.

Study design In 2005, we changed our PDA treatment protocol (in infants ≤27 6/7 weeks gestation) from an “early ligation” approach, with PDA ligation quickly if they failed to close after indomethacin (Period 1: 1/99–12/04), to a “selective ligation” approach, with PDA ligation only if specific criteria were met (Period 2: 1/05–5/09). All infants in both periods received prophylactic indomethacin. Multivariate analysis was used to compare the odds of a composite Abnormal Neurodevelopmental Outcome (Bayley MDI or Cognitive score <70, cerebral palsy, blindness, and/or deafness) associated with each treatment approach at 18–36 months (n=224).

Results—During Period 1, 23% of the infants in follow-up failed indomethacin treatment, and all were ligated; during Period 2, 30% of infants failed indomethacin, and 66% were ligated after meeting pre-specified criteria. Infants treated with the “selective ligation” strategy had fewer Abnormal Outcomes than infants treated with the “early ligation” approach (OR=0.07, p=0.046). Infants ligated before 10 days of age had an increased incidence of Abnormal Neurodevelopmental Outcome. The significant difference in outcomes between the two PDA treatment strategies could be accounted for, in part, by the earlier age of ligation during Period 1.

Conclusions—A “selective ligation” approach for PDAs that fail to close with indomethacin does not worsen neurodevelopmental outcome at 18–36 months.

Keywords

ductus ligation; indomethacin; patent ductus arteriosus; neurodevelopmental outcomes

Patent ductus arteriosus (PDA) are present in up to 70% of preterm infants born before 28 weeks gestation. Left-to-right PDA shunts have been associated with neonatal morbidities

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(like bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and increased mortality); however, no randomized controlled trials (RCT) have been performed to date that address the potential causative role of a persistent PDA in any of these morbidities. Although RCTs have shown that prophylactic indomethacin treatment decreases certain short-term morbidities (like developing a symptomatic PDA, and having a pulmonary and/or intracranial hemorrhage (1, 2)), long-term benefits from prophylactic indomethacin have yet to be demonstrated (3). As a result, the optimal management of PDAs in preterm infants is not clear. Two recent surveys found that 78–96% of neonatologists in the United States would use indomethacin to treat a symptomatic PDA in ELBW infants (4, 5).

Even less information exists to guide neonatologists in what to do when indomethacin treatment fails to close the PDA. Although surgical ligation produces definitive ductus arteriosus closure, it is associated with its own set of morbidities (6–10). Because preterm infants have a high rate of spontaneous PDA closure during the first 2 years after birth (11, 12), early PDA ligation runs the risk of exposing infants to a surgery they might not need. A RCT performed in ELBW infants over 30 years ago addressed the question of whether it is better to surgically close the PDA or to tolerate the long term hemodynamic effects of a persistent PDA (13). Surgical closure of the PDA decreased the need for prolonged ventilatory support (13). Currently there is great controversy about whether these findings are still applicable in the setting of modern neonatal treatment (14). Some neonatologists argue that there is little evidence to justify medical or surgical closure of PDAs (14, 15). However, recent studies using near infrared spectroscopy have raised new concerns about the potential for long-term neurodevelopmental problems following prolonged PDA exposure because of decreased cerebral oxygenation in the presence of a persistent PDA (16).

We previously reported the results of a retrospective cohort study that compared two different approaches to infants with PDAs that remain open after one or more courses of indomethacin treatment: (1) “early ligation,” that limited the exposure to the PDA shunt by proceeding to surgery soon after indomethacin failure; and (2) “selective ligation,” that “tolerated” the presence of the PDA shunt and used surgical ligation only if specific criteria were met (see methods) (12). We found that the “selective ligation” approach decreased ductus ligation and NEC, but had no effect on the incidence of BPD, sepsis, retinopathy of prematurity (ROP), or death.

Despite its apparent short-term benefits, we were concerned that infants treated with the “selective ligation” approach might be at increased risk for neurodevelopmental problems because of their prolonged exposure to the persistent PDA. We now report the cognitive, neurologic and neurosensory outcomes of our previous study population (\at a corrected age of 18 to 36 months.

Methods

This project was approved by the University of California San Francisco’s Institutional Review Board. All infants ≤ 27 6/7 weeks gestation admitted to the William H. Tooley Nursery at the University of California San Francisco between January 1999 and May 2009 were treated with a course of prophylactic indomethacin within 15 hours of birth, provided that no contraindications existed. A detailed description of this approach has been published elsewhere (12, 17). All infants underwent echocardiography 24–36 hours after the last dose of prophylactic indomethacin to determine the response of their PDAs to the medication.

After having received prophylactic indomethacin, infants were examined daily for clinical symptoms of a PDA (systolic murmur, hyperdynamic precordium, widened pulse pressure).

If any of these symptoms were present, the infants had echocardiographic evaluation within 24 hours. If, on echocardiography, a PDA with left-to-right flow was found, the infant was said to have a symptomatic PDA. The decision about whether to administer a second course of indomethacin to an infant with a symptomatic PDA was made by the attending neonatologist and was primarily based on the response of the infant's ductus to the initial course of prophylactic indomethacin; infants whose PDAs closed with prophylactic indomethacin were more likely to be given a treatment course of indomethacin for a symptomatic PDA (18).

Two different approaches of managing a symptomatic PDA were evaluated in this study. These have been described in detail previously (12). In Period 1 (January 1999 through December 2004), PDAs that remained open after indomethacin were managed using an "early ligation" approach, in that they were surgically ligated as soon as possible; this approach was taken to minimize the morbidities thought to be associated with prolonged exposure to a PDA (13). During Period 1, enteral feedings were discontinued until the PDA was closed or ligated. In Period 2 (January 2005 through May 2009), PDAs that failed to close after indomethacin were managed using a "selective ligation" approach. The "selective ligation" approach consisted of continuing enteral feedings and only ligating the PDA if specific criteria were met (12). The specific criteria that were needed before a ligation could be performed included: increasing ventilator requirements over several days, persistent hypotension requiring inotropic support, persistent oliguria/renal failure, and/or feeding intolerance/failure to gain weight. These criteria were attributed to the PDA when no other explanation could be found to explain the infant's deteriorating condition (12). No other changes related to prophylactic indomethacin, feeding advances, or ventilator management occurred between the two periods.

Risk Factors and Neonatal Outcomes

A single neonatologist (RIC) prospectively evaluated and recorded the perinatal and inhospital neonatal risk factors (known to be associated with adverse neurodevelopmental outcomes) (12) (Table I).

All infants had cranial ultrasonograpy within the first week of life. Head ultrasounds were repeated weekly or biweekly for the first 4 weeks. After 1 month, imaging was repeated either before discharge or more frequently if abnormal findings were noted. Intracranial hemorrhage was classified on an I–IV scale (17). Grades III and IV were included in the analyses. Periventricular leukomalacia was defined as echodensities on head ultrasound that progressed to cystic degeneration.

A single cardiologist (AM-G), blinded to clinical data, interpreted all of the echocardiograms. Echocardiographic studies included 2-dimensional imaging, M-mode, color flow mapping, and Doppler interrogation. The ductus was classified as being either closed or open. When the ductus was open, the left-to-right shunt was classified as small, moderate, or large (12).

Late Outcomes

Infants surviving to hospital discharge were enrolled in a prospective high-risk nursery follow-up program, as described previously (19). Neurodevelopmental outcomes are reported for evaluations performed between 18 – 36 months of age. Age was adjusted for prematurity. Neurologic examinations to determine motor outcome were performed by one of three health care providers (two neonatologists and one nurse practitioner) with training in developmental and behavioral pediatrics. Cerebral palsy was defined as hypotonia, spastic diplegia, hemiplegia, or quadriplegia causing functional deficits that required rehabilitative

services; the most recent neurologic examination for each infant that fell in the target time range was used. Audiologic status was assessed using behavioral testing; suspicious examinations were further evaluated by brainstem-evoked responses or pure tone audiometry. A child was considered deaf if he/she had bilateral hearing loss requiring amplification. Vision was assessed using the near point test or Snellen eye chart; children with questionable vision were referred to an ophthalmologist.

Infants underwent testing with the Bayley Scales of Infant Development between 18 and 36 months corrected age. The Bayley test was administered by one of three trained providers. The version of the Bayley test given to subjects changed during the study period, with the Bayley II test being used from January 1999 to October 2005, and the Bayley III test being used from November 2005 onwards. Cognitive outcome was based on the Mental Development Index (MDI) for infants undergoing testing with the Bayley II and on the Cognitive score for infants undergoing testing with the Bayley III. Although the Bayley III includes both cognitive and language components, the Bayley III separates out cognitive and language scores to minimize the effect of language delay on cognitive assessment (20); as we were primarily interested in cognition, we chose to use the Bayley III Cognitive Score in our analyses. An abnormal cognitive outcome was defined as a Bayley MDI or Cognitive score <70 (2 standard deviations (SD) below the mean of 100). The primary outcome of the study was a composite outcome of "Abnormal Neurodevelopmental Outcome," defined as a Bayley MDI or Cognitive score <70, cerebral palsy, blindness, and/or deafness.

Recent studies have shown that Bayley III Cognitive scores can be disproportionally higher than Bayley II MDI scores (21, 22). Moore et al found that a combined Bayley III Cognitive and Language score of <80 was a good predictor of Bayley II MDI score <70 (sensitivity 89%, specificity 99%) (22). Therefore, we examined a second model of abnormal neurodevelopmental outcome (*Alternate* Abnormal Neurodevelopmental Outcome) to validate our findings from the first model; the "*Alternate* Abnormal Neurodevelopmental Outcome" included Bayley II MDI <70 or combined Bayley III Cognitive and Language score <80, cerebral palsy, blindness, and/or deafness.

Statistical Analyses

The χ^2 test was used to compare categorical risk factors and outcomes. The Student t-test and Mann-Whitney test were used to compare mean and median values of continuous variables.

An adjusted multivariate logistic regression model was used to determine the effects of the different treatment approaches ("early ligation" vs. "selective ligation") on the outcome of interest. We first identified the non-PDA perinatal and neonatal risk factors that were most associated with the outcome using bivariate analyses. A model was built for the outcome through forward selection, using $p < 0.2$ as a cutoff to include variables in the model. Variables were added to the model in order of increasing statistical significance. Variables were dropped from the model if their p-value rose to ≥ 0.2 after the addition of other variables. Because the version of the Bayley test changed during the study, we created a variable for the version of the Bayley test that was used to evaluate an infant, and included this variable in the multivariate models, to ensure that any differences in Abnormal Neurodevelopmental Outcome could not be attributed to the change in Bayley test version.

After the models were built, the variable "treatment group" was forced into the model to evaluate the effect of the treatment approach when adjusted by the other predictors. Treatment groups were defined as: 1= individuals whose persistent PDAs were managed using the "early ligation" approach (in Period 1), 2= individuals whose persistent PDAs were managed using the "selective ligation" approach (in Period 2), and 3= individuals with

closed ductus arteriosus after indomethacin. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using a multivariate model. A p-value of <0.05 was considered significant. All analyses were performed using STATA 11 (College Station, TX) statistical software.

Results

A total of 385 infants were included in our initial study. As shown in Table I (total population), the subjects in Period 1 and Period 2 were similar in terms of prenatal and neonatal risk factors (except for the incidence of chorioamnionitis and the time to achieve enteral feeding amounts equal to 80 ml/kg/day).

During Period 1, 24% of the infants failed to close their PDAs with indomethacin; all of them were treated with the "early ligation" approach and had surgical ligation. In Period 2, 25% of the infants failed to close their PDAs with indomethacin; despite being treated with the "selective ligation" approach, 72% of these infants ultimately had surgical ligation after meeting pre-specified criteria.

Follow-Up Population

Follow-up information (either neurodevelopmental outcome or death) was available for 72% (n=276) of the initial population; the rest of the population was either: seen outside the target age range (4%), followed in another referral clinic (typically closer to their homes) (5%), or lost to follow-up (19%). Infants followed in our high risk infant development clinic were more likely to be Caucasian, younger in gestation at birth, and to have had an infection during the neonatal hospitalization (Table I).

There was no difference in follow-up between Period 1 and Period 2 (70% vs. 64%, p=0.32). The demographic variables in Period 1 and Period 2 (among the 224 study infants followed in our high risk infant development clinic) were similar except for the incidence of chorioamnionitis and duration of exposure to the PDA shunt (Table II). Additionally, infants in Period 2 were more likely to have received the Bayley III test (versus the Bayley II test) than infants in Period 1 (Table II).

The unadjusted incidences of Abnormal Neurodevelopmental Outcome and *Alternate* Abnormal Neurodevelopmental Outcome and the individual components that made up the two abnormal outcome variables, by period, were: Abnormal Neurodevelopmental Outcome (28% in Period 1; 11% in Period 2), *Alternate* Abnormal Neurodevelopmental Outcome (30% in Period 1; 18% in Period 2), Bayley test MDI or Cognitive score <70 (18% in Period 1; 0% in Period 2), Bayley test MDI <70 or combined Cognitive and Language score of <80 (20% in Period 1; 10% in Period 2), cerebral palsy (10% in Period 1; 11% in Period 2), blindness (2% in Period 1; 0% in Period 2), and deafness (2% in Period 1; 0% in Period 2).

Infants with ductal closure after indomethacin—To ensure that there were no significant differences in unidentified risk factors that may have altered the infants' risk of Abnormal Neurodevelopmental Outcome between the two study periods, we first examined the outcome among infants whose ductus closed following indomethacin treatment. There were no known changes in treatment practice between the two study periods for this group of infants. Among infants whose ductus closed following indomethacin treatment, the incidence of demographic risk factors between Period 1 and 2 were similar except for chorioamnionitis; there was also a difference in the version of Bayley test administered (Table II). Therefore, we used a multivariate model that included chorioamnionitis and Bayley test version to determine if infants, whose ductus closed following indomethacin treatment, had different odds of Abnormal Neurodevelopmental Outcome between Periods 1

and 2. In this group of infants, there was no significant difference in Abnormal Neurodevelopmental Outcome when infants in Period 2 were compared with infants in Period 1 (OR = 1.21, 95% CI = 0.23 – 6.43, p=0.82). Nor was there a significant difference in *Alternate* Abnormal Neurodevelopmental Outcome when infants in Period 2 were compared with infants in Period 1 (OR = 1.20, 95% CI = 0.34 – 4.28, p=0.78).

Infants who failed indomethacin treatment during the initial hospitalization— Among infants who failed indomethacin treatment, there were no significant differences (between those that were treated with "early ligation" (Period 1) and those treated with "selective ligation" (Period 2)) in the incidence of demographic risk factors - except for the incidence of male sex, the duration of PDA exposure, and the incidence of PDA ligation (Table II). Infants in the "selective ligation" group had fewer mothers who completed high school and were more likely to have been tested with the Bayley III test (Table II).

We used a multivariate model that included all of the potential risk factors for abnormal neurodevelopmental outcome (Table III) to determine if the change from an "early ligation" approach to a "selective ligation" approach was associated with an increase or decrease in long-term morbidity (Table III). In the multivariate model, the odds of Abnormal Neurodevelopmental Outcome among those treated with "selective ligation" was significantly less than among infants treated with "early ligation" (OR = 0.07, 95% CI 0.00–0.96) (Table III). Note that in this model, respiratory severity score, brain injury, and Bayley test version also were significant predictors ($p<0.05$); the model demonstrates that the significant difference in Abnormal Neurodevelopmental Outcome in those who underwent "selective ligation" persisted even after adjusting for these significant (as well as the other nonsignificant) variables in the model.

Infants in the "selective ligation" group had a lower incidence of surgical ligation than infants in the "early ligation" group (Table II). To see whether the incidence of surgical ligation altered the incidence of Abnormal Neurodevelopmental Outcome, we added a variable for "ligation status" (ligation vs. no ligation) to the multivariate model described above. "Ligation status" was not an important predictor of Abnormal Neurodevelopmental Outcome in the adjusted model (OR=0.99, 95% CI 0.38 – 2.60, p=0.99).

We next examined the timing of surgical ligation (by adding a variable for "young postnatal age at the time of ligation" to the multivariate model) to see if this might have an impact on the incidence of Abnormal Neurodevelopmental Outcome. The variable "young postnatal age at the time of ligation" had 3-components: (a) infants with an open ductus who were ligated at ≥ 10 days or infants with an open PDA that were not ligated at all; (b) infants with an open ductus who were ligated at < 10 days; and (c) infants with a closed ductus after indomethacin who did not undergo ligation. Thirty percent of infants in the "early ligation" group (compared with 10% of infants in the "selective ligation" group) had ligation < 10 days after birth. "Young postnatal age at the time of ligation" was a significant predictor of abnormal outcome: infants who were ligated during the first 10 days after birth had a significantly higher incidence of Abnormal Neurodevelopmental Outcome (OR = 11.44, 95% CI 1.85–70.72, p=0.01) than infants with an open ductus who were ligated at ≥ 10 days or were not ligated at all. In addition, after adjusting the model for "young postnatal age at the time of ligation," the risk of Abnormal Neurodevelopmental Outcome between the "selective ligation" and "early ligation" approaches was no longer significantly different (Treatment Approach OR = 0.14, 95% CI 0.01 – 2.01, p=0.15). The effect of "young postnatal age at the time of ligation" on the multivariate model was similar when we compared ligation at < 15 days after birth against ≥ 15 days after birth and no ligation. Being ligated at a young postnatal age could partially account for the difference between treatment approaches.

Similar results were found when we used the second model of abnormal neurodevelopmental outcome (Alternate Abnormal Neurodevelopmental Outcome) (Table III).

Discussion

Our goal was to determine whether prolonged exposure to a persistent PDA increases the risk for Abnormal Neurodevelopmental Outcome. We compared the outcome from two consecutive time periods, one where the PDA was ligated soon after indomethacin failed, and the other where the PDA was allowed to persist until it either closed spontaneously or was surgically closed (after specific clinical criteria were met). Despite concerns (raised by recent near infrared spectroscopy studies) about potential neurodevelopmental risks associated with prolonged PDA exposure, we found no increase in incidence of abnormal neurodevelopment among infants who were treated with the "selective ligation" approach with more prolonged PDA exposure. We found just the opposite, that infants treated with the "early ligation" approach seemed to have worse neurodevelopmental outcomes.

In our follow-up population, most of the infants who failed indomethacin treatment had ligation at some point (100% in the "early ligation" group and 66% in the "selective ligation" group). Several prior studies have found that "ligation status" itself (ligation vs. no ligation) does not appear to be an important predictor of neurodevelopmental outcome when multivariate statistical models are adjusted for other perinatal and neonatal risk factors (10, 17). Our current study supports these prior observations. Although "ligation status" itself may not predict neurodevelopmental outcomes, the timing of surgical ligation does appear to be a significant predictor of Abnormal Neurodevelopmental Outcome (especially when ligations are performed < 10 days after birth). In addition, being ligated at a young postnatal age partially accounted for the difference between our two treatment approaches. Several studies have reported increased problems in the immediate post-operative period (increased cytokine production, poor oxygenation, hypotension, poor cardiac performance, longer duration of intubation, and increased BPD) when surgical ligation is performed early in the neonatal hospitalization (9, 23–25). We hypothesize that the neurodevelopmental benefits observed with the "selective ligation" approach may be due to the infants' more advanced postnatal age and increased maturity at the time of ligation.

There are important caveats in interpreting our results. Our study was not a randomized controlled trial; rather, we evaluated the effects of a change in practice between two consecutive time periods. Although our study cannot provide definitive evidence for the benefits of one treatment over the other, there are several features of our study that enable us to have some confidence in the associations that we observed. During the years bracketed by our study, there appeared to be no significant changes in our study population in the incidence of perinatal and neonatal risk factors (except for clinical chorioamnionitis) or in the incidence of neonatal morbidities (compare Period 1 with Period 2; Table II), nor were there changes in our protocols for prophylactic indomethacin, feeding advances or ventilator management during these periods. When we examined a subgroup of infants (whose ductus closed following indomethacin treatment), where there were no known changes in treatment practice, we found no significant change in the incidence of Abnormal Neurodevelopmental Outcome; this suggests that potential changes in practice, that were unaccounted for or unanticipated, were not significant contributors to the beneficial effects of the "selective ligation" approach in our study. When a treatment approach was applied, it was applied uniformly to all infants during a study period (i.e., none of the infants during Period 2 were treated with an "early ligation" treatment approach, and vice versa during Period 1). Risk factors (like brain injury, gestational diabetes, and high respiratory severity score [a measure of baseline illness severity]), that previously have been shown to be associated with

abnormal neurodevelopment (26–28), were also found to be associated with abnormal neurodevelopment in our study population (Table III). Multivariate statistical models were used to adjust for potential differences that might be due to differences in the period of birth or in other perinatal or neonatal risk factors.

During the time interval bracketed by the study there was a change in the Bayley test instrument used to evaluate cognitive performance. Because the Bayley III test has been shown to overestimate developmental ability when compared with the Bayley II test (21, 29), we adjusted our statistical models for version of the Bayley test used. Although the majority of infants treated during Period 2 were evaluated with the Bayley III, the significant difference between the "selective ligation" and "early ligation" treatment approaches in Abnormal Neurodevelopmental Outcome still persisted even when the statistical models were adjusted for the different Bayley test versions (Table III). In addition, because studies have shown that differences between the Bayley test versions are most pronounced at the low end of the scale (raising concern that the most severely affected infants could be missed with the Bayley III) (21, 22), we examined a second neurodevelopmental outcome model, where a Bayley II MDI <70 or a combined Bayley III Cognitive and Language score of <80 was used to define cognitive abnormality (a cut point of <80 on the combined Bayley III Cognitive and Language score has been shown to have good sensitivity and specificity for predicting a Bayley II MDI of ≤70 (22)). Similar results were found with this *Alternate* Abnormal Neurodevelopmental Outcome model as were found with the Abnormal Neurodevelopmental Outcome model (Table III). Lastly, if the change in Bayley test was the primary cause for the improved outcome in the "selective ligation" group during Period 2, then we also would have expected to see a similar improvement in outcome in the infants whose PDAs closed with indomethacin during Period 2. Because there was no improvement in neurodevelopmental outcome in infants whose PDAs closed with indomethacin, it is unlikely that the change in Bayley test explains the lower odds of Abnormal Neurodevelopmental Outcome in the "selective ligation" group.

In conclusion, we found that neurodevelopmental outcome at 18–36 months was no worse when PDAs that fail to close with indomethacin were treated with a "selective ligation" approach, rather than an "early ligation" approach. This finding provides some reassurance about prolonged exposure to a PDA. Longer-term follow-up of these infants is needed to ensure that the lack of harm (and the apparent benefit) of a "selective ligation" approach persists in later childhood.

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Abbreviations

PDA	Patent ductus arteriosus
MDI	Mental development index
OR	Odds ratio
BPD	Bronchopulmonary dysplasia
NEC	Necrotizing enterocolitis
RCT	Randomized controlled trial
ROP	Retinopathy of prematurity

SD	Standard deviation
CI	Confidence interval
RSS	Respiratory severity score

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Table 1

Demographics of Total Population and Potential Long-Term Study Population

	Total Population		Long-Term Study Population	
	Period 1 (n=216)	Period 2 (n=169)	No Follow-Up (n=109)	Follow-Up (n=224)
Male sex, %	56	50	52	53
Race, % Caucasian	48	38	34*	49*
Gestation in weeks, mean (SD) †	25.8 (1.1)	25.9 (1.1)	26.1 (1.1)*	25.8 (1.1)*
Birth weight in grams, mean (SD)	834 (192)	824 (187)	863 (203)	836 (184)
Antenatal Betamethasone, % †	75	73	76	75
Pre-eclampsia, %	14	21	17	17
Gestational Diabetes, %	7	5	6	7
Chorioamnionitis, %	17*	28*	20	22
Surfactant, %	93	92	91	93
RSS at 24 hours (units), mean (SD) †	2.1 (1.9)	1.9 (1.1)	1.9 (1.5)	2.0 (1.5)
PDAs that failed indomethacin treatment, %	24	25	17	26
PDA ligations, %	24	18	16	22
First enteral feed, days (SD)	8.9 (5.3)	9.6 (8.1)	9.1 (8.2)	9.2 (6.1)
Enteral feedings = 80 ml/kg/day, days (SD)	22 (13)*	26 (13)*	23 (13)	24 (13)
Infection, % †	45	51	36*	49*
Necrotizing Enterocolitis, % †	16	17	12	10
Intracranial Hemorrhage, Grade III or IV, %	9	10	6	7
Cystic Periventricular Leukomalacia, %	10	12	6	9
Brain Injury, % †	15	17	9	12
Bronchopulmonary Dysplasia, % †	32	29	30	27
Retinopathy of Prematurity, % †	14	18	15	13
Death, %	15	12	N/A	N/A
Death or Bronchopulmonary Dysplasia, %	39	36	N/A	N/A

*p<0.05, N/A=not applicable

†Definitions:

Gestation, based on early (<24 weeks gestation) ultrasound dating

Antenatal Betamethasone, receipt of betamethasone more than 6 hours prior to delivery

Respiratory Severity Score (RSS), mean airway pressure x fraction of inspired oxygen, measured at 24 hours after birth

Infection, included both early and late neonatal infections

Necrotizing enterocolitis, Bell's classification ≥II (treated medically or surgically) and "spontaneous perforations" occurring before 7 days of life

Brain injury, intracranial hemorrhage ≥ Grade III, periventricular leukomalacia, or shunt

Bronchopulmonary Dysplasia (BPD), the need for supplemental oxygen to maintain oxygen saturation >90% at 36 weeks corrected age (30)

Retinopathy of prematurity, Stage II with plus disease or ≥ Stage III

Table 2

Demographics Among Long-Term Follow-Up Population: According to Treatment Period and Ductus Status After Indomethacin

	Follow-Up Population					
	Total Follow-Up Group		Ductus Closed Group		Ductus Open Group	
	Period 1 (n=128)	Period 2 (n=96)	Period 1 (n=98)	Period 2 (n=67)	Period 1 (Early ligation) (n=30)	Period 2 (Selective ligation) (n=29)
Male sex, %	57	48	54	54	67 *	34 *
Race, % Caucasian	52	45	49	45	63	45
Gestation in weeks, mean (SD) †	25.8 (1.1)	25.9 (1.0)	26.1 (1.0)	26.1 (1.0)	25.0 (1.1)	25.3 (0.9)
Birth weight in grams, mean (SD)	831 (185)	843 (183)	843 (191)	866 (194)	793 (158)	788 (140)
Antenatal Betamethasone, % †	77	73	83	79	60	59
Pre-eclampsia, %	17	19	22	24	0	7
Gestational Diabetes, %	9	4	10	6	3	0
Chorioamnionitis, %	17 *	30 *	15 *	30 *	20	31
Surfactant, %	92	95	90	97	100	90
RSS at 24 hours (units), mean (SD) †	2.0 (1.8)	2.0 (0.9)	1.7 (1.1)	2.0 (0.7)	3.1 (2.8)	2.1 (1.3)
PDAs that failed indomethacin treatment, %	23	30	0	0	100	100
Median exposure to PDA shunt, days (range)	0 (0–9) *	0 (0–426) *	0	0	1 (0–9) *	10 (2–426) *
PDA ligations, %	23	20	0	0	100 *	66 *
First enteral feed, days (SD)	8.7 (5.3)	9.9 (7.0)	7.2 (3.1)	8.0 (4.9)	13.1 (7.5)	13.9 (9.0)
Enteral feedings = 80 ml/kg/day, days (SD)	23 (14)	25 (11)	19 (10)	22 (10)	34 (15)	31 (12)
Infection, % †	47	52	42	55	63	45
Necrotizing Enterocolitis, % †	10	10	6	10	23	10
Intracranial Hemorrhage, Grade III or IV, %	5	9	5	9	3	10
Cystic Periventricular Leukomalacia, %	6	13	7	10	3	17
Brain Injury, % †	9	16	9	13	10	21
Bronchopulmonary Dysplasia, % †	28	26	18	21	60	38
Retinopathy of Prematurity, % †	12	16	7	10	27	28
Maternal Education, % completed high school	85	82	81	85	96 *	75 *

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	Follow-Up Population					
	Total Follow-Up Group		Ductus Closed Group		Ductus Open Group	
	Period 1 (n=128)	Period 2 (n=96)	Period 1 (n=98)	Period 2 (n=67)	Period 1 (Early ligation) (n=30)	Period 2 (Selective ligation) (n=29)
Age at last Bayley Test, years	2.1 (0.5)	2.2 (0.5)	2.1 (0.5)	2.2 (0.5)	2.1 (0.5)	2.2 (0.5)
Bayley Test version, % Bayley III	20*	99*	23*	100*	11*	97*

*p<0.05;

†Definitions: see Table 1 legend.

Table 3

Effect of Selective Ligation versus Early Ligation PDA Management on Neurodevelopmental Outcome

	Adjusted Odds Ratios			
	Abnormal Neurodevelopmental Outcome Model (Bayley II MDI or Bayley III Cognitive <70, Cerebral Palsy, Blind, or Deaf)		***Alternate* Abnormal Neurodevelopmental Outcome Model (Bayley II MDI <70 or combined Bayley III Cognitive and Language Score <80, Cerebral Palsy, Blind, or Deaf)**	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**
Treatment Approach (Selective ligation vs. Early ligation) †	0.07 (0.00–0.96)	0.046	0.06 (0.01–0.44)	0.006
Epoch (Period 2 vs. Period 1)	—	NS	—	NS
Male Sex	—	NS	—	NS
Caucasian Race	—	NS	—	NS
Gestational Age ‡	—	NS	—	NS
Birth Weight	—	NS	—	NS
Antenatal Betamethasone‡	—	NS	—	NS
Pre-Eclampsia	—	NS	—	NS
Gestational Diabetes	4.19 (0.84–20.92)	0.080	9.32 (1.67–51.91)	0.011
Chorioamnionitis	—	NS	—	NS
Surfactant	—	NS	—	NS
Respiratory Severity Score‡	1.38 (1.04–1.84)	0.025	1.34 (0.91–1.98)	0.142
Infection‡	—	NS	—	NS
Necrotizing Enterocolitis‡	—	NS	4.59 (1.54–13.70)	0.006
Brain Injury‡	17.60 (4.74–65.37)	<0.001	16.74 (4.94–56.75)	<0.001
Bronchopulmonary Dysplasia‡	—	NS	—	NS
Retinopathy of Prematurity‡	—	NS	—	NS
Maternal Education§	—	NS	0.36 (0.13–1.05)	0.060
Age at Bayley Test	—	NS	—	NS
Bayley Test Version (III vs. II)	0.22 (0.08–0.63)	0.005	—	NS

The multivariable models were constructed as described in Methods. The morbidity models included the total follow-up study population (n = 224, see Table 2). Adjusted ORs, CIs, and p-values are displayed for each of the independent variables in the model only if their p-values were <0.20. NS = p-value ≥0.20.

‡Definitions: see Table 1 legend.

§Defined as less than a high school degree versus a high school degree or greater.

†Treatment approach was examined as a trivariate variable: open ductus-"early ligation" approach, open ductus-"selective ligation" approach, closed ductus-no treatment.

Note: Bayley test version is not a significant predictor in the *Alternate* Abnormal Neurodevelopmental Outcome model (p=0.51); this is probably due to the adjustment in the Bayley III Cognitive and Language score cut point to <80 which was designed to bring the Bayley III more in line with the results of the Bayley II (22)).