Timing of Patent Ductus Arteriosus Treatment and Respiratory Outcome in Premature Infants: A Double-Blind Randomized Controlled Trial

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Objective To determine whether “early” ibuprofen treatment, at the onset of subtle patent ductus arteriosus (PDA) symptoms, would improve respiratory outcome in premature infants compared with “expectant” management, with ibuprofen treatment only when the PDA becomes hemodynamically significant (HS).

Study design We conducted a randomized double-blind controlled trial of infants with gestational ages 23 to 32 weeks and birth weights 500 to 1250 g who had echocardiography for subtle PDA symptoms (metabolic acidosis, murmur, bounding pulses). Infants were then randomized to “early” treatment (blinded ibuprofen; n = 54) or “expectant management” (blinded placebo, n = 51). If the PDA became HS (pulmonary hemorrhage, hypotension, respiratory deterioration), infants received open label ibuprofen. Infants with HS PDA at enrollment were excluded from the study. Respiratory outcomes and mortality and major morbidities were determined.

Results “Early” treatment infants received ibuprofen at median age of 3 days; infants in the “expectant group” in whom HS symptoms developed (20%) received ibuprofen at median of 11 days. A total of 49% of “expectant” infants never required ibuprofen or ligation. No significant differences were found in the primary outcome (days on oxygen [O₂] during the first 28 days), death, O₂ at 36 weeks, death or O₂ at 36 weeks, intestinal perforation, surgical necrotizing enterocolitis, grades III and IV intracranial hemorrhage, periventricular leukomalacia, sepsis or retinopathy of prematurity.

Conclusion Infants with mild signs of PDA do not benefit from early PDA treatment compared with delayed treatment. (J Pediatr 2012;160:929-35).

Although the ductus arteriosus is critical in utero to allow most blood to bypass the pulmonary circulation while maintaining fetal systemic blood flow, its persistent patency after birth can cause significant clinical consequences related to excessive pulmonary blood flow and compromised systemic blood flow. Whereas in the term infant the ductus constricts within hours of birth, in the premature infant the ductus may remain patent for a prolonged period or fail to close.¹ The current clinical approach to a patent ductus arteriosus (PDA) in the preterm infant is varied and controversial. Although some clinicians treat a PDA prophylactically, others treat a PDA when mild signs present within a few days after birth. Other clinicians take an “expectant” approach and allow for possible spontaneous closure, treating a PDA at a later time, only when signs indicate hemodynamic significance. In addition, the definition and management of a hemodynamically significant (HS) PDA are both variable and controversial. This wide variation in approach to the PDA is caused by the lack of definitive data on the optimal time to treat for immediate clinical response and long-term complications, such as bronchopulmonary dysplasia (BPD) and pulmonary hypertension.²

There are inherent risks and benefits with either approach. The early treatment of PDA may be beneficial by eliminating both early morbidity (including hypotension, respiratory deterioration, intestinal hypoperfusion) and later morbidity (including BPD). However, because a substantial percentage of PDAs will close without therapy, or may remain open without producing significant symptoms, initiating early treatment may unnecessarily expose many infants to cyclo-oxygenase inhibitors or surgical ligation, both of which are associated with adverse effects. This situation might be avoided by delaying PDA treatment and allowing for the possibility of spontaneous closure without exposure to unnecessary medication or surgery.

Multiple studies have reported an association between PDA and increased risk for BPD.³⁻⁵ Despite studies examining the different treatment modalities and treatment schedules for PDA, none has definitively shown a significant effect on reduction in the incidence of BPD. However, few studies have enrolled a large enough number of infants, particularly extremely premature infants, or have delayed PDA treatment beyond 7 days. Therefore, groups reported from the literature receiving either “early” or “late” treatment ended up differing by only a few days.⁶⁻⁷ Thus, the

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BPD Bronchopulmonary dysplasia
FiO₂ Fraction of inspired oxygen
HS Hemodynamically significant
MV Mechanical ventilation
NEC Necrotizing enterocolitis
O₂ Oxygen
PDA Patent ductus arteriosus
optimal timing for PDA therapy might prevent the progression of lung damage and the development of BPD, while limiting the potential complications of PDA therapy.

The objective of this trial was to determine whether “early” ibuprofen treatment, at the onset of subtle PDA symptoms, would improve respiratory outcome in premature infants compared with “expectant” management, with ibuprofen treatment only if and when the PDA became hemodynamically significant (HS). We hypothesized that “early” pharmacologic treatment of the PDA with ibuprofen would improve respiratory course (as reflected by a reduction in duration of supplemental oxygen (O2) during the first 28 days) compared with “expectant” PDA treatment.

Methods

This prospective double-blind randomized control clinical trial was conducted from January 2008 to August 2010 at the tertiary level neonatal intensive care unit at Holtz Children’s/University of Miami/Jackson Memorial Medical Center (Miami, Florida). The study was approved by the institutional review board of the University of Miami. Written informed parental consent was obtained before enrollment. The trial was registered with ClinicalTrials.gov (NCT00802685).

Eligible infants were those born at Jackson Memorial Hospital or its affiliates, with birth weights between 500 and 1250 g and gestational ages between 23 and 32 weeks who were >24 hours old but ≤14 days old. Infants who were severely small for gestational age (>3 SD less than the mean birth weight for gestational age) or had major congenital malformations, proven sepsis (positive blood culture results), serum creatinine level >1.7, oliguria (urine output <1 cc/kg/hr), pulmonary hypertension (with right-to-left PDA shunt), abdominal pathology (abdominal distension, discoloration, abnormal abdominal radiograph), bleeding diathesis, terminal condition (intractable respiratory failure, intractable hypotension, no expectation of survival beyond 48 hours) were excluded, as were infants with symptoms of a HS PDA at study enrollment (see definition below).

Sample size was determined by using the primary outcome of number of days spent on supplemental O2 during the first 28 days of life. On the basis of earlier data from our neonatal intensive care unit, infants in this birth weight category had a mean duration of 20 ± 8 days of supplemental O2 during the first 28 days. To detect a 20% difference of days of O2 dependence during the first 28 days, an estimated 84 infants per group (168 total) were determined to be needed. On the basis of the census in the neonatal intensive care unit, we estimated that approximately 150 babies would be born in this weight and gestational age category per year and that approximately 100 of them would have PDA. We estimated being able to conduct this study in a 2- to 3-year period. However, after two-thirds planned enrollment (105 of 168 infants), NeoProfen (Ovation Pharmaceuticals, Lebanon, New Jersey) was recalled by the manufacturer and was no longer available in the United States for clinical or research use. This necessitated study termination in August of 2010.

Safety and Efficacy Monitoring/Interim Analyses

Safety was overseen by a data safety monitoring board, which evaluated results when the study was one-third and two-thirds completed (shortly before study termination) for these safety issues: death, intestinal perforations, necrotizing enterocolitis (NEC) requiring surgery, pulmonary hypertension requiring nitric oxide, severe pulmonary hemorrhage, and renal failure (defined as creatinine level >2.0).

Interim efficacy analysis of the primary outcome measure (number of days on O2 at 28 days) was also conducted at one-third and two-thirds of enrollment by using the method of two-sided spending function of O’Brien-Fleming.

Study Procedure

Consent was obtained as soon as possible after birth for all infants meeting eligibility criteria. After 24 hours of age, but not after 14 days of age, eligible infants were observed for the presence of early, mild symptoms of a PDA, specifically defined as metabolic acidosis (base excess < −7), mean blood pressure less than weeks in gestation or requiring vasopressor support, bounding pulses/hyperactive precordium, or systolic murmur (Figure 1; available at www.jpeds.com). When one or more of the aforementioned symptoms was noted, a color Doppler echocardiogram was performed. When the initial echocardiogram results were positive for PDA (defined as the presence of a PDA with either predominantly left-to-right or bidirectional shunt), infants were stratified according to birth weight (500-800 g and 801-1250 g) and randomized (via sealed envelopes prepared by using a random number table) to one of two study groups. When the initial echocardiogram results were negative for PDA, the enrolled infants were observed until 14 days of age, and a repeat echocardiogram was conducted when PDA symptoms developed; when the results of this repeat echocardiogram were positive, the baby was then randomized to one of the two study groups. Clinicians, investigators and nursing staff were blinded to the study group to which the baby was assigned and the medication the baby was receiving. Only the neonatal pharmacists were aware of the study group of each baby and were responsible for preparing the “blinded” ibuprofen or “blinded” placebo study drug. The two study groups were: (1) “Early” treatment (consisting of “study drug,” which for this group was blinded ibuprofen); or (2) “Expectant” treatment (consisting of “study drug,” which for this group was blinded placebo). When infants in either study group, after receiving their initial specific blinded study drug, continued with or developed PDA symptoms that did not meet criteria of hemodynamic significance, they were either observed or received a prolonged course or second course of their assigned blinded study drug at the discretion of the clinical team. For both groups, treatment with ibuprofen (open label) was initiated only when symptoms of a HS PDA developed and a PDA was confirmed with echocardiography. Criteria defining a HS PDA included signs of PDA plus the presence of pulmonary hemorrhage (persistent bloody secretions from the endotracheal tube) alone, or signs of PDA plus cardiomegaly and pulmonary edema on chest x-ray.
radiography plus one of the following: either hypotension not caused by an identifiable cause other than PDA requiring vasopressor dose >10 μg/kg/min or respiratory failure (not caused by an identifiable cause other than PDA), which was defined as the presence of at least two of the following increases in ventilator settings: fraction of inspired oxygen (FiO₂) > 0.5, intermittent mandatory ventilation > 40 breaths/min, peak inspiratory pressure > 20 cm H₂O, or high frequency ventilation with Paw > 13 and FIO₂ > 0.5. These settings needed to be maintained for >8 hours and were required to maintain O₂ saturation between 88% and 95% and PaCO₂ < 65 mm Hg. The study intervention ended at day 28. When the PDA remained open after day 28 and the infant was still requiring mechanical ventilation (MV), the PDA could be treated with open label ibuprofen or PDA ligation at the discretion of the clinical team.

Drug Administration
At randomization, infants in the “early” treatment group received blinded ibuprofen lysine (NeoProfen, Ovation [now Lundbeck] Pharmaceuticals, Deerfield, Illinois); infants in the “expectant” treatment group received blinded placebo (5% dextrose). The dosing schedule for ibuprofen was an initial dose of 10 mg/kg, followed by two doses of 5 mg/kg each, every 24 hours, by slow intravenous infusion; dosing of placebo involved equivalent volumes of dextrose by slow intravenous infusion on the same schedule. When it was determined that an enrolled infant had persistent signs of PDA without meeting hemodynamic significance, a prolonged course of blinded assigned study drug (two additional doses of blinded 5 mg/kg ibuprofen or equivalent volume of blinded placebo) or a repeat course of blinded assigned study drug could be administered at the discretion of the clinical team. When HS PDA developed in infants from either study group before 28 days and PDA was confirmed, infants received unblinded, open-label ibuprofen and, when contraindicated or unsuccessful, PDA ligation.

Study Endpoints
Data were collected on maternal and infant demographics and PDA characteristics of both groups, including age of PDA presentation, age at randomization, percent of babies in each group requiring open label ibuprofen or ligation, time of ibuprofen administration, PDA outcome after 28 days of life, and number in whom contraindications (including renal and abdominal pathology) developed. The primary outcome of this study was the number of days spent on supplemental O₂ by each infant during the first 28 days (as an indicator of evolving BPD). The need for supplemental O₂ was defined as O₂ >21% needed to keep saturations ≥88%. Death and major respiratory outcomes including need for O₂ at 36 weeks corrected post-menstrual age, death or need for O₂ at 36 weeks, and number of days spent on MV during the first 28 days, and the need for O₂ or MV at day 28 was assessed. Secondary outcomes included total duration of O₂, duration of MV, need for O₂ >30% at 36 weeks, pneumothorax, pul-}

monary interstitial emphysema, postnatal steroids, intestinal perforation, necrotizing enterocolitis requiring surgery, intracranial hemorrhage, periventricular leukomalacia, retinopathy of prematurity, and sepsis (defined as positive blood culture results).

Statistical Analysis
Data analyses were conducted on an intention-to-treat basis. Continuous variables in groups were compared with the student t test or Mann-Whitney rank sum test as appropriate, and categorical variables were compared with χ² test and Fisher exact test for the pooled data from all infants and within each strata. Mantel-Haenszel statistics were used to test for independence between the treatments and dichotomous outcome variables controlling for the co-variate of birth weight strata. The Mantel-Haenszel common OR and 95% CI are reported. Statistical analysis was conducted with IBM SPSS Statistics software version 19 (IBM Corp, Armonk, New York and SPSS Inc, Chicago, Illinois), SAS (SAS Institute, Cary, North Carolina), and mQuery software (Statistical Solutions; Saugus, Massachusetts). A P value < .05 was considered to be significant. Statistical analysis was performed with the Biostatistics Collaboration and Consulting Core of the Division of Biostatistics, Department of Epidemiology and Public Health of the University of Miami Miller School of Medicine.

Results
During the study period, there were 399 infants between 500 and 1250 g born at Jackson Health System Hospitals (Figure 2; available at www.jpeds.com). Of those infants, consent was given for 179 infants, but 6 of the consents were withdrawn. One hundred five infants were randomized, and 68 infants were not randomized because of presentation with the exclusion criterion of HS PDA at randomization (n = 10), absence of PDA on echocardiography (n = 55), or other reasons (suspected NEC, oliguria, early death, n = 3). The characteristics of the infants in the “early” and the “expectant” treatment groups, stratified in two weight categories (500-800 g and 801-1250 g) and analyzed as one composite weight group, are seen in Table 1. Of the 105 infants enrolled in the study, 54 were randomized to the “early” group and 51 to the “expectant” group (Figure 2). When stratified by birth weight, 57 infants were enrolled in the 801 to 1250 g group, compared with 48 infants in the ≤800 g group. There were no significant differences in infant demographics between “early” and “expectant” infants in gestational age, sex, race, antenatal steroid exposure, maternal chorioamnionitis, Apgar score at 5 minutes, and early respiratory course. Although more “early” infants in the composite weight group were on O₂ at 24 hours compared with “expectant” infants, this difference disappeared by 72 hours, and there were no differences in proportion of infants needing MV at 24 hours or needing surfactant therapy between groups.
The response of the PDA to “early” compared with “expectant” treatment is summarized in Table II. PDA was diagnosed in infants in both groups with echocardiography at a median of day 3 of life, and infants were randomized to either early treatment (blinded ibuprofen) or expectant treatment (blinded placebo) at day 3 to 4, indicating that all “early” treatment infants received their first dose of ibuprofen at a relatively early age. A significantly greater number of infants in the “expectant” group (blinded placebo) were given a second course of blinded study drug compared with infants in the “early” treatment group (blinded ibuprofen). Of infants in the “expectant” group, only 20% needed open label ibuprofen during the first 28 days for HS PDA and of infants in the “expectant” group, only 20% needed open label ibuprofen in the first 28 days for HS PDA and received it at a median age of 11 days. Thirteen percent of infants who had received early ibuprofen (“early” group), also required open label ibuprofen in the first 28 days for HS PDA. There were no significant differences in groups for the need for open label ibuprofen after 28 days for HS PDA and for need for surgical ligation in the first 28 days of age.

There were no significant differences between the “early” treatment group and the “expectant” treatment group in any of the respiratory outcomes listed in Table III, except a higher proportion of infants in the “early” group required >30% inspired O$_2$ at 36 weeks. Specifically, the primary outcome, number of days on O$_2$ during the first 28 days, did not differ in the treatment groups. There were no differences in total days on O$_2$ or total days on MV, BPD (defined as O$_2$ requirement at 36 weeks post-menstrual age), and the composite outcome of death or O$_2$ at 36 weeks between “expectant” and “early” treatment groups.

Death until discharge did not differ in the groups. Pulmonary complications, including need for postnatal steroids and pneumothorax, were not different, although there was more pulmonary interstitial emphysema in the “early” treatment group. There were no differences in other complications of prematurity, including grades III and IV intracranial hemorrhage, preventricular leukomalacia, necrotizing enterocolitis (requiring surgery), spontaneous intestinal perforation, sepsis or retinopathy of prematurity ≥ stage 3 (Table IV).

Discussion

Currently, the clinical approach to a PDA is variable between institutions, on the basis of the lack of definitive evidence-based data. It remains unclear as to what represents the optimal time to treat a PDA: prophylactic treatment in infants younger than a certain gestational age, early treatment at the onset of mild symptoms, or later when the PDA becomes HS, in relation to immediate clinical consequences, and long-term outcomes, particularly BPD. There are potential complications of medical PDA therapy, such as renal dysfunction and intestinal perforation. There are also complications of surgical PDA closure, such as cardiopulmonary dysfunction,
The approach to PDA treatment, specifically treatment modalities and treatment schedules, in relation to long-term pulmonary outcome remains in question. In the large prospective study of Schmidt et al, prophylactic treatment with indomethacin had no effect on BPD, assessed as O₂ dependence at 36 weeks post-conception. Furthermore, studies in premature baboons indicate that infants with persistence of the PDA have delayed alveolar development and decreased alveolar surface area compared with infants with early closure of the PDA by using ibuprofen. Both of these aspects of developmental derangement, vascular and alveolar, are features of BPD in human infants. However, despite strong evidence that increased flow and pressure in the developing pulmonary vasculature caused by a PDA can produce morphologic and functional alterations in the lung, clinical evidence linking PDA with the development of BPD remains largely epidemiological. Because infants with PDA are exposed to multiple risk factors for lung injury (ie, MV, O₂ exposure, infection, inflammation), these factors are important confounders in the association of PDA and increased risk for BPD.

### Table III. Respiratory outcomes assessed from birth until day 28, 36 weeks PMA, and discharge or death

<table>
<thead>
<tr>
<th>Variables</th>
<th>All infants</th>
<th>Birth weight 500-800 g</th>
<th>Birth weight 801-1250 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days on O₂ first 28 days</td>
<td>Early (n = 54)</td>
<td>21 (7-27)</td>
<td>19 (5-26)</td>
</tr>
<tr>
<td>Total days on O₂</td>
<td>Early (n = 51)</td>
<td>39 (9-133)</td>
<td>37 (10-97)</td>
</tr>
<tr>
<td>Days on MV first 28 days</td>
<td>Early (n = 24)</td>
<td>10 (1-28)</td>
<td>8 (1-28)</td>
</tr>
<tr>
<td>Today days on MV</td>
<td>Early (n = 24)</td>
<td>12 (1-68)</td>
<td>13 (1-59)</td>
</tr>
<tr>
<td>On O₂ at 36 weeks PMA</td>
<td>Early (n = 54)</td>
<td>17 (33)</td>
<td>16 (33)</td>
</tr>
<tr>
<td>Death or On O₂ at 36 weeks PMA</td>
<td>Early (n = 24)</td>
<td>19 (35)</td>
<td>18 (35)</td>
</tr>
<tr>
<td>On O₂ &gt;30% at 36 weeks PMA*</td>
<td>Early (n = 24)</td>
<td>9 (17)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Death or On O₂ &gt;30% at 36 weeks PMA†</td>
<td>Early (n = 30)</td>
<td>11 (20)</td>
<td>4 (8)</td>
</tr>
</tbody>
</table>

*PMA, postmenstrual age. Results expressed as median (10th-90th percentile) or number (%).
†Analyzed as percent of all infants alive at assessment age.
**0.17 (0.03-0.88) expectant compared with early group, Mantel-Haenszel common OR estimate.
10.27 (0.07-0.99) expectant compared with early group, Mantel-Haenszel common OR estimate.

### Table IV. Mortality and morbidity

<table>
<thead>
<tr>
<th>All infants</th>
<th>Birth weight 500-800 g</th>
<th>Birth weight 801-1250 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death to discharge</td>
<td>Early (n = 54)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Postnatal steroids</td>
<td>Early (n = 51)</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Early (n = 24)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Pulmonary interstitial emphysema*</td>
<td>Early (n = 24)</td>
<td>9 (17)</td>
</tr>
<tr>
<td>IVH grades III and IV</td>
<td>Early (n = 24)</td>
<td>6 (11)</td>
</tr>
<tr>
<td>PVL</td>
<td>Early (n = 24)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>NEC (requiring surgery)</td>
<td>Early (n = 24)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Spontaneous intestinal perforation</td>
<td>Early (n = 24)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Early (n = 24)</td>
<td>22 (42)</td>
</tr>
<tr>
<td>ROP stage ≥3†</td>
<td>Early (n = 30)</td>
<td>7 (14)</td>
</tr>
</tbody>
</table>

*IVH, intracranial hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.
Results expressed as number (%).
†0.16 (0.03-0.65) expectant vs. Early, Mantel-Haenszel common OR estimate.
†Analyzed as percent of all infants alive at assessment age.
premature infants. Few, if any, of the previously reported trials of early compared with late medical treatment for PDA have actually delayed PDA treatment after 7 days. Thus, of major importance is determining whether an early treatment approach to PDA (as soon as mild PDA symptoms appear) would improve respiratory outcome compared with an “expectant” approach (either awaiting spontaneous PDA closure or treatment at the presentation of hemodynamic significance), which was the purpose of this study.

When this trial was designed to answer the aforementioned question, it was hypothesized that “early” treatment would improve respiratory outcome (primary endpoint: days of O2 dependence during the first 28 days) compared with “expectant” treatment. The study was powered to detect a 20% difference of days of O2 dependence during the first 28 days (indicative of early evolution to BPD) in groups. By using earlier data from our population, we estimated that 84 infants per group (168 total) would be needed and that the study could be completed within a 3-year period. Ibuprofen (NeoProfen) was selected as the medical therapy because of similar efficacy profile, but reduced renal adverse effects compared with indomethacin. We analyzed the enrolled infants at study termination and found no differences in days of O2 dependence during the first 28 days, BPD (defined as O2 requirement at 36 weeks), or death or BPD in the study groups, both analyzed as a whole or as separate stratified weight groups, although there was a higher number of infants on O2 >30% at 36 weeks in the “early” treatment group. This finding was contrary to our hypothesis that early treatment would be beneficial for respiratory outcome. There were no major differences in other complications of prematurity. Additional statistical analysis and extrapolation with the effect size demonstrated by the enrolled infants (not reported here) indicated that no statistical difference would be present in respiratory outcomes (days of O2 dependence during the first 28 days, BPD at 36 weeks) if the study enrollment had continued to its initial goal of 168 infants. The study specifically excluded infants whose initial PDA presentation was that of hemodynamic significance. Randomizing these infants to early placebo was not feasible because of the possibility that delayed treatment could have been detrimental in this sicker group of infants. Thus, the findings of this study cannot be directly extrapolated to those infants who have early HS PDA as defined here.

The strengths of this study include having a high number of enrolled infants (despite early termination) compared with earlier studies and the lowest mean gestational age and birth weight (approximately 25-26 weeks, approximately 850 g) of the study population. We blinded the intervention so that clinicians were kept unaware of the study group of each infant. In addition, the study resulted in a spread of treatment of 8 days (rather than ≤4 in earlier studies) between “early” ibuprofen (which in this study was at day 3-4) compared with “expectant” management (only 20% needed open label ibuprofen for HS PDA, at a median of day 11). Also, this was a single site study, designed with input from a group of neonatologists whose clinical approach to the premature infant was largely consistent. Finally, this study allowed assessment of spontaneous PDA closure rate, found to be 49% in this very low birth weight population of infants. A major weakness, as aforementioned, was the premature study termination before reaching the enrollment goal because of ibuprofen unavailability. The choice of ibuprofen, rather than indomethacin, might also be considered a weakness of this study. Despite data indicating similar rates of PDA closure with either drug, a recent meta-analysis demonstrated an increased risk of BPD with ibuprofen compared with indomethacin treatment.

Taking the strengths and weaknesses in account, the study results suggest a lack of benefit from early PDA treatment at the onset of mild clinical signs compared with delay of PDA treatment until the onset of clear hemodynamic signs. On the basis of these results, plus the finding of a high spontaneous PDA closure rate, delaying therapy until a HS PDA is present could prevent unnecessary and potentially toxic intervention for PDA in critically ill premature infants.

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References

Figure 1. Study flow diagram.

Figure 2. Consolidated Standards of Reporting Trials (CONSORT) diagram.