When to Treat Hemodynamically Insignificant Patent Ductus Arteriosus in Preterm Infants

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CONTEXT
Patent ductus arteriosus (PDA) is a common clinical finding among preterm infants. It closes spontaneously by day 3 of life in 58% of the preterm infants.[1] PDAs are usually classified into a hemodynamically insignificant (HIS) and hemodynamically significant (HS). However, their defining criteria are variable. Fraction of HIS-PDAs may convert to HS-PDAs but it is usually difficult to predict this conversion. In addition, treatment of PDA is not without sequelae. Thus, whether and when to treat HIS-PDAs was and still controversial. Sosenko et al. aimed to explore whether early treatment of HIS-PDA would improve respiratory outcome in preterm infants compared with treatment only when the HIS-convert into HS-PDA.

METHODS
Superiority stratified randomized controlled trial from January 2008 to August 2010 at the tertiary level neonatal intensive care unit in the United States of America.

Population
Fixed sample size of 168 infants was planned but only 105 infants were enrolled. This is because of unavailability of the study drug (NeoProfen). Infants were stratified according to birth weight (500 to 800 g and 801 to 1250 g).

Inclusion
Infants who were born at study center 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 with subtle PDA. The subtle PDA defined as positive echocardiogram for PDA with either left-to-right or bidirectional shunt and one or more of the following: Metabolic acidosis (base excess<–7), mean blood pressure less than weeks in gestation or requiring vasopressor support, bounding pulses/hyperactive precordium, or systolic murmur.

Exclusion
Infants with birth weight>3 SD less than the mean birth weight for gestational age or had major congenital malformations, proven sepsis, 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) and with symptoms of a hemodynamically significant (HS) PDA at study enrollment. Criteria defining the 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 radiography plus one of the following: Either hypotension not caused by an identifiable cause other than PDA requiring vasopressor dose>10 mg/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.

Intervention
The study intervention ended at day 28.

Early treatment group
Blinded 10 mg/kg slow intravenous infusion of ibuprofen-lysine (NeoProfen), followed by two doses of 5 mg/kg each, every 24 hours.

Expectant treatment group
Blinded equivalent volumes of 5% dextrose
After receiving their initial specific blinded study drug, when infants of both study groups continued with or developed PDA symptoms that did not meet criteria of HS, they were either observed or received two additional doses or second course of their assigned blinded study drug at the discretion of the clinical team. When infants of both study group developed HS-PDA before 28 days, and PDA was confirmed, they received unblinded, open-label ibuprofen and when contraindicated or unsuccessful, PDA ligation.

Outcomes
Primary
The number of days spent on supplemental O2 by each
infant during the first 28 days as a proxy of early evolution to bronchopulmonary dysplasia (BPD).

Secondary

Total duration of O\textsubscript{2}, duration of mechanical ventilation, need for O\textsubscript{2}>30% at 36 weeks, pneumothorax, pulmonary interstitial emphysema, postnatal steroids, intestinal perforation, necrotizing enterocolitis requiring surgery, intracranial hemorrhage, periventricular leukomalacia, retinopathy of prematurity, and blood-culture-proven sepsis.

Allocation concealment

Sealed envelopes prepared by using a random number table.

Blinding

Double-Blind, only the pharmacists were aware of the study group of each baby and were responsible for preparing the “blinded” ibuprofen or “blinded” 5% dextrose.

RESULTS

There were no significant differences between the “early” treatment group and the “expectant” treatment group in the primary, the secondary outcomes, or complications of prematurity except two observations. A significantly lower proportion of pulmonary interstitial emphysema (2/51 (4%) versus 9/54 (17%); Mantel-Haenszel common odds ratio: 0.16; 95% confidence interval: 0.03 to 0.85) and severe BPD (2/51 (4%) versus 9/54(17%); OR: 0.17; 95% CI: 0.03 to 0.88) were observed in the “expectant” treatment group.

COMMENTS

This RCT showed that number of days of O\textsubscript{2} requirement during the first 28 days was comparable in early and late ibuprofen treatment for HIS-PD. Rather; early treatment may be deleterious as it associated with one of the secondary outcomes, severe BPD. As a result, “wait and see” approach may be appropriate for HIS-PDA.

This RCT scored 5 out of 5 on the Jadad scale, the most widely used scale to assess a quality of RCTs. Yet, it equivocally fills some of the empty spaces in the PDA treatment puzzle; therefore, it should be interpreted cautiously. Although, there was a safety and efficacy monitoring, complications of ibuprofen that may break the blindness such as oliguria was not addressed clearly. The negative result may be false as the study is underpowered by premature termination for unavailability of ibuprofen. Ibuprofen may associate with increased risk of BPD and pulmonary hypertension compared to indomethacin treatment. Accordingly; indomethacin is superior to ibuprofen in a placebo-controlled trial addressing respiratory outcomes. The echocardiogram results were dichotomized into presence or absence of PDA without taking into account the other PDA characteristics, including size and hemodynamic significant of PDA. At least, these PDA characteristics need to be reported as it is a possibility that there is imbalance between the study groups similar to pulmonary interstitial emphysema.

Abstracted from

Sosenko IR, Fajardo MF, Claure N, Bancalari E. Timing of patent ductus arteriosus treatment and respiratory outcome in premature infants: A double-blind randomized controlled trial. The Journal of Pediatrics 2012;160(6):929-35 e1. Epub 2012/01/31. doi: 10.1016/j.jpeds.2011.12.031.

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