Effects of Prophylactic Indomethacin on Vasopressor-Dependent Hypotension in Extremely Preterm Infants

Melissa Liebowitz, MD[1], Jane Koo, MD[1], Andrea Wickremasinghe, MD[2], Isabel Elaine Allen, PhD[3], and Ronald I. Clyman, MD[1,4]

Objective To determine whether a moderate-to-large patent ductus arteriosus (PDA) is responsible for vasopressor-dependent hypotension, occurring at the end of the first postnatal week.

Study design We performed a retrospective, double cohort controlled study of infants delivered at ≤27^{+6} weeks' gestation (n = 313). From January 2004 through April 2011, all infants were treated with prophylactic indomethacin ([PINDO] epoch). From May 2011 through December 2015, no infant was treated with indomethacin until at least 8 postnatal days (conservative epoch). Echocardiograms were performed on postnatal days 6 or 7. Hypotension was managed by a predefined protocol. The primary outcome was the incidence of dopamine-dependent hypotension, defined as having received at least 6 μg/kg/min dopamine for at least 24 hours during postnatal days 4-7.

Results As expected, the incidence of moderate-to-large PDA at the end of the first week differed significantly between epochs (PINDO = 8%; conservative = 64%). In multivariate analyses, infants in the PINDO epoch had a significantly lower incidence of vasopressor-dependent hypotension (11%) than infants in the conservative epoch (21%; OR = 0.40, 95% CI 0.20-0.82). Infants in the PINDO epoch also required less mean airway pressure, had a lower respiratory severity score, and lower mode of ventilation score than infants in the conservative epoch during postnatal days 4-7. The effects of PINDO on both the incidence of vasopressor-dependent hypotension and the need for respiratory support were no longer significant when analyses were adjusted for "presence or absence of a moderate-to-large PDA."

Conclusion PINDO decreases vasopressor-dependent hypotension and the need for respiratory support at the end of the first postnatal week. These effects are mediated by closure of the PDA. *(J Pediatr 2017;182:21-7).*

See editorial, p 10

Systemic hypotension occurs commonly in infants born extremely preterm and is associated with an increased incidence of neonatal mortality and morbidity (intraventricular hemorrhage, bronchopulmonary dysplasia, neurodevelopmental delay).[1-9] Vasopressors frequently are used to treat this condition despite the absence of clear guidelines to discriminate physiologic from pathologic hypotension.[5,10,11]

During the immediate postnatal period, the underlying causes of hypotension are multifactorial. They include perinatal asphyxia, hemorrhage/hypovolemia, inflammation/infection, and factors associated with delayed postnatal transition (eg, myocardial depression, relative adrenal insufficiency, impaired vascular regulation).[12] By the end of the first postnatal week, however, most episodes of hypotension can be attributed to identifiable causes (eg, bacteremia, necrotizing enterocolitis [NEC], gastrointestinal perforations, surgery, and patent ductus arteriosus [PDA]) or nonspecific causes associated with immaturity and illness (like dysregulated cytokine, vasodilator, and/or cortisol production or release).[13]

Infants born extremely preterm frequently develop a moderate-to-large PDA at the end of the first week. When other identifiable causes of hypotension have been ruled out, clinicians often attribute the cause of vasopressor-dependent hypotension to the presence of a PDA (disregarding the possible involvement of any of the nonspecific causes mentioned previously). Although it is true that a moderate-to-large PDA can lower systemic blood pressure (BP)[14-16] and is associated with the presence of vasopressor-dependent hypotension at the end of the first week,[13,17] no study to date has determined whether the PDA actually is responsible for the vasopressor-dependent hypotension or whether its presence is just a surrogate for nonspecific causes related to immaturity/illness.

Indomethacin, given either prophylactically (within 24 hours of birth) or within the first few days after birth, is effective in achieving ductus closure.[18,19]

BP	Blood pressure	PINDO	Prophylactic indomethacin
FiO_2	Fraction of inspired oxygen	RCT	Randomized controlled trial
NEC	Necrotizing enterocolitis	RSS	Respiratory severity score
PDA	Patent ductus arteriosus		

From the [1]Department of Pediatrics, University of California San Francisco, San Francisco, CA; [2]Department of Pediatrics, Kaiser Permanente Santa Clara Medical Center, Santa Clara, CA; [3]Department of Epidemiology & Biostatistics; and [4]Cardiovascular Research Institute, University of California San Francisco, San Francisco, CA

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Although more than 20 randomized controlled trials (RCTs) have investigated the effects of early PDA treatment on neonatal morbidities, none have mentioned its effect on the incidence of vasopressor-dependent hypotension.[18,19] Therefore, we performed the following retrospective double cohort controlled study to examine whether early treatment of the PDA decreases the incidence of vasopressor-dependent hypotension at the end of the first postnatal week.

Before May 2011, all infants in our nursery who delivered at ≤27^{+6} weeks' gestation were treated with prophylactic indomethacin ([PINDO] epoch). After April 30, 2011, PINDO was no longer used, and infants were only treated with indomethacin if the PDA persisted beyond 7 days (conservative epoch; see Methods). In the following study, we hypothesized that infants treated with PINDO would have a lower incidence of vasopressor-dependent hypotension at the end of the first week and that closure of the moderate-to-large PDA would explain this effect.

Methods

This project was approved by the institutional review board of the University of California San Francisco. Infants were included in the study if they were born between January 2004 and December 2015, delivered at ≤27^{+6} weeks' gestation, and were admitted to the intensive care nursery at the University of California San Francisco within 24 hours of birth. Detailed descriptions of our approach to respiratory and hemodynamic support have been published previously.[20-22] Two distinct epochs of PDA management existed during this 12-year period. During the first epoch, before May 2011, all infants without contraindications (n = 284) were treated with a course of PINDO starting within 15 hours of birth. Six potential PINDO doses were given at 24-hour intervals. An echocardiogram was performed before the third PINDO dose, and doses 4-6 were given only if there was any evidence (even minimal) of ductus patency on the echocardiogram. An echocardiogram was repeated at the end of the first week. Following the PINDO treatment, infants with a small or closed ductus were examined daily for a change in clinical symptoms indicative of a PDA (systolic murmur, widened pulse pressure, hyperdynamic precordium). If any of these occurred, an echocardiogram was performed within 24 hours. Infants with a persistent moderate-to-large PDA after the first week were followed to determine if or when retreatment or ligation would be necessary.

In May 2011, we made a change to a more conservative treatment approach. During epoch 2 (May 2011 through December 2015, n = 127) PINDO was no longer used. PDAs were no longer treated with indomethacin until at least 8 days of age to allow for spontaneous closure.[23] During epoch 2, all infants had an echocardiogram on postnatal days 6 or 7.

Our goal was to determine whether a moderate-to-large PDA was responsible for vasopressor-dependent hypotension at the end of the first postnatal week if other identifiable causes of hypotension were excluded. Therefore, infants who died or developed identifiable causes of hypotension (bacteremia, NEC, or spontaneous intestinal perforations) during the first 7 days were excluded from our study population (**Table I**). None of the study infants underwent surgical ligation during the first 7 postnatal days. The effects of a moderate-to-large PDA (and of the 2 different treatment approaches) on other short-term and long-term neonatal morbidities will be reported separately.

A single neonatologist prospectively evaluated and recorded all of the perinatal/neonatal risk factors during the hospitalization (**Table I**). Gestational age was determined by the date of last menstrual period and early ultrasound scans (before 24 weeks' gestation). Small for gestational age was defined as birth weight less than the 10th percentile for gestational age via use of the growth curves from Olsen et al.[24] All infants were examined with serial bedside cranial ultrasound scans initiated within the first week of life. Intraventricular hemorrhage was classified with the 4-level grading system.[25]

The echocardiographic studies included 2-dimensional imaging, M-mode, color flow mapping, and Doppler interrogation as previously described.[26] A moderate-to-large PDA was defined by one or more of the following echocardiographic criteria: internal ductus diameter ≥ 1.5 mm (or PDA:left pulmonary artery ≥ 0.5); ductus flow velocity ≤ 2.5 m/s or mean pressure gradient across the ductus ≤ 8 mm; left pulmonary artery diastolic (or mean) flow velocity > 0.2 (or > 0.42) m/s; and/or reversed diastolic flow in the descending aorta.[22,27]

During the time period of our study, a standardized approach was used in our nursery that determined when volume expanders and vasopressors would be initiated and included the rate at which they would be increased or decreased (see below).[21] An arterial line and transducer were used to measure BP continuously in all infants receiving dopamine infusions or hydrocortisone for BP support.

Hypotension was defined as "mean BP less than the third percentile for postmenstrual age that lasted more than 15 minutes."[28,29] Operationally, this meant that infants were considered to be hypotensive, and require treatment for their hypotension, if their mean BP was less than ([postmenstrual age in mm Hg] – [3-4 mm Hg]).

When infants failed to maintain an adequate BP (defined as "BP greater than the hypotensive range"), no more than 2 fluid boluses could be given initially to correct presumed hypovolemia. If the fluid boluses were unsuccessful in maintaining an adequate BP, dopamine support could be added. Infusion of dopamine was started at a rate of 5 μg/kg/min. The dose could be increased by 2 μg/kg/min every 15-30 minutes until an adequate BP was achieved. If a dopamine infusion rate of >15 μg/kg/min failed to maintain an adequate BP, hydrocortisone (starting at 1 mg/kg/d, dosed at 0.25 mg/kg/dose every 6 hours) could be added. When attempting to wean the dopamine infusion, the rate was decreased by 2 μg/kg/min every hour as long as an adequate BP was maintained.