Prophylactic Indomethacin Compared with Delayed Conservative Management of the Patent Ductus Arteriosus in Extremely Preterm Infants: Effects on Neonatal Outcomes

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Objective To determine whether prophylactic indomethacin (PINDO) has more or less morbidity than delayed conservative management of the moderate-to-large patent ductus arteriosus (PDA).

Study design We performed a prospective double cohort controlled study of infants delivered at ≤27$^{6/7}$ weeks gestation (n = 397). From January 2005 through April 2011, all infants were treated with PINDO (n = 247). From May 2011 through August 2016, no infant was treated with indomethacin until at least 8 postnatal days (conservative epoch, n = 150). Echocardiograms were performed on day 7 and at planned intervals until the PDA was small or closed. A single neonatologist prospectively collected all data.

Results The incidence of moderate-to-large PDA on day 7 and duration of exposure to moderate-to-large PDA were significantly less in the PINDO epoch (incidence = 10%, median = 2 days) than the conservative epoch (incidence = 67%, median = 14 days). Ligation rates were low in both epochs (PINDO = 14%, conservative = 5%). In multivariate analyses, PINDO infants had a significantly lower incidence of bronchopulmonary dysplasia (BPD) (risk ratio = 0.68, CI: 0.46-0.89) and BPD or death (risk ratio= 0.78, CI: 0.62-0.95) than conservative infants. There were no differences between the epochs in death, intraventricular hemorrhage grades 3 and 4, necrotizing enterocolitis, or retinopathy of prematurity receiving treatment. The effects of PINDO on BPD and BPD or death were no longer significant when analyses were adjusted for presence of a moderate-to-large PDA on day 7. The significant effects of PINDO were independent of whether or not a ligation was performed.

Conclusions PINDO decreases BPD and BPD or death compared with delayed conservative PDA management. These effects are mediated by closure of the PDA. *(J Pediatr 2017;187:119-26).*

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Extremely preterm infants frequently develop a moderate-to-large patent ductus arteriosus (PDA) at the end of the first week. Early pharmacologic treatment of the PDA is effective in closing the PDA, decreasing the incidence of hemorrhagic pulmonary edema[1-3] and hypotension, and decreasing the need for early ventilator and inotropic support.[4,5] However, long-term benefits appear to be lacking.[2,4,6-9] Although retrospective observational studies demonstrate an association between the presence of a PDA and long- term morbidities (necrotizing enterocolitis [NEC], bronchopulmonary dysplasia [BPD]), no association has been found in the randomized controlled trials (RCTs) that have explored this issue.[2,4,6-9] Based on the evidence from the existing RCTs, the American Academy of Pediatrics Committee on Fetus and Newborn recently concluded that "routine treatment to induce closure of the ductus, either medically or surgically, in the first 2 weeks after birth does not improve long-term outcomes" and that "prophylactic use of indomethacin may not be justified by an expectation of better long-term outcomes".[10]

Although these RCTs failed to show any long-term benefits, it might be a mistake to conclude, based on their results, that exposure to a PDA during the first 2 weeks has no long-term consequences. Most of the prior RCTs enrolled patients based on whether the PDA was "present," without taking into account either the magnitude or the duration of the left-to-right shunt. Recent studies have shown that the development of BPD is associated with persistent moderate-to-large PDAs but is not associated with persistent small, nonsignificant PDAs.[11] In addition, the average difference between the groups in length of exposure to the PDA was less than 6 days. Therefore, it is possible that longer exposure to a moderate-to-large PDA may affect long-term morbidity.

BPD	Bronchopulmonary dysplasia	PINDO	Prophylactic indomethacin
BPD/death	BPD or death before 36 weeks	RCTs	Randomized controlled trials
IVH	Intraventricular hemorrhage	RR	Risk ratio
NEC	Necrotizing enterocolitis	sIVH	Serious IVH
PDA	Patent ductus arteriosus		

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We performed a prospective double cohort controlled study to examine whether a "conservative" approach to PDA treatment (that allows infants to be exposed to a moderate-to-large PDA shunt for at least 8 days) is associated with an increase or decrease in morbidity compared with an approach that uses prophylactic indomethacin (PINDO).

Before May 2011, all infants in our nursery who delivered at ≤27$^{6/7}$ weeks gestation were treated with PINDO (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 section). We prospectively followed both groups to insure that infants treated with the conservative approach did not have a higher incidence of long-term neonatal morbidities.

Methods

This project was approved by the Institutional Review Board of the University of California San Francisco. This study is part of an ongoing prospective study begun in 1992 to evaluate different methods of PDA treatment in extremely low birth weight infants.

Infants were included in the current study if they were born between January 2005 and August 2016, delivered at ≤27$^{6/7}$ weeks gestation, and 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 previously published.[5,12-14]

During the first epoch (PINDO), before May 2011, all infants (n = 247) were treated with a course of PINDO starting within 15 hours of birth, provided there were no contraindications. Six potential PINDO doses (a 0.2 mg/kg loading dose followed by five 0.1 mg/kg maintenance 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 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 "constricted" (small or closed) ductus (see below for criteria) 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 with echocardiograms to determine if or when retreatment or ligation would be necessary.

Echocardiograms were performed initially every 7 days for the first 2-3 weeks; then, every other week until the PDA was no longer moderate-to-large in size. During the PINDO epoch, the ductus was "constricted" (small or closed) on day 7 in 90% of the infants (69% were closed, 21% were small) (**Table I**); in 77% of the infants, the ductus stayed small or closed from day 7 through hospital discharge (**Table I**). Moderate-to-large PDAs that failed to close or reopened after indomethacin treatment were ligated only if the infants were either hypotensive and required inotropic support for more than 3

Table I. Incidence of demographic characteristics

Variables	Prophylactic epoch (n = 247)	Conservative epoch (n = 150)	Variables	Prophylactic epoch (n = 247)	Conservative epoch (n = 150)
Prenatal variables:			Neonatal variables (continued):		
Singleton (%)	67	61	Caucasian (%)	39	48
Preeclampsia (%)	19	23	Female (%)	47*	60
Chorioamnionitis (%)	28*	17	Outborn (%)	31*	19
Maternal diabetes mellitus (%)	6*	15	5 min Apgar ≤5 (%)	31*	42
Cesarean delivery (%)	66	75	Respiratory distress syndrome (%)	94	93
Fetal presentation (%)			Tracheal intubation during first 24 h (%)	95*	82
Vertex	64*	47	Mechanical ventilation at 24 h (%)	60*	45
Breech	30	43	RSS at 24 h†		
Transverse	5	10	0.00-1.49 (%)	32*	26
Betamethasone (%)			1.50-1.99 (%)	29	21
None or ≤6 h	28	19	≥2.00 (%)	40	53
7-23 h	8	11	Fluid intake on d 1 and 2 – mL/kg/d (m ± SD)	159 ± 38	166 ± 33
1-9 d (or second course)	49	57	Bacteremia or pneumonia (%)‡	40*	23
≥10 d (single course)	14	13			
			PDA treatment variables:		
Neonatal variables:			PDA status at 7 d§		
Gestational age, wk (mean ± SD)	26.1 ± 1.2	26.0 ± 1.2	Permanently constricted¶ (%)	77*	29
Gestation ≤25 wk (%)	45	45	Closed at 7 d (%)	69	17
Birthweight, g (mean ± SD)	813 ± 197	802 ± 200	Small at 7 d (%)	8	12
Fenton birthweight/age z score			PDA moderate-to-large (%)	10	67
≥–1.0 SD (%)	84	82	Constricted (small) at 7 d but reopened later (moderate-to-large) (%)	13	4
–1.0 to –1.28 SD (%)	4	11			
<–1.29 SD (%)	11*	7	PDA ligation (%)	14*	5

RSS, respiratory severity score.
*P value < .05.
†RSS, means airway pressure × fraction of inspired oxygen, measured at 24 hours after birth.
‡Bacteremia, culture-positive bacteremia. Pneumonia, sudden respiratory deterioration in arterial blood gases associated with (1) new progressive infiltrates in the chest radiograph that persist for more than 3 days and (2) either blood leukocytosis, leukopenia, or an increase in immature neutrophil forms, and/or (3) associated temperature and/or glucose instability.
§PDA status at 7 days: n = 349; 48 infants died before day 7 (13% of the conservative epoch's population died before 7 days; 11% of the prophylactic epoch's population died before 7 days).
¶Constricted, ductus was either closed or small on echocardiogram.